

# Treatment of tuberculosis in adults and children

Guideline Version 3.0 March 2021



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<https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/diseases-infection/diseases/tuberculosis/guidance/guidelines>

**Note, updates after May 2021 are amended in the online version of Treatment of tuberculosis in adults and children ONLY — printed copies may not be current**

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# What this guideline covers

- Treatment regimens for drug susceptible and mono-resistant tuberculosis (TB) (pulmonary and extra-pulmonary) in adults and children
- Additional considerations for children with TB
- Microbiological testing
- Ancillary testing
- Treatment monitoring.

# What this guideline does not cover

Management of multi-drug resistant tuberculosis.

**The below areas are covered by separate guidelines**

- Management of TB in pregnant women and newborn infants
- TB HIV co-infection
- TB and chronic kidney disease
- Management of latent TB.

## Key Points

- The standard TB treatment regimen is 6 months of combination therapy.
- Use of both rifampicin and pyrazinamide in the regimen are key pre-requisites to enable a six-month duration.
- Never add a single drug to a failing regimen.
- Dosing is weight based (mg/kg).
- Co-administration of pyridoxine (vitamin B6) with isoniazid is no longer routinely recommended.
- Different regimens are recommended for drug resistance or intolerance. Individualised treatment is required for multi-drug resistant TB.
- Intermittent regimens are no longer recommended but thrice weekly treatment in the continuation phase may be utilised when adherence/access to care issues make daily therapy not feasible.
- Patients who have previously received drug therapy for TB should always be discussed with a clinician experienced in TB management before commencing a drug regimen.
- Extended treatment regimens are recommended for disseminated TB, CNS TB, or smear positive pulmonary TB with extensive cavitation.
- Corticosteroids should be given at the initiation of antimicrobial therapy for TB of the central nervous system and considered for pericardial disease.

# Standard regimens for drug susceptible pulmonary tuberculosis

The standard short course treatment of drug susceptible pulmonary tuberculosis has a strong evidence base. A series of trials conducted under the auspices of the British Medical Research Council (BMRC) in Singapore, Hong Kong, India and East Africa underpin the regimens below.<sup>1</sup> Abbreviations for TB drugs are outlined in the table on page 2. Regimens are commonly expressed as a number (of months) and drugs abbreviated as 1 to 3 letters required for that duration. All first line drugs can be denoted by a single letter.

## Six-month

The standard treatment regimen is 6 months of isoniazid and rifampicin, supplemented in the first 2 months by pyrazinamide and by ethambutol until the isolate is confirmed susceptible to the 3 other drugs 2HRZ [E]/4HR.<sup>2</sup> This conditional use of ethambutol is denoted by the square brackets in the regimen description: [E]. If the isolate is known to be susceptible to isoniazid and rifampicin prior to the commencement of therapy, ethambutol may be omitted from the regimen. The first 2 months of therapy is known as the '**intensive phase**' and the remainder of the treatment course as the '**continuation phase**'.

## Extended duration

For drug susceptible (DS) TB, the standard treatment regimen above is extended to 9 months (2HRZ[E]/7HR) if there is extensive disease, especially with cavitation and/or if cultures are still positive after completion of the intensive phase. Longer durations are also appropriate where there is drug resistance, intolerance or significant interruption to therapy (see below).

## Additional considerations for children (age 0 to 14 years)

### a) Weight based dosing

Anti-tuberculosis drugs are dosed in children according to weight. Significant weight gain may occur as the child responds to treatment. The child's weight should be monitored monthly during treatment and doses adjusted in line with any significant changes in weight.<sup>3</sup>

### b) Ethambutol

Ethambutol can be used safely in children of all ages in the standard fully susceptible regimen as there is low risk for toxicity at current dosing and duration (less than 2 months). Although considered safe, where possible, visual acuity monitoring should be performed especially in regimens with prolonged ethambutol use and ophthalmological review should be considered if planned duration is greater than 2 months. In the absence of laboratory drug susceptibility results, ethambutol may be omitted in paucibacillary disease (smear negative pulmonary or nodal TB) if isoniazid resistance is unlikely.<sup>4</sup>

# Recommended drug dosages

Although dosing is weight based, many adults in Australia will weigh more than 50kg and be eligible for standard doses of isoniazid (300mg/day) and rifampicin (600mg/day).

Doses of ethambutol are more likely to vary between adult patients. Combination tablets are not registered in Australia but may be used for patients who have commenced therapy in overseas countries and have their own supply. Newer combination formulations may be available via the pharmaceutical special access scheme (SAS).

Drug Name	Adult Dosages		Dosages in children (<14 years)	Parental Product Availability
	Daily	Thrice-Weekly*	Daily	
Isoniazid (H)	10mg/kg to 300mg	15mg/kg to 900mg	10mg/kg (range 7 to 15mg/kg) to maximum 300mg	IV Ampoule 50mg in 2mL (via Special Access Scheme)
Rifampicin (R)	10mg/kg to maximum 600mg (in practice 450mg if <50kg, 600mg if ≥50kg)	600mg	15mg/kg (range 10 to 20mg/kg) to maximum 450mg if <50kg and 600mg if ≥50kg	IV Vial 600mg
Ethambutol (E)	15mg/kg up to maximum 1200mg daily dose		20mg/kg (range 15 to 25mg/kg) to maximum 1200mg	None Available
Pyrazinamide (Z)	25mg/kg to maximum 2g See table		35mg/kg (range 30 to 40mg/kg) to maximum 2g	None Available
Pyridoxine (B6)	Not routine# 25mg	50mg	Not routine# 1 to 2mg/kg; Typically, 5 to 10mg in neonates	IV Ampoule 100mg in 1mL (via Special Access Scheme)

\*Thrice weekly only in exceptional circumstances for continuation phase or as endorsed by TEAG.

# Prescribe if patients are at risk for peripheral neuropathy (e.g. pregnant women, children on isoniazid who are exclusively breastfed, persons with HIV, diabetes, malnutrition, chronic kidney disease, alcohol abuse, or persons of advanced age).

# Accessing anti-tuberculosis drugs on the Special Access Scheme

In Australia, pyrazinamide requires Special Access Scheme (SAS) approval under the Therapeutic Goods Act. Pyrazinamide access can be streamlined by use of the Cat C SAS pathway where use requires notification within 28 days rather than approval prior to use (Cat B) or use for life threatening disease (Cat A).

Parenteral Isoniazid and pyridoxine are not registered medicines in Australia but are also accessible under SAS provision. Supply can be organised by liaising with the local hospital pharmacy who can advise on the necessary paperwork including SAS application forms and Queensland Public Hospital Individual Patient Request forms. SAS Application Forms can be downloaded at:

For Cat C special access scheme form via Central Pharmacy website:

<https://qheps.health.qld.gov.au/central-pharmacy/products/special-access-scheme/sas-order-form>

OR

Refer to the TGA website:

<https://www.tga.gov.au/form/special-access-scheme>

## Drug resistance or intolerance

### Detection of drug resistance

All strains of *Mycobacterium tuberculosis* detected in Queensland must be referred to the Queensland Mycobacterium Reference Laboratory (QMRL) for confirmation of identification and drug susceptibility testing (DST) telephone (07) 3646 0034.

#### a) Rapid detection of resistance

The GeneXpert instrument, using the Xpert MTB/RIF Ultra assay can be used to detect *M. tuberculosis* DNA from respiratory samples using PCR technology. The assay also detects mutations which confer rifampicin resistance. For patients likely to have acquired TB in settings where the risk of multidrug resistance (resistant to isoniazid and rifampicin) is significant, the detection of rifampicin resistance by Xpert MTB/RIF is highly predictive of MDR-TB. Some extrapulmonary specimens may also be tested with the Xpert assay. The MTB/RIF Ultra assay performs well for diagnosis of TB meningitis from CSF samples<sup>5</sup> and will be performed on request for CSF samples with evidence of an inflammatory response. Testing of other extrapulmonary samples should be discussed with the laboratory.

#### b) Conventional DST

This is performed using the BACTEC 960 MGIT liquid culture system. All *M. tuberculosis* strains receive first line DST (isoniazid, rifampicin, ethambutol, streptomycin and pyrazinamide). Drug resistant strains receive supplementary DST to the second line agents. First and second line testing each requires 10 to 14 days for a result in addition to the time taken for initial

isolation (2 to 6 weeks). Slow growing strains may need repeat testing before a reportable susceptibility result is obtained.

#### **c) Rapid detection of resistance from culture isolates**

This may be performed using a variety of molecular methods including line probe assays for the detection of resistance to rifampicin, isoniazid, fluoroquinolones and amikacin as well as targeted sequencing of resistance genes. Such testing should be discussed with the QMRL on a case by case basis.

#### **d) Whole genome sequencing (WGS)**

Routine use of WGS for characterisation of TB strains is performed in some overseas countries – for example UK and other Australian jurisdictions. WGS has been used for research purposes in the QMRL and transition to routine use is under development at the time of guidelines revision. WGS is performed on cultured isolates of *M. tuberculosis* and enables prediction of antimicrobial resistance and genetic comparison for typing purposes.

## Drug intolerance

In the event of an adverse drug reaction, careful assessment is required and clinical liaison with a clinician experienced in managing such issues is recommended. Some adverse events may represent an absolute contra-indication to continued use of an agent whereas others may be managed symptomatically without necessarily abandoning the use of the drug. Comments below on monoresistance also apply to intolerance where ongoing use of the particular agent is contra-indicated.

## Isoniazid monoresistance

Isoniazid resistance is the most common form of drug resistant TB and occurs in 5 to 10% of microbiological confirmed cases in Australia. The World Health Organization has published recent guidance for treatment of INH resistant TB. The inclusion of a fluoroquinolone is recommended with levofloxacin the preferred agent as impact on QTc prolongation and drug interactions including that with rifampicin is considered less than with moxifloxacin. The WHO recommended regimen is 6RZE-Lfx. The WHO recommendations are based on careful review of the literature involving diverse populations. Earlier studies in Hong Kong, prior to the use of fluoroquinolones, showed reasonable success with the 6HRZE treatment regimen. Furthermore, a recent review of Queensland data<sup>6</sup> demonstrated excellent outcomes with a fluoroquinolone free regimen.

A 6 month daily regimen consisting of all first-line drugs (6[H]RZE) is acceptable, subject to observing an appropriate clinical, radiological and bacteriological response, in particular – early bacteriological clearing of infection. This regimen allows the protection of fluoroquinolone use for periods where use is essential (MDR-TB).

An alternative regimen is at least 9 months of ethambutol and rifampicin, usually supplemented in the first 2 months by pyrazinamide (2RZE/7RE). It is recommended that in Queensland the use of a fluoroquinolone is favoured in the setting of extensive pulmonary or disseminated disease. Discussion with a TB clinical expert is recommended for any case of TB where a fluoroquinolone is proposed to be used, especially if the patient is pregnant, breastfeeding or HIV infected.



Strains demonstrating isoniazid resistance which also possess *rpoB* mutations occurring in the presence of rifampicin susceptibility on laboratory testing will likely not have satisfactory outcomes using the above regimens. These strains should be considered to be multi-drug resistant and should be referred to the TB Expert Advisory Group (TEAG) for treatment recommendations.

## Rifampicin monoresistance

Rifampicin monoresistance is rare in Australia (<1% of TB cases). The WHO recommends that RR-TB be managed as per its recommendations for MDR-TB guidelines as it is often used as a surrogate marker of MDR-TB where full DST may not be available.<sup>7</sup> However, it is unclear if this is appropriate within the Australian setting where DST is available, and a variety of regimens have been successfully used incorporating HZE plus Moxifloxacin +/-amikacin. As case numbers are low, the efficacy of these regimens is difficult to prove. Cases with Rifampicin monoresistance should be promptly referred to the TEAG via a clinician from the Metro South Clinical TB Service or a Regional TB Control Unit for peer reviewed management recommendations (as is required for MDR/XDR-TB cases).

## Ethambutol monoresistance

For isolates resistant to ethambutol but susceptible to isoniazid, rifampicin and pyrazinamide, a standard 2HRZ/4HR regimen is appropriate. Ethambutol monoresistance is rare. Additional information should be sought from the Queensland Mycobacterium Reference Laboratory as supplementary information may be available – for example MIC determination or mutational analysis.

## Pyrazinamide monoresistance

For isolates resistant to pyrazinamide, but susceptible to isoniazid and rifampicin a 2HRE/7HR regimen should be used. Pyrazinamide mono-resistance is rare excluding *M. bovis* which is constitutively resistant to pyrazinamide.

## Multi-drug resistance (MDR-TB)

MDR-TB is TB resistant to at least isoniazid and rifampicin (and possibly other drugs). MDR-TB should only be treated by clinicians experienced in managing TB. All cases of MDR-TB must be referred to TEAG for review.

# Common drug side effects

Drug	Adverse effects	Comments
Isoniazid	<ul style="list-style-type: none"> <li>• Raised transaminases (10 to 20%)</li> <li>• Hepatitis (0.6% monotherapy, 2.6% H+R)</li> <li>• CNS effects (fatigue, drowsiness, headache, depression/neuropsychiatric)</li> <li>• Acne (especially in SE Asian subjects)</li> <li>• Nausea, vomiting, diarrhoea.</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of hepatotoxicity increases with age*, heavy alcohol consumption, liver disease.</li> <li>• Rarely neuropathy may affect the optic nerve.</li> </ul>
Rifampicin	<ul style="list-style-type: none"> <li>• Red-orange discolouration of urine and body fluids</li> <li>• Nausea, vomiting, diarrhoea</li> <li>• Thrombocytopenia</li> <li>• Flu like syndrome.</li> </ul>	<ul style="list-style-type: none"> <li>• Flu like syndrome (myalgia, arthralgia, fever malaise, mild haemolysis) more likely with intermittent therapy.</li> <li>• Interrupted therapy may be associated with shock, acute renal failure, haemolytic anaemia and thrombocytopenic purpura – these features are an absolute contraindication to re-challenge.</li> <li>• Liver enzymosis may be cholestatic or transaminitis.</li> </ul>
Pyrazinamide	<ul style="list-style-type: none"> <li>• Arthralgia</li> <li>• Gout</li> <li>• Nausea, vomiting, diarrhoea</li> <li>• Hepatitis</li> <li>• Facial flushing</li> <li>• Rash</li> <li>• Photosensitivity</li> <li>• Difficulty with diabetic control.</li> </ul>	<ul style="list-style-type: none"> <li>• Elderly are more prone to GI side-effects and to hepatitis.</li> <li>• Avoid pyrazinamide if pre-existing history of clinical gout.</li> </ul>

Ethambutol	<ul style="list-style-type: none"> <li>• Rash</li> <li>• Nausea</li> <li>• Optic neuritis (retrobulbar)</li> <li>• Increased serum urate / gout</li> <li>• Hypersensitivity reactions are rare.</li> </ul>	<ul style="list-style-type: none"> <li>• Visual disturbance risk is increased with longer duration and higher dose.<sup>#</sup> Usually occurs after months of therapy but rarely within days. Typically, this is a central (axial neuritis) and manifest by blurred vision, decreased acuity, central scotomas, loss of ability to detect green and sometimes red colour. More rarely optic neuritis affects peripheral nerve fibres: visual field constriction but acuity and colour vision intact.</li> <li>• Visual acuity, colour vision and fields should be checked monthly, an example of a colour blindness test can be found at <a href="http://www.color-blindness.com/color-blindness-tests/">http://www.color-blindness.com/color-blindness-tests/</a></li> <li>• Risk of ocular toxicity is increased in renal impairment.</li> <li>• Patients should undergo an ophthalmology review if their ethambutol treatment extends for 2 months or longer. Patients need to be educated at the commencement of treatment about visual symptoms.</li> </ul>
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\* In isoniazid preventive therapy (IPT) recipients ALT >5 x normal found in 0.45% age <35, 0.85% age 35 to 49 and 2% age 50 and over.<sup>8</sup>

# TB patients taking ethambutol for greater than 2 months: risk of optic neuritis [15mg/kg/day – <1%], [25mg/kg/day – 5-6%] [>35mg/kg/day – 18%].<sup>9</sup>

## Which agent is most likely to cause a given symptom or adverse effect?

	Most likely <span style="font-size: 2em;">→</span> Least likely			
Hepatitis – ALT/AST predominant	Isoniazid	Pyrazinamide	Rifampicin	Ethambutol (very rare)
Hepatitis – cholestatic	Rifampicin			
Upper GIT symptoms	Rifampicin	Pyrazinamide	Isoniazid	Ethambutol
Arthralgia	Pyrazinamide	Rifampicin (flu like symptoms)	Isoniazid (drug induced lupus)	Ethambutol
Hypersensitivity (fever plus rash plus other)	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol

## Common drug interactions

Drug	Drug interactions	Comments
Isoniazid	Phenytoin, other anticonvulsants	Histamine syndrome can result with fish ingestion or food rich in monoamines (avoid cheese, red wine if INH causes flushing)
Rifampicin	Extensive drug interactions via cytochrome P450 hepatic pathway including oral and depot contraceptives, warfarin, protease inhibitors	Alternate contraception must be counselled where applicable
Ethambutol	Nil significant	
Pyrazinamide	Increases half-life of probenecid	

## HIV Testing

Co-infection with HIV greatly influences the prognosis of tuberculosis and has a significant bearing on treatment and monitoring. All TB patients should be tested for HIV infection.

## Baseline testing, and monitoring on treatment

Baseline laboratory testing should include FBC, urea and electrolytes, urate, liver function test (LFT) and CRP in addition to HIV. If LFTs are abnormal investigations should include hepatitis B and C serology. LFTs should be checked again within 4 weeks, with ongoing monitoring if abnormal at baseline or 4 weeks, patient complains of nausea or other symptoms, age over 50 or underlying liver disease, heavy alcohol intake or coadministration of hepatotoxic drugs. Repeat testing of CRP may be useful in monitoring progress of extra-pulmonary disease or where satisfactory progress is in doubt.

For pulmonary tuberculosis, sputum should be re-examined after 2 months of therapy to document smear and culture conversion. Failure to achieve such outcomes may be an indication of drug resistance or identify patients (even with drug susceptible disease) who would benefit from a longer duration of therapy.

Sputum should also be collected, if possible, in the sixth month of short course therapy to document microbiological cure.

In the management of PTB, a CXR should be performed after 2 months and at the end of therapy. Additional imaging may be necessary if overall clinical or laboratory progress is not satisfactory.

## Follow up after treatment ceased

If the patient's treatment course was uncomplicated, with good compliance and included isoniazid and rifampicin for the whole treatment course, then appropriate follow-up is 6 to 12 months post treatment with repeat imaging. However, if the treatment course was complicated by either drug interruptions, non-compliance, drug resistance other than rifampicin resistance, delayed culture conversion or there are any other clinical concerns for increased risk of relapse, then patients should have a follow up at 6, 12, and 24 months. These recommendations are considered a minimum requirement and additional follow up may be indicated on a case by case basis. For pulmonary TB cases, a follow up CXR should be performed at these visits. Rifampicin resistant TB (including MDR-TB) or where rifampicin has not been used throughout the treatment course should be followed up more rigorously: 6, 12, 18, 24 and 36 months. A recrudescence of symptoms would prompt appropriate investigations. The appropriate TB Control Unit should be informed of follow up findings.

# Use of intermittent treatment regimens

Queensland Department of Health endorses the use of thrice-weekly treatment only in exceptional circumstances and only in the continuation phase. All thrice-weekly treatment must use directly observed therapy (DOT). Twice weekly regimens using the standard drugs, and weekly regimens using rifapentine in place of rifampicin, have been studied but are associated with higher failure rates, and not recommended. Intermittent therapy is not recommended in HIV infected tuberculosis patients.

## Extrapulmonary Tuberculosis (EPTB)

### Lymph node TB

TB lymphadenitis is the most common form of EPTB and as contiguous with the pulmonary lymphatic system, is not considered to be disseminated TB when occurring together with pulmonary TB. Standard short course therapy (2HRZ[E]/4HR) is sufficient in most cases where TB is known to be susceptible to first line drugs. FNA diagnosis is less associated with complication of healing than open excision.

### Bone and joint TB

Standard short course therapy (2HRZ[E]/4HR) is sufficient in most cases where TB is known to be susceptible to first line drugs. The continuation phase is sometimes extended up to 12 months, but this regimen is not supported by published evidence unless infection is also disseminated or there is concomitant CNS involvement.

### Pericardial TB

Duration of therapy for DS-TB of the pericardium is the standard short course regimen unless there is clinical evidence of disseminated disease. A recent meta-analysis concluded that there is no mortality benefit from adjunctive corticosteroids for pericardial TB but there may be a protective effect against constrictive pericarditis in some patients. American Thoracic Society, Centers for Disease Control and Prevention and Infectious Diseases Society of America guidelines suggest (in the absence of clear evidence) that subjects with large pericardial effusions, early signs of constriction or those with high levels of inflammatory cells or markers in pericardial fluid may benefit.

## TB of the central nervous system

Standard treatment is **extended to 12 months** (2HRZ[E]/10HR). The optimum dose of rifampicin has not been determined and is a subject under study in a number of settings, but higher doses are generally favoured. Expert opinion should be sought.

Adjunctive corticosteroids are usually recommended to prevent clinically dangerous paradoxical reactions.

## Disseminated or miliary TB

Standard treatment is **extended to 12 months** (2HRZ[E]/10HR).

For children, if central nervous system (CNS) disease is excluded, give standard 6 months treatment (2HRZ[E]/4HR). If CNS TB suspected or confirmed, extend to 12 months (2HRZ[E]/10HR).

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# Document approval details

## Document custodian

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## Approval group

Tuberculosis Expert Advisory Group

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## Version control

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1.0	June 2006	Rescinded	26 June 2006	
2.0	Sept 2014	Sept 2017	15 Sept 2014	
2.1	July 2015	Sept 2017	17 July 2015	Section on disseminated or miliary TB update to include: For children, if central nervous system (CNS) disease is excluded, give standard six months treatment (2ERZ[E], 4 HR). If CNS TB suspected or confirmed, extend to twelve months (2HRZ[E]/10HR).
3.0	March 2021	March 2024		Update on pyrazinamide dose, use of pyridoxine, rifampicin resistance, isoniazid resistance