

Guideline

Treatment of tuberculosis in adults and children

Version 2.1 – July 2015

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What this guideline covers:

- treatment regimens for drug susceptible and mono-resistant tuberculosis (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:

- TB in pregnancy
- TB HIV co-infection
- TB and chronic kidney disease
- Management of latent tuberculosis.

KEY POINTS

- Standard tuberculosis (TB) treatment regimens are six or nine months of combination therapy.
- Active use of both rifampicin and pyrazinamide are key pre-requisites to enable a six-month regimen.
- Never add a single drug to a failing regimen.
- Dosing is weight based (mg/kg).
- Pyridoxine (vitamin B6) should be co-administered with isoniazid in all adults.
- Different regimens are recommended for drug resistance or intolerance. Individualised treatment is required for multi-drug resistant TB.
- Daily or thrice-weekly treatment is recommended; twice-weekly regimens are *not* recommended.
- Patients who have previously received drug therapy for tuberculosis 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 can be considered for pleural/pericardial effusions, severe miliary disease, endobronchial disease and abdominal TB.
- Rifampicin and to a lesser extent, isoniazid, may both have significant drug interactions which should be carefully considered.

Standard regimens for pulmonary tuberculosis

The standard short course treatment of 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 (Fox, 1999).

Six-month

The standard treatment regimen is six months of isoniazid and rifampicin, supplemented in the first two months by pyrazinamide, and by ethambutol until the isolate is confirmed susceptible to the three other drugs (2[E]HRZ/4HR) (Centers for Disease Control and Prevention, American Thoracic Society and Infectious Diseases Society of America., 2003). 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.

Nine-month

The standard treatment regimen is nine months of isoniazid and rifampicin, supplemented with ethambutol until the isolate is confirmed susceptible to those two drugs (9[E]HR) (Centers for Disease Control and Prevention, American Thoracic Society and Infectious Diseases Society of America., 2003).

Additional considerations for children (age 0-14 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 (Taketomo, 2013).

b) Ethambutol

Previous local and international guidelines have recommended against using ethambutol in young children unless resistance to isoniazid and/or rifampicin is known or suspected. This is because it is not possible to screen with Snellen and Ishihara tests in young children. Initial treatment for young children with uncomplicated disease from areas with a low prevalence of isoniazid resistance can be with three drugs (HRZ). However, recent WHO guidelines recommend the addition of ethambutol 20mg/kg to this regimen in children who have HIV, non-pulmonary TB or extensive or cavitary lung disease or who are from areas with a high prevalence of isoniazid resistance (World Health Organisation, 2010). Optic neuritis is unlikely to develop, provided that the recommended dose and duration are not exceeded. The decision whether to cease ethambutol in the intensive phase will depend on demonstration of susceptibility

to isoniazid and rifampicin (if culture positive), HIV status and, if culture negative, an assessment as to the epidemiological likelihood of drug resistance.

c) Pyridoxine

Pyridoxine is not routinely recommended for children taking isoniazid but should be considered in exclusively breast feeding infants and children with HIV infection or nutritional deficiencies.

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 available in Australia but may be used for patients who have commenced therapy in overseas countries.

Drug Name	Adult Dosages		Dosages in children	Parenteral Product Availability
	Daily	Thrice-Weekly	Daily	
Isoniazid (H)	5 mg/kg to 300 mg	15 mg/kg to 900 mg	10 mg/kg (range 10–15 mg/kg) to maximum 300 mg	IV Ampoule 50mg in 2mL <i>(via Special Access Scheme)</i>
Rifampicin (R)	10 mg/kg to maximum 600 mg (in practice 450 mg if <50 kg, 600 mg if ≥50 kg)	600 mg	15 mg/kg (range 10–20 mg/kg) to maximum 600 mg	IV Vial 600mg
Ethambutol (E)	15 mg/kg	30 mg/kg	20 mg/kg (range 15–25 mg/kg)	None Available
Pyrazinamide (Z)	30–40 mg/kg to max 2 g (in practice 1.5 g if <50 kg, 2 g if ≥50 kg)	2 g if <50 kg, 2.5g if ≥50 kg	35 mg/kg (range 30–40 mg/kg) to maximum 2 g	None Available
Pyridoxine (B6)	25mg	50mg	Not routine; Not routine; 1-2mg/kg; Typically 5-10mg in neonates	IV Ampoule 100mg in 1mL <i>(via Special Access Scheme)</i>

Accessing anti-tuberculosis drugs on the Special Access Scheme

Parenteral Isoniazid and pyridoxine are not registered medicines in Australia but are accessible under the Special Access Scheme (SAS) provision of the Australian Therapeutic Goods Act. 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. Oral pyrazinamide also requires SAS approval.

SAS Application Forms can be downloaded at:

<http://www.tga.gov.au/hp/access-sas.htm#forms>

Individual Patient Request forms can be downloaded at:

http://www.health.qld.gov.au/ghcss/mapsu/documents/lam/ipa_request.pdf

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) [tel.(07) 3646 0034].

a) Rapid detection of resistance

The Gene Xpert instrument, using the Xpert MTB/RIF assay can be used to detect *M. tuberculosis* DNA from respiratory samples using real time 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 detection. Some extrapulmonary specimens may also be tested with the Xpert assay – such testing 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 10-14 days for a result. Slow growing strains may need repeat testing before a reportable result is obtained.

c) Rapid detection of resistance from culture isolates

This may be performed using a variety of molecular methods and should be discussed with the QMRL on a case by case basis.

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

Based on Hong Kong studies where 2EHRZ/4HR provided good results for isoniazid resistant TB, a six-month daily regimen consisting of all first-line drugs (6EHRZ) is acceptable, subject to observing an appropriate clinical, radiological and bacteriological response, particular early bacteriological clearing of infection.

An alternative regimen is at least 12 months of ethambutol and rifampicin, usually supplemented in the first two months by pyrazinamide (2ERZ/10ER). There is currently insufficient evidence to support a shorter regimen including these drugs with a fluoroquinolone. Some reputable authorities e.g. Curry Centre, support the use of a fluoroquinolone in this setting for extensive disease but this guideline does not support this in most cases. Discussion with a TB clinical expert is recommended for any case of TB where a fluoroquinolone is proposed to be used.

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 and should be discussed with a clinician from the Metro South Clinical TB Service or a Regional TB Control Unit. These strains should be considered to be multi-drug resistant.

Rifampicin monoresistance

An appropriate regimen is at least 18 months of ethambutol and isoniazid, usually supplemented in the first two months by pyrazinamide (2EHZ/16EH).

Alternatively, the following regimens can also be considered:

- 2EHMZ, 10-16EHM: This regimen is 12 – 18 months of isoniazid, ethambutol and moxifloxacin with pyrazinamide for the first two months. 12 months may be acceptable with the use of a fluoroquinolone provided an appropriate bacteriological and clinical response is demonstrated.

- 2EHMZAK, 10 EHM: Addition of amikacin (or other injectable aminoglycoside) allows the alternative regimen to be given for the shorter duration of 12 months. The same regimen without moxifloxacin is also acceptable. In general the use of an injectable aminoglycoside is recommended for rifampicin monoresistance when disease is extensive.
- 9HZAK This regimen is also acceptable but the prolonged use of amikacin (or other aminoglycoside) carries significant risk of toxicity and would only be considered when an active fluoroquinolone agent was not able to be used due to allergy or other contraindication e.g. prolonged QT interval.
- Cases with Rifampicin monoresistance should be discussed with a clinician from the Metro South Clinical TB Service or a Regional TB Control Unit, particularly if alternative regimens are to be used.

Ethambutol monoresistance

For isolates resistant to ethambutol but susceptible to isoniazid, rifampicin and pyrazinamide, a standard 2HRZ/4HR regimen is appropriate. Ethambutol monoresistance is uncommon. Additional information should be sought from the Queensland Mycobacterium Reference Laboratory as supplementary information may be available (e.g. mutational analysis).

Pyrazinamide monoresistance

For isolates resistant to pyrazinamide, but susceptible to isoniazid and rifampicin (such as *M. bovis*), a 9HR regimen should be used.

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.

Treatment must be individualised based on drug susceptibility results, but is usually as many first-line drugs as possible (ethambutol and/or pyrazinamide), an injectable agent (usually amikacin, a fluoroquinolone, moxifloxacin), and other second-line drugs as appropriate. A regimen should include a minimum of three (preferably five) drugs to which the organism is known to be susceptible. Despite laboratory resistance, isoniazid may be kept in the treating regimen (Curry International Tuberculosis Center, 2011; National Institute for Health and Care Excellence, 2011) and is recommended in most cases where isoniazid resistance is documented to be at a low level only.

Recommendations on pyrazinamide dosage

Queensland Health recommends 30–40 mg/kg of pyrazinamide to a maximum of 2g per day. This dose is higher than recommended by other authorities. This is because the original randomised controlled trials conducted by the BMRC used dosages of 1.5g daily for participants less than 50kg, and 2g for those 50kg and over.

Common drug side effects


Drug	Adverse effects	Comments
Isoniazid	<ul style="list-style-type: none"> • Raised transaminases (10-20%) • Hepatitis (0.6% monotherapy, 2.6% H+R) • Peripheral neuropathy • CNS effects (fatigue, drowsiness, headache, depression/neuropsychiatric_) • Acne (especially in SE Asian subjects) • Nausea, vomiting, diarrhoea. 	<ul style="list-style-type: none"> • Risk of hepatotoxicity increases with age*, heavy alcohol consumption, liver disease. • Rarely neuropathy may effect optic nerve.
Rifampicin	<ul style="list-style-type: none"> • Red-orange discolouration of urine and body fluids • Nausea, vomiting, diarrhoea • Thrombocytopenia • Flu like syndrome. 	<ul style="list-style-type: none"> • Flu like syndrome (myalgia, arthralgia, fever malaise, mild hemolysis) more likely with intermittent therapy. • Interrupted therapy may be associated with shock, acute renal failure, haemolytic anaemia and thrombocytopenic purpura – these features are an absolute contraindication to re-challenge. • Liver enzymosis may be cholestatic or transaminitis.
Pyrazinamide	<ul style="list-style-type: none"> • Arthralgia • Gout • Nausea, vomiting, diarrhoea • Hepatitis • Facial flushing • Rash • Photosensitivity • Difficulty with diabetic control. 	<ul style="list-style-type: none"> • Elderly are more prone to GI side-effects and to hepatitis. • Avoid pyrazinamide if pre-existing history of clinical gout.
Ethambutol	<ul style="list-style-type: none"> • Rash • Nausea • Optic neuritis (retrobulbar) • Increased serum urate / gout • Hypersensitivity reactions are rare. 	<ul style="list-style-type: none"> • Visual disturbance risk is increased with longer duration and higher dose[#]. Usually occurs after months of therapy but rarely within days. Typically 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. • Visual acuity, colour vision and fields should be checked monthly, an example of a colour blindness test can be found at http://www.color-blindness.com/color-blindness-tests/ • Risk of ocular toxicity is increased in renal impairment.

		<ul style="list-style-type: none"> Patients should undergo an ophthalmology review if their ethambutol treatment extends for two months or longer. Patients need to be educated at the commencement of treatment about visual symptoms.
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* In IPT recipients ALT >5 x normal found in 0.45% age <35, 0.85% age 35-49 and 2% age 50 and over (Fountain, 2005).

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%]

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

	Most likely cause 			Least likely cause
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 syn.)	Isoniazid (drug induced lupus)	Ethambutol
Hypersensitivity (fever plus rash plus other)	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol

Common drug interactions

Drug	Drug interaction	Comments
Isoniazid	Phenytoin, other anticonvulsants	Histamine syndrome can result with fish ingestion or food rich in monamines (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 probenacid	

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 screened for HIV.

Baseline testing, and monitoring on treatment

Baseline laboratory testing should include FBC, urea and electrolytes, Urate, 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 four weeks, with ongoing monitoring if abnormal at baseline or four weeks, patient complains of nausea or other symptoms, age over 60 or underlying liver disease, heavy alcohol intake or co-administration 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 two 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 two 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

All TB patients should be followed clinically for at least two years following cessation of planned therapy. Typically a schedule for follow up would be at 6, 12, and 24 months where the strain is drug susceptible and isoniazid and rifampicin have both been part of the regimen throughout. This is 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 6, 12 and 24 months. Drug resistant TB (or where H and R have not been used throughout) should be followed up more rigorously: 3, 6, 12, 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 daily or thrice-weekly treatment only. 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.

Ideally the intensive phase of treatment (first two months) is given daily (2HREZ 4H₃R₃). At a minimum, the first two weeks of treatment are recommended be given daily before initiating thrice-weekly treatment.

The only fully intermittent treatment regimen recommended includes all four drugs for the full six months (6E₃H₃R₃Z₃).

Intermittent therapy is not recommended in HIV infected tuberculosis patients.

Extrapulmonary Tuberculosis

Bone and joint TB

Standard short course therapy (2EHRZ, 4 HR) is sufficient in most cases where TB is known to be susceptible to first line drugs. The continuation phase is sometimes extended to 7 or 10 months but this regimen is not supported by published evidence unless infection is disseminated, treatment interruption or drug resistance is suspected or proven.

Central nervous system TB

Standard treatment is **extended to twelve months** (2EHRZ/10HR). Adjunctive corticosteroids are usually recommended to prevent clinically dangerous paradoxical reactions.

Disseminated or miliary TB

Standard treatment is **extended to twelve months** (2EHRZ/10HR).

For children, if central nervous system (CNS) disease is excluded, give standard six months treatment (2EHRZ, 4 HR). If CNS TB suspected or confirmed, extend to twelve months (2EHRZ/10HR).

Smear positive pulmonary TB with extensive cavitation on plain radiography of the chest

Standard treatment is **extended to nine months** (2EHRZ/7HR) unless there has been documented culture conversion at two months, because there is a higher risk of relapse with six months of treatment.

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Revision history

Version number	Date of issue	Date of next revision	Approval date	Comments
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: <i>For children, if central nervous system (CNS) disease is excluded, give standard six months treatment (2EHRZ, 4 HR). If CNS TB suspected or confirmed, extend to twelve months (2EHRZ/10HR).</i>

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