Chapter 15: *M. Tuberculosis*, TB Medicines and Monitoring

*Dr Adrian C Harrison*

*Respiratory Physician, Green Lane Hospital, Auckland*

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References
Summary

*M. tuberculosis* and the host response

- Characteristics of *M. tuberculosis* and the host response to TB are reviewed in the full text. Many aspects are pertinent to understanding certain characteristics of TB epidemiology, infection and disease, as well as clinical tests.

The eradication of TB with drug treatment

- The three phases in the eradication of TB are reviewed.
  - Phase I: rapid bactericidal activity occurs. Actively multiplying organisms are killed in this stage. Isoniazid, alone or in combination, is much more bactericidal than rifampicin and other drugs in this phase.
  - Phase II: this lasts up to two months. The rate of killing is slower, presumably because the remaining bacilli are metabolising more slowly. The decrease in the sputum colony counts is similar for different drug regimens (provided purely bacteriostatic drugs are not given alone), so there is no point adding more drugs to standard regimens in an attempt to shorten the period of infectivity when treating infectious cases with susceptible organisms.
  - Phase III: the ‘sterilisation phase’. The drugs act on intracellular bacilli, including those that are mainly dormant but have brief periods of active metabolism – ‘persisters’ are eliminated. In this phase, rifampicin is much more bactericidal than isoniazid. Pyrazinamide is also important in eradicating this population of organisms.

- The early bactericidal and sterilising properties of the antituberculous drugs are summarised as follows (see Table 15.1 for details):
  - isoniazid has high early bactericidal activity, but is inefficient at achieving (TB) sterility
  - rifampicin and pyrazinamide are crucial in achieving sterilisation by killing persisting semi-dormant bacilli
  - with regimens containing rifampicin and isoniazid, there is no benefit from continuing pyrazinamide beyond two months; but with isoniazid resistance, pyrazinamide may be usefully continued throughout the full course of treatment
  - ethambutol is effectively devoid of sterilising activity (isoniazid/ethambutol in particular is a weak, ineffective regimen)
  - aminoglycosides are only actively bactericidal against rapidly growing organisms.

- Concentration-dependent and concentration-independent killing and post-antibiotic effects are discussed in the context of TB medicines in the full text.

Mechanisms of drug actions

- See Table 15.2 and accompanying discussion.

Drug resistance

- The main types of drug resistance are:
  - primary resistance: the organisms transmitted were resistant to one or more TB drugs
• Naturally occurring resistance to anti-tuberculous drugs can also occur, and varies from drug to drug. Cavities contain approximately $10^8$–$10^9$ bacilli and there is a higher risk of naturally resistant organisms being present in TB cavities. Consideration should be given to adding additional drugs if there are other factors present for resistant organisms. A longer duration of treatment, compared with that for minor disease, is often appropriate.

• Because of naturally occurring drug resistance, multiple drug therapy is essential for TB disease.

• Secondary resistance to a particular drug is unlikely to occur within two months, if the drug in question has been taken as part of a multi-drug regimen, in which all doses have included all drugs and the organism is susceptible to most drugs in that regimen. Thus, stopping an effective regimen which has been taken regularly, prior to achieving a cure, should not predispose to the development of secondary resistance.

Drug doses and administration

• See Table 15.3 for dosage recommendations for anti-tuberculous 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 Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’.

• Ethambutol: the daily dose of ethambutol should be 15 mg/kg, unless there are good reasons for a higher (or lower) dose. The risk of optic neuritis is greater with higher doses.

Use of pyridoxine

• Always use pyridoxine when prescribing isoniazid for people at risk of peripheral neuropathy from other causes (eg, those with diabetes, chronic renal failure, malnourished people, alcoholics, those taking certain oncology agents and pregnant women).

• Many TB clinicians (including the chapter author) recommend routine use of pyridoxine 10–25 mg/day for everyone taking pyridoxine, as the development of peripheral neuropathy can occur without other risk factors. Moreover pyridoxine is cheap (especially with non-pharmacy brands) and easy to take.

Drugs in fixed-dose combinations (FDCs)

• See full text.

Administration of ethambutol

• Ethambutol and renal impairment: avoid using ethambutol with moderate and severe renal impairment. Doses for use in renal disease and dialysis are found in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’ and Table 17.1.

• Ocular toxicity: this is the main potential side-effect of ethambutol.
  – Baseline assessment of visual acuity and red-green colour perception are needed.
  – Ophthalmological assessment should be obtained as a baseline before starting treatment in patients with abnormal visual acuity.
  – Patients must be advised to report visual deterioration: such complaints necessitate a semi-urgent ophthalmological opinion.
– Small children, the elderly, adults with already marked visual impairment or renal impairment and those who cannot be relied upon to report visual deterioration should all be offered another agent, if possible.
– Hospital and public health staff should each enquire every two months (as a minimum) about visual deterioration, particularly where communication difficulties are present.
– Opinions differ about the necessity to monitor visual acuity: testing every two months seems advisable, and this is the usual practice with the Green Lane Hospital TB Service.

• Formal ophthalmological monitoring: where ethambutol is prescribed for people with comprehension or communication difficulties, formal ophthalmological assessment should be done regularly (eg, at monthly intervals). This is particularly important if renal impairment is present.

**Administration of Amikacin**

• See Table 15.4 and accompanying discussion.

**Pharmacological considerations with anti-tuberculous agents**

1. **Isoniazid**
   - Food and antacids may reduce the absorption of isoniazid, which is best taken on an empty stomach, or one to two hours before an antacid.
   - The relevance of isoniazid acetylator status:
     – it is unlikely that slow acetylator status has much significance in most subjects; no guidelines recommend routine testing of acetylator status
     – fast acetylator status would only be a consideration if once/week regimens become available.
   - Serum isoniazid levels may be appropriate where:
     – there is hepatotoxicity or other hypersensitivity reactions, and
     – the resistance pattern and/or other drug side-effects make reintroduction of isoniazid highly desirable.

2. **Rifampicin**
   - Rifampicin is best taken on an empty stomach, wherever possible. The time at which the maximum serum concentration occurs is delayed from approximately two hours to six hours, and the peak serum concentration is reduced by a third if rifampicin is taken after a fatty meal.
   - Antacids do not affect the absorption of rifampicin.
   - Rifampicin is excreted in urine, sweat, tears and other bodily fluids, colouring them orange. Soft contact lenses may be permanently discoloured.

3. **Rifabutin**
   - This drug should be taken straight after food, as serum concentrations of rifabutin are thereby enhanced.
4. **Ethambutol**
   - Absorption is unaffected by food.

5. **Pyrazinamide**
   - Food does not impair the absorption of pyrazinamide.

6. **Quinolones**
   - Ingestion with food delays the time to peak serum concentration by an additional one to two hours with these agents, but the extent of absorption is not changed.
   - Antacids or ferrous sulphate may interfere with the absorption of quinolones if both are taken together. See Table 15.8, Clinically important interactions with TB drugs.

7. **Directly observed therapy (DOT) – before or after food?**
   - In many subjects the timing is not critical.
   - When starting DOT, enquire about symptoms of malabsorption routinely. The combination of malabsorption and post-cibal administration of DOT containing rifampicin may result in treatment failure or the selection of rifampicin-resistant organisms.

**Monitoring**

**Monitoring infectivity**
- Patients with positive pre-treatment sputum should have repeat sputum tests at fortnightly intervals until conversion is documented.
- In people who are strongly acid-fast bacilli (AFB) smear-positive, it seems likely that two weeks of treatment is not sufficient to lower the infectious potential to a minimal level (ie, to a level of infectiousness equivalent to people with smear-negative, culture-positive TB). Isolation should continue until non-infectiousness can be virtually guaranteed, and usually this will mean the person is smear-negative. See Chapter 9: ‘Infection Control’.

**Radiological monitoring**
- Failure of the chest radiograph to show improvement after three months of treatment requires consideration of the following possibilities:
  - the diagnosis is not TB: re-investigation is needed
  - the TB had produced scarring prior to treatment
  - mixed pathology may be present: TB and other condition(s)
  - non-adherence to the medication programme has occurred
  - drug resistance was present from the outset, or has developed.
- Chest CT scanning is useful for monitoring mediastinal lymph node TB which is advanced or extensive initially. Consider giving longer treatment if a necrotic node appearance persists, or nodes do not diminish greatly in size during treatment.


**Monitoring for adverse drug reactions**

- Baseline haematology and biochemistry tests should be done on adults about to start TB treatment. Initial abnormalities need follow-up.
- Repeat blood tests two to three and six to eight weeks after adults start regimens containing hepatotoxic agents. Ongoing blood tests are unnecessary after the first two months of treatment if results are normal and no new symptoms develop.
- Symptoms of possible drug toxicity are an indication for appropriate blood tests.
- With pre-existing mild hepatic disease, or with substantial alcohol intake, it is prudent to monitor liver function (e.g., fortnightly for the first month, monthly for the next two months, and two-monthly thereafter). See also Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’.
- Nursing review (including a pill count) once a month is the minimum acceptable for patients on TB treatment. Instruct patients to watch for common drug reactions.
- Medical review every two to three months is acceptable, provided there are no risk factors for poor compliance, the patient can be relied on to report symptoms, and monthly review by a public health nurse is being carried out.

**Therapeutic drug monitoring**

- Improvements are needed in the methods of testing, the reliability of results, turnaround time, and the range of drugs available for testing. This will only occur if there is increased awareness and more frequent – but appropriate – requests for testing by clinicians.
- For situations where therapeutic drug monitoring may be indicated with first-line drugs, see section 15.6.4.

**Drug side-effects**

**Common drug side-effects**

- These are listed in Table 15.5.

**Dermatological side-effects**

- Pyrazinamide is the most common cause of dermatological side-effects with TB drugs.
- Isolated skin rash is very uncommon with isoniazid, but rash commonly occurs as part of a wider hypersensitivity reaction to this drug.
- Skin rash due to rifampicin is usually mild and can take a variety of forms.
- Ethambutol rarely causes dermatological side-effects.
- Photosensitivity can occur with pyrazinamide and the fluoroquinolones.

**Hepatotoxicity from TB-drug treatment**

- Treating TB involves giving several potentially hepatotoxic drugs – isoniazid, rifampicin and pyrazinamide. Ethambutol very rare causes hepatic dysfunction.
- Chronic hepatitis B carriers tolerate isoniazid well.
• Isoniazid hepatotoxicity is associated with increasing age (see Table 15.6) and daily alcohol consumption. Time of onset: 15% during the first month, 30% during the second month, and 54% 2–11 months after starting isoniazid.

• Rifampicin is the usual cause of a cholestatic pattern. There is no evidence that hepatotoxicity with rifampicin is age-related.

• The hepatotoxicity with rifampicin and isoniazid seems to be additive rather than synergistic.

• Pre-existing hepatic dysfunction and its management is discussed in Chapter 17, section 17.2.

**Amikacin toxicities**

• See full text.

**Paradoxical reactions to TB treatment**

• A paradoxical reaction to TB treatment is defined as ‘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.

• Paradoxical reactions may have local or systemic components, or both. They occur more frequently in HIV-infected subjects who are on TB treatment and then commence antiretroviral agents.

• The differential diagnosis of apparently 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 secondary drug resistance or development of primary drug resistance
  – drug reaction
  – concurrent infection or malignancy.

• The diagnosis of paradoxical reactions may be difficult. Investigation aims at detecting other possible causes of deterioration at sites of previous TB. Tissue sampling is particularly important in severely ill people and in those with major immunosuppression.

**The management of paradoxical reactions**

• Once the 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 incising, though this would rarely be indicated.

**Management of drug reactions**

*Always consider the need for a new, temporary regimen*
Stopping all anti-tuberculous treatment

- Whenever considering stopping anti-tuberculous treatment, particularly if planning to give an oral steroid to counteract treatment side-effects, consideration must always be given to covering the TB with a new, temporary regimen. This regimen should continue until full doses of all drugs in the definitive regimen have been started.
- The duration of any period off all TB treatment (while awaiting resolution of TB-drug side-effects) depends on the clinical situation.
  - A person who is acutely ill with TB, or is infectious, should be given an alternative regimen immediately on stopping treatment.
  - For a non-infectious, well person there are no absolute rules. However, a period of four weeks is an arbitrary maximum period off all treatment, based on the fact that the opportunity for the development of infectiousness, or the spread of disease to other sites is possible after this length of time.

Progressive, but non-effective partial regimens

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

Repeated periods on partial or no treatment:

- These are particularly to be avoided. A second episode of no or partial treatment is an indication for starting a temporary regimen and continuing it for several weeks, until there is certainty that the difficulties have been fully resolved.

Agents in the temporary regimen

- These could include amikacin or streptomycin, ciprofloxacin, ethambutol and ethionamide (or prothionamide).

Rules for managing TB drug side-effects

- See ‘Practice points’ box, section 15.8.1.

Other items in this section

- See full text for discussion of drug challenges, drug densitisation and the management of skin side effects, hepato-toxicity and uncontrollable vomiting.

Interactions with anti-tuberculous drugs

- The interaction between rifamycins and oral contraceptives, and management of contraception, are discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’.
- The rifamycin–warfarin interaction is extremely important. There is the potential for:
  - sub-therapeutic anticoagulation occurring when a person on warfarin starts rifampicin
- A dangerous degree of anti-coagulation occurring when rifampicin is stopped, thereby effectively reducing the hepatic metabolism of warfarin.
- Allopurinol and pyrazinamide taken concurrently may result in acute attacks of gout. Manoeuvres to avoid this are given in the full text.
- For other drug interactions see Table 15.8.
Introduction

This chapter addresses the scientific background to the treatment of TB disease. It also provides information about anti-tuberculous drugs and their use. However, neither this nor the other treatment chapters attempts to be a comprehensive guide to the use of TB medications. Treatment regimens for active and inactive TB are discussed in Chapter 16: ‘Treatment of Tuberculosis’. The use of TB medicines in special clinical situations is the subject of Chapter 17, and their use in HIV is reviewed in Chapter 18.
15.1 M. tuberculosis and the host response

15.1.1 Characteristics of M. tuberculosis

*Mycobacterium tuberculosis* has a number of features that are important to its ability to survive and cause disease. Several are directly relevant to difficulties with treatment. These features include the fact that it:

- is a strictly aerobic bacterium
- has a long replication time (16–18 hours)
- possesses a thick, lipid-containing cell wall, which is the source of much of its virulence and persistence (e.g., the cell wall structure prevents it drying out and disintegrating quickly). Several antibiotics act via an effect on the cell wall
- has the ability to survive and multiply intra-cellularly
- has the ability to switch off metabolic activity and lie dormant for prolonged periods
- has resistance to conventional antibiotics and a (low) level of natural resistance to TB antibiotics (see section 15.4).

15.1.2 The host response to TB

The body’s responses to *M. tuberculosis* are important, and have a direct bearing on the clinical type of disease that results. This is a complex and expanding topic which is beyond the scope of this chapter. Key aspects of the immune response to *M. tuberculosis* include the following.

- *M. tuberculosis* binds to macrophages and monocytes – the alveolar macrophage is the body’s initial defence against this organism. Strain virulence, complement and cytokine release influence the initial binding of the organism to these cells. To become active against mycobacteria, macrophages must be activated. Activating factors include IFN-γ and TNF-α (see below), and also Vitamin D. Certain Vitamin D receptor polymorphisms may be associated with susceptibility to TB.¹
- Phagocytosis of the organism occurs – inside the macrophage a variety of complex killing mechanisms come into play, as a result of interaction between phagocytic cells and lymphocytes. Some bacilli are killed within the macrophage, but some survive and multiply.
- Although many T-lymphocytes play a part in defence against TB, there is no doubt that the CD4+ T-lymphocyte is the main effector cell in the cell-mediated immunity against TB. CD 8+ T-lymphocytes are also important.
- Interferon-γ (IFN-γ) is an important part of the defence against mycobacteria. It is released from CD4+ T-lymphocytes and natural killer (NK) T-lymphocytes. An important role of IFN-γ against TB is in the activation of macrophages. Children with defective receptors for IFN-γ or interleukin-12 (IL-12) are susceptible to TB.
- There is a complex array of interleukins and cytokines which activate and inactivate macrophages. Malnutrition unrelated to TB can markedly affect cytokine production, as can TB treatment.
• Tumour necrosis factor (TNF-α) produced by macrophages may play a dual role, helping macrophage activation on the one hand, while greater production resulting in increased plasma levels has been associated with deterioration in patients with severe TB. This cytokine, like IL-12, also facilitates the production of IFN-γ by NK cells, and subsequently by T-lymphocytes.

• Apoptosis (programmed cell death) of macrophages reduces the viability of mycobacteria contained within them.

• *M. tuberculosis* has a number of strategies that enable it to avoid being killed by macrophages. By altering the pattern of cytokine release from infected macrophages, it reduces macrophage activation and T-cell recruitment. The severity of the disease can affect the cytokine response.

• Some CD4+ T-lymphocytes differentiate into memory T-lymphocytes, and these mediate delayed hypersensitivity – the process that underlies the reaction to tuberculin in the Mantoux test (see Chapter 2: ‘Mantoux Testing’).

The ‘atypical’ clinical picture of TB seen in AIDS (see Chapter 18: ‘Tuberculosis and HIV’) and occasional cases of TB that are unresponsive to appropriate TB medicines are examples of the direct clinical relevance of understanding the host response to TB. For further reading, see.1–5
15.2 The eradication of TB with drug treatment

15.2.1 The three phases in the eradication of TB

These are relevant to the phases of TB treatment, as discussed in Chapter 16: ‘Treatment of Tuberculosis’. These are theoretical concepts based on animal models and studies in humans, and the duration of the phases are not exact.

**Phase I**

Phase I is said to last about two days, during which time rapid bactericidal activity occurs. The organisms being killed are actively multiplying at this stage, and they are thought to comprise 90% of the bacterial population (see also 15.2.2). There are large differences between drug regimens with respect to the speed with which colony counts decrease. Isoniazid, alone or in combination, is much more bactericidal than rifampicin and other drugs in this phase. It is likely that this phase does not stop abruptly on day three, but rather becomes less important as the bacterial number decreases with time. The effectiveness of drugs in reducing colony counts during this two-day phase is called their early bactericidal activity (or EBA).

**Phase II**

Phase II lasts up to two months. The rate of killing is slower, presumably because the remaining viable bacilli are metabolising more slowly. During this phase the decrease in the sputum colony counts is similar for different drug regimens (provided purely bacteriostatic drugs are not given alone). For this reason there is no point in adding more drugs to standard regimens in an attempt to shorten the period of infectivity, when treating infectious cases with susceptible organisms.

**Phase III**

In Phase III, or the ‘sterilisation phase’, the drugs act on intracellular bacilli, including those that are mainly dormant but have brief periods of active metabolism. In this third phase, ‘persisters’ (which demonstrate very occasional bursts of metabolic activity) are eliminated, and rifampicin is much more bactericidal than isoniazid for this population of organisms.

Although three phases can be identified, they probably all start at the commencement of treatment. Despite the fact that most replicating bacteria are killed rapidly during the first one to two weeks of treatment, there is no known relationship between EBA and the outcome of treatment. Time to sputum sterilisation is a very important predictor of outcome.

15.2.2 The early bactericidal and sterilising properties of the anti-tuberculous drugs

<table>
<thead>
<tr>
<th>Extent of activity</th>
<th>Prevention of drug resistance</th>
<th>Early bactericidal activity</th>
<th>Sterilising activity</th>
</tr>
</thead>
</table>

Table 15.1: Grading of anti-tuberculous drugs

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Guidelines for Tuberculosis Control in New Zealand 2003
Chapter 15: *M. Tuberculosis*, TB Medicines and Monitoring
Isoniazid has high early bactericidal activity and kills rapidly growing bacilli in lesions. It is thought to be responsible for killing about 95% of these organisms during the first two days of treatment. However, it is inefficient at ultimately sterilising these lesions.\textsuperscript{13}

Rifampicin and pyrazinamide

These are crucial in achieving sterilisation by killing persisting semi-dormant bacilli. Their use in daily treatment regimens is discussed in Chapter 16: ‘Treatment of Tuberculosis’, section 16.4. Rifampicin is the most important anti-TB drug from a sterilising viewpoint. Rifabutin is the best of the rifamycins at cell penetration, and is an excellent sterilising drug, killing intra-cellular bacilli.

It used to be thought that pyrazinamide worked by killing organisms within macrophages in an acidic environment. However, the intra-cellular environment around bacilli is not acidic. It is now believed that this drug kills both extra-cellular, semi-dormant organisms whose growth is slowed by an acidic environment, and those within macrophages.\textsuperscript{12}

Pyrazinamide is a pro-drug, the active agent being pyrazinoic acid. The latter is formed by the action of the enzyme pyrazinamidase – which is identical with nicotinamidase – on pyrazinamide. Amidase activity is present in \textit{M. tuberculosis} organisms susceptible to pyrazinamide, but not in those resistant to it. The gene encoding for this amidase, \textit{pncA}, has been identified.\textsuperscript{14} It remains to be seen whether resistance to pyrazinamide can occur by a mechanism other than by \textit{pncA} mutation.

With regimens containing rifampicin and isoniazid there is no benefit from continuing pyrazinamide beyond two months, because by then there is insufficient acute inflammation and insufficient acidity for pyrazinamide to be bactericidal. There are also concerns about continuing pyrazinamide beyond two months because this drug has been found to antagonise the bactericidal activity of isoniazid and rifampicin in macrophages.\textsuperscript{15} With isoniazid resistance, however, pyrazinamide may still be useful in the continuation phase of treatment.
Ethambutol

Ethambutol is very useful for preventing the development of drug resistance, but ‘is effectively devoid of sterilizing activity’. High relapse rates occurred with 12-month regimens of isoniazid/ethambutol, despite two initial weeks of daily streptomycin.

Amikacin

Even with serum levels that are well in excess of the minimal inhibitory concentration (MIC) of *M. tuberculosis*, amikacin has ‘only just detectable’ early bactericidal activity. This contrasts with *in vitro* studies in which amikacin and other aminoglycosides have been shown to be highly bactericidal. Possible explanations for this paradox include:

- aminoglycoside activity is critically dependant on pH, with greatly lessened activity at an acidic pH
- there is poor penetration of all aminoglycosides into bronchial secretions, concentrations there being only 15–20% of that in the bloodstream.

Aminoglycosides are only actively bactericidal against rapidly growing organisms; they are not active against occasionally metabolically active ‘persisters’. Consequently, aminoglycosides do not have useful sterilising ability. These agents are most likely to be useful against mycobacteria in phase II of treatment (as discussed in 15.2.1), when the degree of inflammation has subsided as a result of other multi-drug treatment. Donald et al 2001 conclude that the role of aminoglycosides, like that of ethambutol, is probably mainly in preventing the emergence of resistance to other drugs.

15.2.3 Concentration-dependent and concentration-independent killing

Bactericidal agents active against the cell wall of aerobic bacteria

These agents exhibit saturable bacterial killing at concentrations above the MIC. In other words, drugs working on the cell wall have a concentration-independent pattern of action. For these agents, the aim should be to maintain plasma drug concentrations above the MIC for the entire administration interval.

TB antibiotics that are active against the mycobacterial cell wall (see Table 15.2) probably include ethambutol, isoniazid, ethionamide, prothionamide and thiacetazone.

Bactericidal agents with intra-cellular targets

Agents in this category exhibit non-saturable (or concentration-dependent) killing. ‘Concentration-dependent killing’ means that increasing doses above the organism’s MIC induces more rapid killing of the pathogen. Optimal antibacterial effects with these agents require:

- *either* high maximum plasma concentrations in relation to the MIC
- *or* a long period of antimicrobial exposure (ie, the time in which ‘the area under the curve vs plasma concentration,’ is above the MIC).

TB drugs with intracellular targets include aminoglycosides, fluoroquinolones, the rifamycins and possibly pyrazinamide (see Table 15.2). While Ciprofloxacin has useful
early bactericidal activity, its sterilising ability after two months is inferior (in combination with isoniazid, rifampicin) to isoniazid, rifampicin, pyrazinamide, ethambutol, with sterilising rates of 67% with isoniazid, rifampicin, ciprofloxacin \( (n = 11) \) and 100% with isoniazid, rifampicin, pyrazinamide, ethambutol \( (n = 9) \). The role of ciprofloxacin in combination regimens appears to be as a bactericidal rather than as a sterilising agent.\(^{20}\)

### 15.2.4 Post-antibiotic effect

The ‘post-antibiotic effect’ refers to the persistent inhibitory bactericidal effect against organisms that is seen after the drug has been eliminated from the blood stream. It probably represents the time required for the organism to recover from cellular injury. At present the only clinical relevance of the post-antibiotic effect is the ability to use aminoglycosides in a once-a-day dosage. This is associated with reduced renal toxicity. Fluoroquinolones have a prolonged post-antibiotic effect against most gram-negative pathogens. Whether this effect occurs with mycobacteria seems not to have been studied.\(^{21}\)
### 15.3 Mechanisms of drug actions

**Table 15.2: Mechanisms of action of the anti-tuberculuous drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Poorly understood: may involve depletion of nicotinamide-adenine dinucleotide, inhibition of mycolic acid synthesis, and/or inhibition of mycobacterial catalase activity; most likely inhibits cell-wall structural integrity</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Interferes with mycobacterial mRNA synthesis by binding to DNA-dependent RNA polymerase</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Inhibits synthesis of arabinogalactan and lipoarabinomannan, thereby interfering with cell-wall structure</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Poorly understood: activity depends on its conversion to pyrazinoic acid by mycobacterial pyrazinamidase/nicotinamidase*</td>
</tr>
<tr>
<td>Amikacin and other aminoglycosides</td>
<td>Inhibition of protein synthesis at the ribosomal level</td>
</tr>
<tr>
<td>Fluoro-quinolones</td>
<td>Inhibit DNA gyrase</td>
</tr>
<tr>
<td>Prothionomide</td>
<td>Bactericidal effect by inhibiting mycolic acid synthesis (resistance to prothionomide is unrelated to inhibition of catalase enzyme activity, as occurs with isoniazid)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Inhibits ribosomal protein synthesis</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Cycloserine is a structural analogue of D-alanine. It competitively blocks enzymes involved in the synthesis of the dipeptide D-alanine:D-alanine. Thus it inhibits mycobacterial cell wall synthesis.</td>
</tr>
<tr>
<td>Para-amino-salicylic acid</td>
<td>PAS is a structural analogue of PABA,** competitively blocking the conversion of PABA into folic acid (an essential purine needed for DNA synthesis).</td>
</tr>
</tbody>
</table>

* See section 15.2.2.
** PABA = para-amino benzoic acid.
15.4 Drug resistance

15.4.1 Types of drug resistance

There are two types of drug resistance: primary and secondary.

- Primary resistance refers to the fact that the organisms transmitted were resistant to one or more TB drugs.
- Secondary resistance means that new resistance developed as a result of inadequate drug treatment.

General bacterial mechanisms of drug resistance include barrier mechanisms (affecting permeability), degrading or inactivating enzymes, and genetic drug target modification. The last is the main mechanism of resistance to TB drugs, and is due to endogenous chromosomal mutation, and not to acquired resistance from an exogenous genetic source such as plasmids.

Limited studies suggest that the development of resistance may, in some instances, come at a physiological cost to the organism, in the form of reduced virulence or ‘fitness’.

15.4.2 ‘Natural’ drug resistance

There is a degree of naturally occurring resistance to anti-tuberculous drugs, which 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 both isoniazid and rifampicin.

Cavities contain approximately $10^8$–$10^9$ bacilli and so there is a significantly higher risk of naturally resistant organisms being present in cavitary TB. Consideration should be given to adding additional drugs (if there are other factors present for resistant organisms). A longer duration of treatment, compared with that for minor disease, is often appropriate.

Because of naturally occurring drug resistance it is essential to give multiple drug therapy for TB disease. With TB infection, because of the small number of infecting organisms, monotherapy is successful. In treating TB infection, knowledge of the susceptibility of the organism from the index case is enormously helpful. Treatment of TB infection is the subject of Chapter 3: ‘Latent Tuberculosis Infection’.
15.4.3 The molecular basis of drug resistance

The molecular basis of drug resistance is well described for all the first-line agents, the aminoglycosides and the quinolones. Resistance to pyrazinamide was covered in section 15.3.

Rapid and reliable genotypic methods of detecting TB drug resistance may be available in the future. This is most likely to be useful with rifampicin resistance, where mutations occur in a relatively small part of the TB genome, corresponding to the β sub-unit of the RNA polymerase. In contrast, with isoniazid resistance, multiple genes may be involved, and molecular biological testing is more complex.

15.4.4 Development of resistance

Secondary resistance to a particular drug is unlikely to occur within two months, if the drug in question has been taken as part of a multi-drug regimen, in which all doses have included all drugs, and the organism is susceptible to most drugs in that regimen. Stopping an effective regimen which has been taken regularly, prior to achieving a cure, should not predispose to the development of secondary resistance.
15.5 Drug doses and administration

15.5.1 Drug doses

Table 15.3 shows dosage recommendations for anti-tuberculous medicines. The following notes should be taken into account when using that table.

Isoniazid

Children

10 mg/kg/day is generally recommended for treatment of TB disease in children. A dose of 5 mg/kg/day may be adequate for treatment of latent tuberculosis infection (LTBI) in children. Douglas and McLeod point out that doses of ‘5 mg/kg/day achieve serum concentrations 60–100 times the MIC and produce satisfactory clinical outcomes’.

Adults

5 mg/kg/day is the accepted daily dose for adults. Higher doses are not required for tuberculous meningitis or miliary tuberculosis: a higher dosage may increase the risk of adverse reactions.

Obese patients

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 Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’.

Ethambutol

The daily dose of ethambutol should be 15 mg/kg, as noted later in this section (15.5.3), unless there are good reasons for a higher (or lower) dose. The risk of optic neuritis is greater with higher doses. The maximum daily dose of ethambutol is 2.5 g/day. Higher doses are appropriate with intermittent therapy.

Pyrazinamide

The maximum daily dose of pyrazinamide is 2.0 g. Higher doses are appropriate with intermittent therapy.
Table 15.3: Dosage recommendations for anti-tuberculous agents

<table>
<thead>
<tr>
<th>A. First-line agents</th>
<th>Daily dose (mg/kg)</th>
<th>Twice-weekly dose</th>
<th>Thrice-weekly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Child†</td>
<td>Adult</td>
<td>Child†</td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose/day</td>
<td>5–10</td>
<td>5</td>
<td>20–40</td>
</tr>
<tr>
<td>Max dose/week**</td>
<td>300 mg</td>
<td>300 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>Rifabutin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guidelines not complete</td>
<td>5 mg/kg</td>
<td>300–600 mg/ day effective</td>
<td></td>
</tr>
<tr>
<td>Rifampicin††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose/day</td>
<td>10–20</td>
<td>10</td>
<td>10–20</td>
</tr>
<tr>
<td>Max dose/week</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose/day</td>
<td>20–35</td>
<td>20–30</td>
<td>50–70</td>
</tr>
<tr>
<td>Max dose/week</td>
<td>2 g</td>
<td>2 g</td>
<td>4 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Second-line agents</th>
<th>Daily dose (mg/kg)</th>
<th>Twice-weekly dose</th>
<th>Thrice-weekly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>Child†</td>
<td>Adult</td>
<td>Child†</td>
</tr>
<tr>
<td>Max dose</td>
<td>1.0 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ciprofloxacin</td>
<td>500–1000</td>
<td>500–1500 mg</td>
<td></td>
</tr>
<tr>
<td>• Ofloxacin</td>
<td>1500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Moxifloxacin</td>
<td>800 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin IM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose/week</td>
<td>1 g</td>
<td>1 g</td>
<td>1.5 g</td>
</tr>
<tr>
<td>Amikacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose IM, IV</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose, IM, IV</td>
<td>15–30</td>
<td>15–30</td>
<td></td>
</tr>
<tr>
<td>Capreomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose IM</td>
<td>15–30</td>
<td>15–30</td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose</td>
<td>15–20</td>
<td>15–20</td>
<td></td>
</tr>
</tbody>
</table>

* American Thoracic Society
** Bednall et al
†† Child: less than 12 years of age
‡ An intravenous form of Rifampicin is available
† Prothionamide and ethionamide are given in divided doses.

See also Chapter 17, sections 17.1 and 17.3.
15.5.2 Use of pyridoxine

It is essential to give pyridoxine when prescribing isoniazid for people at risk of peripheral neuropathy from other causes (e.g., those with diabetes, chronic renal failure, malnourished people, alcoholics, those taking certain oncology agents and pregnant women). Many TB clinicians (including the chapter author) recommend routine use of pyridoxine 10–25 mg/day for everyone taking pyridoxine, as the development of peripheral neuropathy can occur without other risk factors. Moreover, pyridoxine is cheap (especially with non-pharmacy brands) and easy to take.

Drugs in fixed-dose combinations (FDCs)

General

FDC tablets contain two or more medicines within the same tablet or capsule. The main advantages are reduced risk of resistance developing to the drugs in the event of missed doses, potentially fewer medication errors, and fewer prescription items to order. However, a key disadvantage of many FDC formulations is reduced bioavailability of some drugs— in particular rifampicin. Another is that the number of tablets is not reduced, and the flexibility in obtaining an optimal dose of some agents, such as pyrazinamide, may be lost by using FDCs. Only those FDCs that have been proven to provide unaltered bioavailability of the component drugs should be used.35

Rifinah

The numbers in the names ‘Rifinah 150’ and ‘Rifinah 300’ refer to the dose (mg) of the rifampicin component. The dose of isoniazid in these two preparations is 100 and 150 mg respectively. Thus, in order to provide a satisfactory dose of isoniazid, ‘Rifinah 150’ should be used in persons weighing under 50 kg, while ‘Rifinah 300’ should be used in those over 50 kg.

Rifater

This FDC, which is widely used in many parts of the world, contains rifampicin, isoniazid and pyrazinamide. Unaltered bioavailability of the component drugs has been proven. Rifater is not available in New Zealand because it would be economically unprofitable for the supplier.

Drug suspensions (syrups)

See Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.5.5.

15.5.3 Administration of ethambutol

Doses

Standard doses are listed above in 15.5.1. Briefly, a dose of 15 mg/kg/day is usual, unless severe or drug-resistant TB necessitates 25 mg/kg/day. The higher dose should not be given for longer than two months. Ideal weight should be used in calculations for obese people. The maximum daily dose is 2.5 gm/day.
**Ethambutol and renal impairment**

Ethambutol should be avoided in the presence of renal impairment. This is not always possible, and the doses for use in renal disease and dialysis are found in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.3 and Table 17.1.

**Ocular toxicity**

Ocular toxicity is the main potential side-effect of ethambutol. Baseline assessment of visual acuity and red–green colour perception are needed. Ophthalmological assessment should be obtained as a baseline before starting treatment in patients with abnormal visual acuity. Patients must be advised to report visual deterioration. Such complaints necessitate a semi-urgent ophthalmological opinion.

Enquiring every two months (as a minimum) about visual deterioration is essential. Hospital and public health staff should both enquire, particularly where communication difficulties are present. Opinions differ about the need to monitor visual acuity: testing every two months seems advisable, and this is the usual practice with the Green Lane Hospital TB Service.

**Formal ophthalmological monitoring**

Where ethambutol is prescribed for people with comprehension or communication difficulties, formal ophthalmological assessment should be done regularly – for instance, at monthly intervals (level III evidence).* This is particularly important if renal impairment is present.36

**When to avoid ethambutol**

Relative contraindications to ethambutol are: small children, the elderly, adults with already marked visual impairment or renal impairment, and those who cannot be relied on to report visual deterioration. All these should be offered another agent, if possible.

15.5.4 Administration of Amikacin

**General**

Aminoglycoside administration has traditionally been by multiple dosing, usually every 8 to 12 hours. There is now a large body of experience which supports the use of extended-interval or once-daily dosing of aminoglycosides for most indications. This approach results in a high peak serum concentration, which declines over a 24-hour period to essentially result in a drug-free period at the end of the dosing interval. Advantages of once-daily dosing include reduced toxicity and increased convenience.

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* See Chapter 16, Introduction, for an explanation of levels of evidence.
Doses with normal weight and renal function

Dosing of amikacin is based on body weight and must also be adjusted for renal insufficiency. The weight used to calculate the dose should be the actual bodyweight for non-obese individuals. For these subjects the usual daily dose is 15 mg/kg, given by IV infusion (or rarely, IM).

Dosing weight

Obese people (those with an actual bodyweight greater than 25% above lean body weight) require a dose adjustment because aminoglycosides are primarily distributed into extracellular fluid. Doses based on actual body weight in the obese may lead to excessively high serum levels, while doses calculated using ideal (lean) body weight will result in inadequate concentrations. The method of calculating the dosing weight in obesity is discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.1.

Doses with (stable) renal impairment

Modifications are required to the dose and/or dosing interval when significant renal impairment is present. The first step is estimation of creatinine clearance, but only if the serum creatinine is stable:

Estimated creatinine clearance (ml/min) = \[(140 – age) \times \text{lean body weight (kg)}\] 
\[\frac{815 \times \text{serum creatinine (mmol/L)}}{\text{}}\]

Note that:
- this value should be multiplied by 0.85 in women
- this equation may overestimate creatinine clearance in severe liver disease and malnutrition.

Once the estimated creatinine clearance has been calculated, and the correct dosing weight is known, an appropriate amikacin dose can be calculated. A variety of methods have been proposed, such as that shown in Table 15.4, but prescribers are advised to consult their local guidelines, hospital pharmacist or clinician experienced in the use of aminoglycosides.

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>&gt; 80 ml/min</th>
<th>50–80 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt; 10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin dose</td>
<td>15 mg/kg</td>
<td>75%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Dose interval</td>
<td>Q 24 h</td>
<td>Q 24 h</td>
<td>Q 24 h</td>
<td>Q 24–48 h</td>
</tr>
</tbody>
</table>

Prolonged treatment with amikacin and normal renal function

Depending on the severity of the TB, amikacin is generally given daily for 14 days, five days per week for another 14 days and then thrice weekly thereafter, if still required.
**Administration method**

See amikacin in section 15.5.6.

**Monitoring**

*Serum amikacin trough levels* should be measured just before a dose. Trough levels only are required with once-a-day dosing. The trough level should be < 1 mg/L if toxicity is to be avoided. If the estimated creatinine clearance is < 50 ml/min or serum creatinine is increasing, then trough levels should be monitored frequently.

*Plasma creatinine concentration:*
- normal renal function: monitor creatinine every one to three weeks.
- with long-term dosing: fortnightly creatinine clearance is recommended.

*Monitoring ototoxicity and vestibular dysfunction:* with long-term dosing, fortnightly audiometry should be done. Electronystagmography is usually only carried out if vestibular symptoms develop.

**Amikacin toxicity**

See section 15.7.

### 15.5.5 Nebulised aminoglycoside treatment

This should be regarded as an unproven treatment.

Nebulised aminoglycoside was reported to diminish the period of sputum smear-positivity, and thus the period of infectivity, in 13 of 19 subjects in South Africa.\(^3\)\(^7\) Gentamicin sulphate (80 mg in 2–3 ml saline) or kanamycin sulphate in the same dose and dilution were nebulised eight-hourly in subjects who were sputum smear- and culture-positive after a mean period of two months of appropriate conventional treatment. The *M. tuberculosis* organism displayed some degree of drug resistance in 12 out of 19 subjects.

The median interval between instituting aerosol therapy and the first negative sputum smear was 23 days among patients who converted to negative smears. Follow-up sputum smears remained negative in five out of seven subjects whose sputum was retested one month or longer after smear conversion. No side-effects were reported.

This initial report therefore suggests that patients with prolonged sputum smear-positivity may have a shortened period of infectivity, if nebulised aminoglycoside is added to their oral regimen. Treatment could be started in patients with extensive pulmonary disease (particularly with extensive cavitary disease) without waiting for the response to two months of standard treatment.

*This form of treatment is regarded as experimental* at the time of publication of these guidelines. Further studies are required. Standard safety monitoring should be performed with this form of administration, as detailed in section 15.6.
15.5.6 Pharmacological considerations with anti-tuberculous agents

Isoniazid

Absorption
Food and antacids may reduce the absorption of isoniazid, which is best taken on an empty stomach, or one to two hours before an antacid.38

Acetylator status and elimination
Tri-modal rather than bimodal elimination of isoniazid is now accepted. The eliminator phenotypes are classed as fast acetylator, slow acetylator and intermediate acetylator. The intermediate acetylator genotype is constituted of co-dominant fast and slow alleles. Differences between fast and slow acetylation of isoniazid mean that:

• fast acetylators acetylate isoniazid 5–10 times faster than slow acetylators
• the elimination half-life in fast acetylators is approximately 50% of that of slow acetylators19
• the peak serum level (C_max) is lower in fast acetylators;19 the mean daily isoniazid exposure (AUC) in fast acetylators is half that of slow acetylators
• the hydazine metabolite reaches a lower level and persists at a lower level in the serum than in slow acetylators.39

Testing acetylator status
Acetylator status is not easily determined, as sulphamethazine, the agent traditionally employed in the sulphamethazine test, is not available. Acetylator phenotype may be determined by measuring the ratio of the acetylated and parent drugs in urine.40 For further reading, see Pea et al and Parkin et al.3941

Hepatotoxicity and acetylator status
A number of large studies found no association between acetylator status and susceptibility to isoniazid hepatotoxicity.42–45

More recently, acetylator status has been reported to be a factor affecting the incidence of hepatotoxicity from combined treatment with isoniazid and rifampicin.46 In a prospective study, 77 Japanese subjects were classified according to their N-acetyltransferase 2 (NAT2) genotype. This was determined by PCR-RFLP testing of peripheral blood lymphocytes. Hepatotoxicity was observed in slow acetylators: the degree was not clinically important in this group, but might become relevant with concurrent pyrazinamide, alcohol, other medications or illness.

Practice points

i. The relevance of isoniazid acetylator status
• It is unlikely that slow acetylator status has much significance in most subjects. No guidelines recommend routine testing of acetylator status.
• Fast acetylator status would only be of consideration if once per week regimens become available.

ii. Serum isoniazid levels may be appropriate where reintroduction of isoniazid is highly desirable:
• hepatotoxicity or other hypersensitivity reactions, and
• resistance pattern and/or other drug side-effects make management difficult without isoniazid.

**Rifampicin**

Rifampicin is best taken on an empty stomach, wherever possible. The time at which the maximum serum concentration occurs is delayed from approximately two hours to six hours, and the peak serum concentration is reduced by one-third, if rifampicin is taken after a fatty meal. (The importance of high peak levels was explained earlier: see section 15.2.3). Lesser reductions are seen with carbohydrate meals.

Only free rifampicin, and not plasma protein-bound rifampicin (which accounts for 75% of the total serum rifampicin level) is available to interact with mycobacteria. Hence, in order 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, despite post-cibal administration of this drug.47 48 Antacids do not affect the absorption of rifampicin.48

Rifampicin is excreted in urine, sweat, tears, and other bodily fluids, colouring them orange. Soft contact lenses may be permanently discoloured.

**Rifabutin**

This drug should be taken straight *after* food, as serum concentrations of rifabutin are thereby enhanced.49 This is the opposite of the effect of food on rifampicin blood levels.

**Ethambutol**

Absorption is unaffected by food.50 Major caution is needed with this drug in the presence of renal impairment (with and without dialysis). For more information, see 15.5.1. This drug should be avoided with renal impairment whenever possible.

**Pyrazinamide**

Food does not impair the absorption of pyrazinamide.

**Prothionamide and ethionamide**

These drugs have a narrow therapeutic-side effect profile. They are well absorbed after food. The effect of antacids is uncertain.
**Quinolones**

Ingestion with food delays the time to peak serum concentration by an additional one to two hours with these agents, but the extent of absorption is not changed. Antacids or ferrous sulphate may interfere with the absorption of quinolones if both are taken together. See Table 15.8.

**Streptomycin**

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

**Amikacin**

Amikacin is normally given by intravenous infusion over half an hour. If given intramuscularly, the peak serum concentration occurs an hour later.

**Directly observed therapy (DOT) – before or after food?**

In many subjects the timing is not critical, and most DOT treatment is successful despite little attention being paid to this point. For the convenience of all concerned this is fortunate. However, caution is required. As discussed above (see section 15.5.6), rifampicin levels are lower when the drug is taken after food – especially after a fatty meal, and appropriate advice should be given to people who are to take DOT.

When starting people on DOT the prescriber must remember and enquire about symptoms of malabsorption routinely. The combination of malabsorption and post-cibal administration of DOT containing rifampicin may result in treatment failure or the selection of rifampicin-resistant organisms.
15.6 Monitoring

15.6.1 Monitoring infectivity

Patients with positive pre-treatment sputum should have repeat sputum tests at monthly intervals until conversion is documented. Eighty-five percent of these patients are expected to be smear- and culture-negative after two months of treatment. Special measures are needed for those who remain sputum-positive, and a clinical TB expert should be consulted.

Documenting sputum conversion to negative is important epidemiologically. The WHO use sputum conversion data as an indicator of the effectiveness of a TB control programme.

The infectious potential of sputum smear-positive people on treatment remains controversial. Many clinicians worldwide either ignore this possibility, or follow the generally held opinion that the majority of infectious patients pose no public health risk after two weeks of full treatment. A study of this subject, using time for cultures to become positive as a surrogate for infectivity, was conducted at Green Lane Hospital, Auckland. The following points are relevant from that study.

- When sputum remained smear-positive it was always culture-positive. Even after two months of treatment the organisms were still viable.
- With sputum smear-negative, culture-positive TB the median time for cultures to become positive was 14 days.
- When sputum contained 10–100 (or more) acid-fast bacilli (AFB) per high-powered field after two weeks of treatment, the median time for cultures to become positive was 10 days (AC Harrison, A Morris, L Calder, personal communication).

Thus, in people who are strongly AFB smear-positive, it seems likely that two weeks of treatment is not sufficient to lower the infectious potential to a minimal level (ie, to a level of infectiousness equivalent to people with smear-negative, culture-positive TB). How long these people should be held in isolation is discussed in Chapter 9: ‘Infection Control’.

15.6.2 Radiological monitoring

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. Failure of the chest radiograph to show improvement after three months of treatment requires considering the following possibilities:

- the diagnosis is not TB: re-investigation is needed
- the TB had produced scarring prior to treatment
- mixed pathology may be present – TB and other condition(s)
- non-adherence to the medication programme occurred
- drug resistance was present from the outset, or has developed.
Chest CT scanning is useful for monitoring the progress of mediastinal lymph node TB which is advanced or extensive initially. Comparison of a before/early treatment-CT with another done just before planned completion of treatment may lead to revising the treatment cessation date. A longer length of treatment may be appropriate if lymph nodes continue to have a necrotic appearance, or have not diminished greatly in size during treatment (level III evidence* – ie, expert opinion).

Serial imaging and extrapulmonary sites: the need for and the frequency of repeat imaging will depend on:

• the site of involvement (eg, abdominal ultrasound for intra-abdominal disease; cerebral CT or MRI for intra-cerebral TB)
• the severity of involvement at the site(s) of disease.

15.6.3 Monitoring for adverse drug reactions

Pre-treatment blood tests

Baseline haematology and biochemistry tests should be done in adults who are to be given treatment for TB (level III evidence: Ministry of Health Tuberculosis Working Group). Initial abnormalities need follow-up.

Routine blood testing during treatment

Expert opinion in New Zealand recommends repeating blood tests two to three and six to eight weeks after adults start taking regimens containing hepatotoxic agents. Ongoing blood tests are unnecessary after the first two months of treatment if results are normal and no new symptoms develop. Overseas experts recommend clinical monitoring, without regular blood tests, in people who are asymptomatic – even in the elderly, who have a higher incidence of hepatotoxicity.53

The New Zealand recommendation to monitor liver function is based on the following:

• serious hepatic dysfunction can develop before patients develop symptoms
• even an occasional death from TB-drug induced hepatitis is unacceptable
• iatrogenic hepatic failure necessitating liver transplantation is also unacceptable.

Symptoms suggesting possible drug toxicity are an indication for appropriate blood tests.

Monitoring and hepatic dysfunction

In people with pre-existing mild hepatic disease, or those with substantial alcohol intake, it would be prudent to monitor liver function; for example, fortnightly for the first month, monthly for the next two months, and two-monthly thereafter. Monitoring and treatment for those with severe hepatic dysfunction is discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.2.

* See Chapter 16, Introduction, for an explanation of levels of evidence.
Monitoring by a nurse

Nursing review (including a pill count) once a month is the minimum acceptable for patients receiving self-administered anti-tuberculous treatment. Patient education about TB includes instruction to watch for common drug reactions.

Medical appointments

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

Monitoring with drugs causing specific toxicities

For precautions with ethambutol, see section 15.5.3.

Use of an aminoglycoside necessitates pre-treatment and follow-up (eg, fortnightly) audiology testing and creatinine clearance estimations. Monitoring drug levels is discussed in the next section.

15.6.4 Therapeutic drug monitoring

Monitoring amikacin levels

See section 15.5.4.

Laboratory methods

Colorimetric methods are often used to measure TB drug levels for clinical purposes. Not all drugs can be tested accurately with this method.

Chromatography techniques (eg, high-pressure liquid chromatography, or HPLC) are probably the best, but if levels are only required occasionally, the costs of setting up the methodology and time lost by interrupting other HPLC tests to occasionally measure the level of an anti-tuberculous drug become important disadvantages. Measurement of TB drug levels by HPLC is being set up at the Biochemistry Department (Toxicology Division) at Auckland Hospital during 2002.

Immuoassay methods would be convenient, but the present low frequency of testing would mean that the reagents would deteriorate within six months. Thus immunoassay methods could not be justified on a cost basis unless batches were measured several times a month.
**Indications for, and use of, therapeutic drug monitoring**

Therapeutic drug monitoring may be required if the disease does not show the expected improvement, and also if, for other reasons, non-adherence or malabsorption are suspected. Malabsorption is particularly likely in patients with HIV infection, cystic fibrosis or diabetes mellitus. In HIV patients there may be up to 70% reduction in serum TB drug concentrations compared with control subjects. Sub-therapeutic drug concentrations indicate significant risk of drug resistance developing.

There should be a low threshold for checking ethambutol levels in patients with renal impairment, though recommendations in Chapter 17: ‘Treatment of Tuberculosis in Special Circumstances’, section 17.3, will usually allow effective dosing.

Other indications for therapeutic drug monitoring are:
- unexpectedly slow improvement of TB disease
- possible lack of adherence to treatment
- malabsorption
- ascites (see Chapter 17, section 17.2)
- drug side-effects, especially if re-introduction of the offending drug is desired
- risk factors for drug toxicity are present
- severe obesity (eg, BMI > 30) (see Chapter 17, section 17.1).

Unfortunately, therapeutic drug monitoring has not advanced greatly in recent years, and this limits clinicians’ ability to identify individuals who may require higher doses of anti-tuberculous medicines, and to ascertain whether toxicity is dose-related, or idiosyncratic.

Improvements are needed in the methods of testing, the reliability of results, turnaround time, and the range of drugs available for testing. This will only occur if there is increased awareness, and more frequent – but appropriate – requests for testing by clinicians.
### 15.7 Drug side-effects

Common drug side-effects are listed in Table 15.5.

**Table 15.5: Adverse effects of TB medicines**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td>Ototoxicity (lowest incidence with streptomycin); renal damage, skin rashes, fevers, circum-oral paraesthesiae, neuromuscular blockade</td>
</tr>
<tr>
<td>(amikacin, capreomycin, kanamycin, streptomycin)</td>
<td></td>
</tr>
<tr>
<td><strong>Para-aminosalicylic acid</strong></td>
<td>Gastrointestinal effects, hepatitis, fever, rash and hypothyroidism</td>
</tr>
<tr>
<td><strong>Cycloserine</strong></td>
<td>Dose-related CNS effects (drowsiness, vertigo, disorientation, confusion, coma and psychosis)</td>
</tr>
<tr>
<td><strong>Ethambutol</strong></td>
<td>Optic neuropathy (dose-related); peripheral neuropathy, arthralgia or rash are rare</td>
</tr>
<tr>
<td><strong>Ethionamide</strong></td>
<td>Gastrointestinal effects, liver toxicity; rarely hypothyroidism, hypotension, hypoglycaemia, alopecia, convulsions and neuropathy</td>
</tr>
<tr>
<td><strong>fluoroquinolones</strong></td>
<td>Gastrointestinal disturbances, dizziness, anxiety, depression, confusion and convulsions; rarely achilles tendon rupture, arthropathy and photosensitivity. For use in children consult a paediatric TB expert.</td>
</tr>
<tr>
<td><strong>isoniazid</strong></td>
<td>Isoniazid hepatotoxicity; see above, and also Table 15.6. Hypersensitivity reactions are unusual. Peripheral neuropathy, optic neuritis, fever, hepatitis, ataxia, euphoria, convulsions, tinnitus, insomnia, hyperglycaemia, gynaecomastia, dry mouth, epigastric discomfort, urinary retention, anaemia, arthralgias. Contraindicated in manic states and porphyria. 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. Very rare hypersensitivity reactions can include eosinophilia, angitis, toxic psychosis, and meningo-encephalitis. Toxic doses decrease the synthesis of the inhibitory neurotransmitter, GABA. CNS depression or stimulation may result.</td>
</tr>
<tr>
<td><strong>pyrazinamide</strong></td>
<td>Gastrointestinal side effects, hyperuricaemia, hepatotoxicity, fever, anorexia, nausea and vomiting; precipitation of gout (see section 15.9); arthralgias, urticaria, sideroblastic anaemia.</td>
</tr>
<tr>
<td><strong>rifabutin</strong></td>
<td>Rash, gastrointestinal disturbance, neutropaenia; uveitis, particularly in combination with macrolide antibiotics.</td>
</tr>
<tr>
<td><strong>rifampicin</strong></td>
<td>Gastrointestinal disturbance, cholestatic hepatic dysfunction, transient elevation of hepatic enzymes. Danger with intermittent therapy – flu-like syndrome, shock, acute renal failure, death. Rare reports of rifampicin-induced light chain proteinuria and renal failure, attributed to dehydration associated with fluid restriction for SIADH.</td>
</tr>
<tr>
<td><strong>thiocetazone</strong></td>
<td>Nausea, vomiting and diarrhoea, bone marrow depression, vertigo, ataxia, tinnitus and occasional liver toxicity. Cutaneous hypersensitivity can occur.</td>
</tr>
</tbody>
</table>
15.7.1 Dermatological side-effects

Dermatological side-effects of various anti-TB drugs are as follows.

- Pyrazinamide is the most common cause of dermatological side-effects with TB drugs, accounting for 26 of 31 (84%) of all rashes in 1317 patients in one study.\textsuperscript{55} It also often causes facial flushing or transient pruritis.

- Isolated skin rash occurs in about 2% of people taking isoniazid, and can take a variety of forms. However, rash commonly occurs as part of a wider hypersensitivity reaction to this drug. A dose-related skin response can occur with isoniazid.

- Skin rash due to rifampicin is usually mild, and can take a variety of forms.

- Ethambutol rarely causes dermatological side-effects.

- Photosensitivity can occur with pyrazinamide and the fluoroquinolones.

The management of dermatological problems caused by TB treatment is discussed in section 15.8. Oral or topical corticosteroid treatment may be required for severe adverse skin reactions.

15.7.2 Hepatotoxicity from TB drug treatment

Treating TB involves giving several potentially hepatotoxic drugs – isoniazid, rifampicin, and pyrazinamide. Ethambutol very rarely causes hepatic dysfunction.

Isoniazid hepatotoxicity is associated with increasing age (see Table 15.6) and daily alcohol consumption. It has a time of onset of 15% during the first month, 30% during the second month, and 54% 2 to 11 months after starting isoniazid.\textsuperscript{56} The possibility that slow isoniazid acetylator status may predispose to hepatotoxicity from combined treatment with rifampicin and isoniazid is discussed in section 15.5.6. Chronic hepatitis B carriers tolerate isoniazid well.

Rifampicin is the usual cause of a cholestatic pattern. There is no evidence that hepatotoxicity with rifampicin is age-related.\textsuperscript{57,58} The hepatotoxicity with rifampicin and isoniazid seems to be additive rather than synergistic.

There are very rare reports of hepatotoxicity with ethambutol. Most reviews and reports make no mention of this side effect.

For the monitoring of liver function during the first two months of treatment, see section 15.6.3; and for the management of drug-induced hepatotoxicity, see section 15.8.5.

Oral corticosteroid treatment may sometimes be tried in order to speed up the resolution of very slowly resolving drug-induced hepatitis (see Chapter 16: ‘Treatment of Tuberculosis’, section 16.10.7.)
Table 15.6: Age and frequency of hepatotoxicity with isoniazid

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Rare</td>
</tr>
<tr>
<td>20–34</td>
<td>≤ 0.3</td>
</tr>
<tr>
<td>35–49</td>
<td>≤ 1.2</td>
</tr>
<tr>
<td>≥ 50</td>
<td>≤ 2.3</td>
</tr>
</tbody>
</table>

Source: Van Scoy and Wilkowske 1987.59

15.7.3 Amikacin toxicities

Auditory and vestibular toxicity

Amikacin can cause both auditory and vestibular toxicity. Auditory effects are greater than vestibular ones with amikacin. Damage begins in the basal end and progresses to the apical end of the cochlea. Symptomatic hearing loss begins with high frequency loss, and as administration continues lower frequency loss occurs. In at least 50% of cases auditory toxicity is irreversible. Vestibular damage may be reversible, however. Early detection helps prevent hearing loss in the frequency range that can affect communication. Testing high-frequency ranges is essential for the reason just discussed.

High trough serum levels and advanced age are the most important predisposing factors to ototoxicities. Other factors include the duration of administration, total dosage, high fever and bacteremia, dehydration, and prior renal or ear disease. Ototoxicity occurs quite independently of nephrotoxicity. Some studies show that ototoxicity can develop at nontoxic serum levels, but is more likely to occur if serum levels exceed the recommended range.60

Nephrotoxicity

This is related to dose, duration of treatment and age, and is more likely in those with pre-existing renal impairment, dehydration or liver disease, and in patients receiving loop diuretics or other nephrotoxic agents.

15.7.4 Paradoxical reactions to TB treatment

A paradoxical reaction to TB treatment is defined as ‘worsening of disease at a pre-existing site, or the development of new tuberculosis lesions following initiation of appropriate treatment’.61 These reactions generally occur about one to three months after the start of treatment.

They are thought to result from:

- an immunological host response to mycobacterial products, which have been released as a result of treatment-induced bacterial cell death and dissolution
- 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-infected people. However, they occur more frequently in HIV-infected subjects who are on TB treatment and then commence anti-retroviral agents. Tuberculin skin-test conversion has been described as being associated with the onset of paradoxical TB reactions.

TB-related paradoxical reactions and immune reconstitution syndrome in the context of HIV are discussed in Chapter 18, ‘TB and HIV Infection’, section 18.4.2.

**The differential diagnosis of apparently paradoxical reactions**

The differential diagnosis includes:

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

**The diagnosis of paradoxical reactions**

This may be difficult, depending on the site of involvement and whether or not immunosuppression is part of the clinical situation. Investigation is aimed at detecting other possible causes of deterioration at sites of previous TB, as discussed in section 15.4. Tissue sampling is particularly important in severely ill people and in those with major immunosuppression.

**The management of paradoxical reactions**

Once the 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 incising, though this would rarely be indicated.
15.8 Management of drug reactions

15.8.1 Always consider the need for a new, temporary regimen

Stopping all anti-tuberculous treatment

Whenever considering stopping anti-tuberculous treatment – particularly if planning to give an oral steroid to counteract treatment side-effects – consideration must always be given to covering the TB with a new, temporary regimen. This regimen should continue until full doses of all drugs in the definitive regimen have been started.

The duration of any period off all TB treatment (while awaiting resolution of TB-drug side-effects) depends on the clinical situation.

- A person who is acutely ill with TB, or is infectious, should be given an alternative regimen immediately on stopping treatment.
- For a non-infectious, well person there are no strict rules. However, a period of four weeks is an arbitrary maximum period off all treatment, based on the fact that the opportunity for the development of infectiousness, or the spread of disease to other sites, is possible after this length of time.

Progressive but non-effective partial regimens

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

Repeated periods on partial or no treatment

These are particularly to be avoided. A second episode of no or partial treatment is an indication for starting a temporary regimen and continuing it for several weeks, until there is certainty that the difficulties have been fully resolved.

Agents in the temporary regimen

These could include amikacin or streptomycin, ciprofloxacin, ethambutol and ethionamide (or prothionamide).
Practice points

Rules* for managing TB drug side-effects

1. Maximum period off all drugs (*infectiousness could develop during this time*): 4 weeks
2. Maximum period on a partial regimen: 10 days
3. Temporary regimen: include at least three of the following – amikacin or streptomycin, ethambutol, ciprofloxacin, prothionamide.

* These are not based on direct evidence. See text.

15.8.2 Drug challenges

When troublesome side-effects occur, the offending agent(s) need(s) to be identified. Firstly, all treatment must be stopped and the reaction allowed to resolve. Drugs are then re-introduced sequentially, allowing 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, building up to the full dose over several days.

This procedure may necessitate covering the patient with additional agents to prevent resistance emerging during the challenge period.

If there is no reaction the process is repeated with the next drug selected. With less severe reactions it is occasionally possible to introduce full doses. If a clinician is unfamiliar with conducting drug challenges they may wish to consult a clinical TB expert with more experience.

Table 15.7: Drug challenge doses for mild-to-moderate reactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Days 3 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>50 mg</td>
<td>100 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>75 mg</td>
<td>150 mg</td>
<td>450–600 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>250 mg</td>
<td>500 mg</td>
<td>Full dose</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>100 mg</td>
<td>400 mg</td>
<td>Full dose</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>100 mg</td>
<td>500 mg</td>
<td>Full dose</td>
</tr>
</tbody>
</table>

Source: NHMRC 1989.63

15.8.3 Drug desensitisation

Rapid desensitisation protocols have been published for use in patients sensitive to rifampicin and ethambutol,64 and isoniazid.65 The methodology is based on protocols for treating penicillin allergy. So far only small numbers of patients have been studied, with greater success reported for rifampicin and ethambutol than for isoniazid hypersensitivity.

Desensitisation should be carried out cautiously, with full resuscitation resources available. The procedure should only be considered when suitable replacement drugs are not available.
15.8.4 Management of skin side-effects

Minor rash and itch are common with anti-tuberculous drugs. It should be noted that sometimes the skin side-effects are only short-lived and the treatments listed below might only be needed for a matter of days to weeks. The TB drugs may not have to be stopped, or if they are, it is sometimes possible to resume them successfully. Some of the following measures may be helpful.

- **Soap:** before assuming that TB drugs are the cause of the symptoms, check that the patient has not recently changed their usual brand of soap. Some soap brands are more prone to cause irritation than others, and it may be worth using:
  - a ‘simple’ soap containing no perfumes or other additives to try to minimise side effects (eg, Dove soap)
  - a soap substitute (eg, BK liquid soap substitute, or Cetaphil bar or lotion).

- **Skin moisturisers** may be useful for dry, itchy skin, for example:
  - ung simplex (paraffin ointment)
  - a barrier cream (eg, containing dimethicone)
  - refer to New Ethicals Catalogue, Guide to OTC section, Dermatological products.

- **Hydrocortisone 1% ointment in ung simplex:** this should be the starting point for trying steroid ointments, unless very severe reactions necessitate more potent steroid treatment.

- **Pruritis:**
  - antihistamines: a non-sedating antihistamine such as loratidine might be tried, although older, non-sedating antihistamines may also be successful, and at a lesser cost, if tolerated
  - Pinetarsol gel or solution may be a useful anti-pruritic cleansing preparation
  - BK bath oil or lotion may also have anti-pruritic properties
  - a number of other over-the-counter remedies are available.

15.8.5 Management of drug-induced hepatotoxicity

Cross-sensitivity may occur between drugs that are chemically related, such as the rifamycins. Other examples include isoniazid and ethionamide (both of which are derivatives of iso-nicotinic acid). Generally, drugs that are closely chemically related should not be used if marked hepatotoxicity occurs with one of them. However, rifabutin may be tried cautiously after recovery from rifampicin hepatotoxicity, where clinically indicated.

Mild, transient and asymptomatic increases in serum hepatic enzyme concentrations (eg, to three times the upper limit of normal) occur in about 20% of people during the early weeks of treatment. Treatment should not be interrupted because of these changes.
Authors vary in the degree of ‘transaminitis’ that is accepted and drug therapy allowed to continue. In general, if the person is asymptomatic, levels that are five-fold higher than the normal range can simply be watched while treatment continues. Van den Brande et al recommend that a five- to tenfold rise in transaminase levels, in the absence of symptoms, can be compatible with continuation of treatment. In that study, 10% of their patients showed a normalisation of transaminase levels despite continuation of isoniazid and rifampicin.53

If clinical hepatitis occurs – with anorexia, nausea, vomiting, hepatic tenderness and/or jaundice – all drugs should be stopped. Any correctable factors (such as prolonged bleeding time) should be corrected.

Often it is sufficient just to wait and see how rapidly the hepatotoxicity settles. Progressive, rapid improvement often occurs. On the other hand, it sometimes takes many weeks for abnormal liver function to return to normal, and this may be a situation where oral steroid treatment is required and/or a temporary regimen is prescribed (see section 15.8.1).

Clinical judgement is needed to decide whether to try to reinstitute 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 in several.66

15.8.6 Uncontrollable vomiting

Although nausea is not uncommon with TB drug treatment, it can be managed with usual agents. Theoretically it is possible that agents such as metoclopramide, which stimulate gastric emptying, may have an effect on TB drug levels. However, there is no literature available on this subject. It may be preferable to use prochlorperazine (Stemetil) or cyclizine (Marzine) if prolonged administration is needed.

Persistent vomiting may necessitate a drug challenge and elimination of the offending agent, once other causes have been excluded.

Very severe vomiting is uncommon with anti-tuberculous drug treatment. In one extreme case, where multiple drug-resistant TB was present, persistent vomiting caused sub-therapeutic drug levels. A percutaneous gastrojejunostomy tube was placed, and crushed tablets were administered through it. Clinical cure was achieved. Pharmacokinetic studies showed that drug levels peaked and began to decline earlier than is observed with oral administration. The practical importance of this is that blood levels needed to be taken an hour after this method of administration, instead of at two hours, which is the usual recommended sampling time after oral doses.67
15.9 Interactions with anti-tuberculous drugs

The interaction between rifamycins and oral contraceptives, and management of contraception, are discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.4.3.

The rifamycin–warfarin interaction is extremely important. There is the potential for:

- *sub-therapeutic anticoagulation* occurring when a person on warfarin starts rifampicin.\(^{68}\) Patients who are taking both agents, and who have an absolute indication for anticoagulation, need monitoring at least weekly. If therapeutic anticoagulation proves difficult, consider the use of low molecular weight heparin.

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

Allopurinol may paradoxically increase serum urate levels if given with pyrazinamide.\(^{69}\) Pyrazinamide may have to be avoided in patients with troublesome gout, as it can precipitate acute attacks of gout in those disposed to such 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 0.6 mg BID. If this manoeuvre is successful, the colchicine should be continued, and stopped when the pyrazinamide is discontinued.

For other drug interactions, see Table 15.8.

### Table 15.8: Clinically important interactions with TB drugs

<table>
<thead>
<tr>
<th>TB 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 Cipro + antacids</td>
</tr>
<tr>
<td></td>
<td>Anti-epileptics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 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>Antipsychotics</td>
<td>Plasma haloperidol may increase</td>
<td>Adjust dose if needed</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Anti-fungals</td>
<td>The antifungal blood level may be decreased</td>
<td>No problem using Fluconazole</td>
<td></td>
</tr>
<tr>
<td>• Ketoconazole</td>
<td>Mar ked rise in cyclosporin levels</td>
<td>Monitor cyclosporin blood levels</td>
<td></td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>About 30% of people on both get CNS toxic effects of Disulfiram</td>
<td>Reduce dose or discontinue Disulfiram</td>
<td></td>
</tr>
<tr>
<td>TB 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>Enfluorane</td>
<td>Enhanced defluorination of this anaesthetic agent may lead to accumulation of nephrotoxic fluoride</td>
<td>Avoid concurrent use of these two agents. More likely in isoniazid rapid acetylators</td>
<td></td>
</tr>
<tr>
<td>Histamine-rich food: cheese, sauerkraut, yeast extract, tuna</td>
<td>Flushing, chills, headache, wheeziness, palpitations, diarrhoea, vomiting, burning</td>
<td>Dietary advice; if necessary, give antihistamine</td>
<td></td>
</tr>
<tr>
<td>Tyramine-rich foods</td>
<td>Red wine, cheese, yeast extract</td>
<td>Due to slight monoamine oxidase effect of isoniazid. Dietary advice.</td>
<td></td>
</tr>
</tbody>
</table>

Rifampicin and rifabutin

a. Reduced levels of:

**Anti-arythmics**
- dispyramide
- mexilite
- propafenone
- quinidine

**Antifungals**
- itraconazole
  - Raised rifabutin level
  - Monitor serum level; may increase antifungal dose
- fluconazole
  - Reduced absorption, halving the rifampicin level
  - Give at least 12 hours apart. Check rifampicin level
- ketoconazole
  - Raised rifabutin level
  - As for clarithromycin

**Anti-retrovirals**
- nevirapine*
  - Probably not important – excellent ‘reserve effect’ with usual dose of this agent
  - Less interaction occurs with rifabutin and anti-retroviral agents: use it instead of rifampicin**

**Clarithromycin (and possibly other macrolides)**
- Raised rifabutin levels; risk of uveitis
  - Keep rifabutin dose at or below 300 mg/day; acute uveitis: stop rifabutin; ophthalmology review

**Corticosteroids**
- gluco- and mineralocorticoids
  - Profound reduction in steroid levels
  - Increase steroid dose 2–3-fold; reduce when rifamycin is discontinued.

**Diazepam, Nitrazepam**
- Monitor serum level; may need to increase dose

**Digitalis preparations**
- Likely with renal impairment
  - Monitor levels; dose may need to be doubled

**Immunosuppressive agents**
- cyclosporin
  - Levels are reduced by about 50%; significance uncertain
  - May need 3–5-fold increase in cyclosporin dose
- tacrolimus

**p-aminosalicylic acid (PAS)**
- Serum rifampicin may increase
  - Ensure these two agents are taken eight hours apart
<table>
<thead>
<tr>
<th>TB drug</th>
<th>Interacting agent</th>
<th>Effect</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin concurrent isoniazid</td>
<td>Markedly reduced anti-epileptic effect especially in fast acetylators Further reduction in phenytoin isoniazid counteracts covering of serphenybin by rifampicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>• tobutamide</td>
<td>Monitor diabetic control</td>
<td>Monitor diabetic control</td>
</tr>
<tr>
<td></td>
<td>• possibly others (eg, glibenclamide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</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 text)</td>
<td>Warfarin dose may need to be doubled or tripled at the start, and be similarly reduced when the rifamycin is stopped (see text)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>No interactions of note</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Allopurinol (see text also)</td>
<td>Acute gout</td>
<td>Avoid allopurinol; try colchicine instead May need to abandon use of pyrazinamide</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Antacids, containing aluminium, calcium and magnesium</td>
<td>Reduced absorption of Ciprofloxacin</td>
<td>Avoid antacids; or give ciprofloxacin 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 ciprofloxacin</td>
</tr>
<tr>
<td>Iron and zinc</td>
<td>As for Cipro + antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucralfate</td>
<td>As for Cipro + antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide and prothionamide</td>
<td>Increased risk of hepatotoxicity with rifampicin, isoniazid and pyrazinamide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Ribera et al 2001
** Centers for Disease Control and Prevention 1998
References


63 NHMRC. Tuberculosis in Australia and New Zealand into the 1990s. Canberra: National Health and Medical Research Council, 1989.


