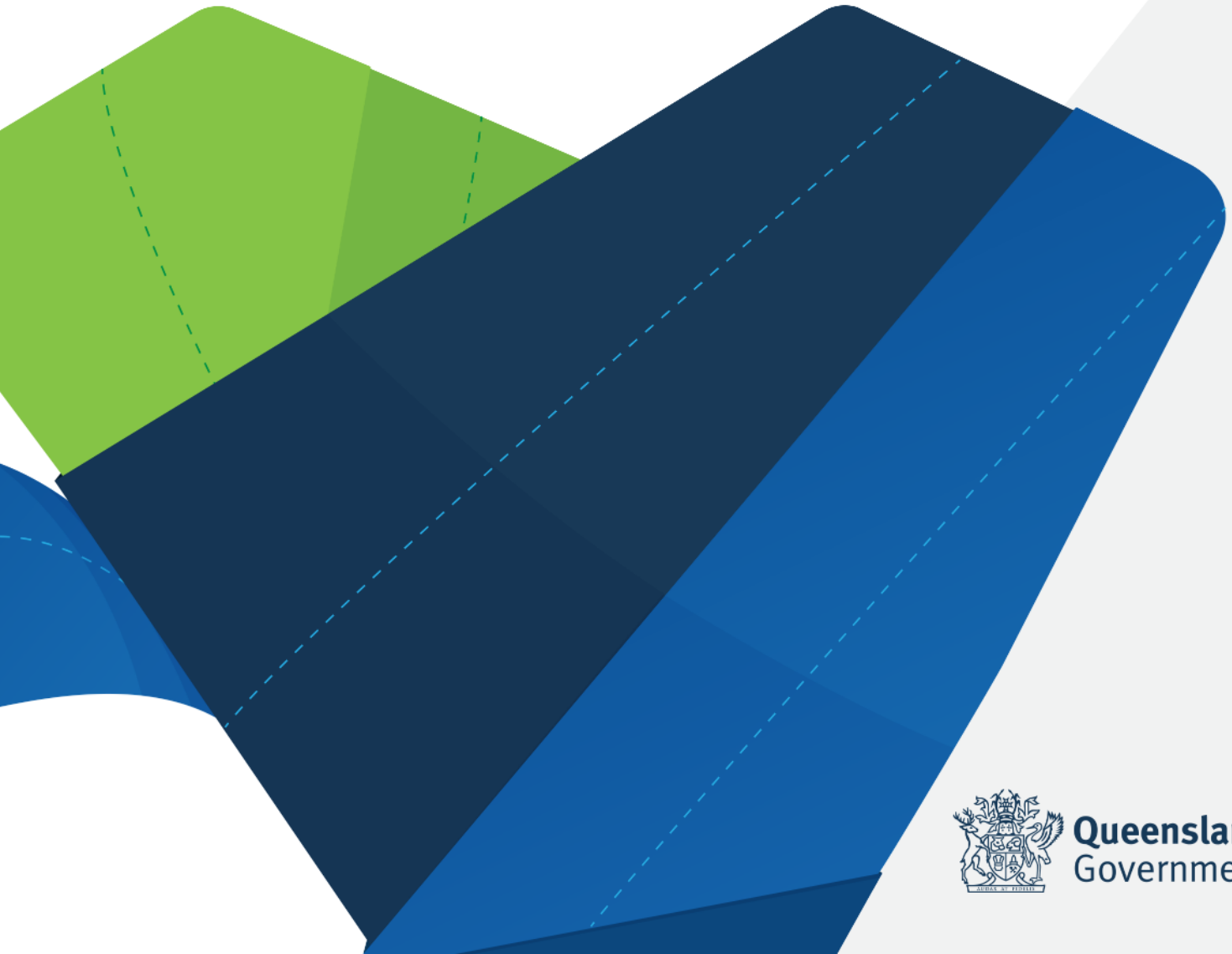
Treatment of tuberculosis in renal disease

Guideline, Version 4.0 July 2021



Queensland Government

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

Contents

Key critical points

- Renal failure is a risk factor for developing tuberculosis (TB).
- Diminished renal clearance of drugs used to treat TB puts the patient at increased risk of toxicity.
- Careful calculation of dose and frequency is required to maximise pharmacokinetic/pharmacodynamic (PkPD) targets and minimize the risk of toxicity coupled with clinical and laboratory monitoring for adverse effects.
- Of the most commonly used agents to treat TB (the first line agents of rifampicin, isoniazid, ethambutol and pyrazinamide) only ethambutol is predominantly eliminated renally and drug accumulation in the presence of renal disease can lead to irreversible ocular toxicity.
- Co-existent disease and administration of other medications may have important consequences for the risk of adverse effects and drug-drug

1. General considerations

Renal failure is a risk factor for developing tuberculosis (TB). Extra-pulmonary TB is more common in patients with chronic renal disease when compared to those with normal renal function. Peritoneal disease is especially frequent in patients on chronic ambulatory peritoneal dialysis (CAPD).

There are no randomised controlled trials that provide evidence to guide TB treatment in renal failure. Current treatment guidelines are based on reports from case series, the known pharmacological characteristics of the drugs used, and recommendations of experts in the area, including international agencies involved in TB control.

The following factors will influence treatment of a patient with chronic kidney disease and TB:

- drug pharmacokinetics, including the proportion of drug excreted by kidneys and its clearance by dialysis (both haemodialysis and peritoneal dialysis), which affects the serum levels of drugs and consequently, the toxicity
- the severity of anticipated toxicity with raised blood levels of drugs and the availability of alternate effective agents to cure the patient of TB
- co-existent illnesses and possible drug interactions which may affect therapy.

2. Recommendations

1. Standard 6 or 9 month regimens are generally used but ethambutol is withheld for:
    a. drug susceptible or bacteriologically-negative disease
    b. where susceptibilities are not yet available, but drug resistance is not suspected.
2. Prolongation of treatment is an individual decision based on the specific clinical circumstances and may occur in cases with immunosuppression or extensive disease. In general, standard dosages are used and, where indicated, a reduction in frequency of dosing is preferred to lower dosage so as not to compromise the regimen with sub-therapeutic drug levels.
3. Drug-resistant disease is treated with appropriate drugs as indicated by susceptibility testing, detailed according to guidelines.
4. Haemodialysis (HD) often leads to elimination of most TB drugs and medications are usually given after dialysis. There is a paucity of data regarding elimination of drugs in CAPD.
5. Careful monitoring of patients is essential as side effects (mainly neuropsychiatric problems, hepatitis and optic neuropathy) are noted to occur at higher levels in patients with renal failure and especially those on dialysis.
6. Therapeutic drug monitoring is advocated with aminoglycosides. Monitoring of some other TB drugs is available in Queensland but should only be considered in complex cases with advanced renal disease in consultation with a consultant physician experienced in treating TB or with a Regional Tuberculosis Control Centre.
7. The treatment of TB in patients with mild renal impairment, and with glomerular filtration rate (GFR) between 30 to 60mL/min, should be individualised using standard drugs in dose ranges in the lower range of usual recommendations for patients with normal renal function, with careful monitoring of side effects.
8. Ethambutol is used to prevent the emergence of rifampicin resistance with isoniazid resistant isolates. In Australia, isoniazid resistance occurs in 7 to 10 percent of isolates, predominantly in overseas born patients. In these situations, where ethambutol use is considered essential (until full drug sensitivity test results are available), refer to the table for dosing recommendations.
9. All but first line drugs must only be used after discussion with a consultant physician experienced in treating TB or with a Regional Tuberculosis Control Centre.

Guide to use of individual agents in renal failure

Antimycobacterial agent and normal dose	Dosage adjustment according to established degree of renal function					Comments and recommendations
	Estimated creatinine clearance (CrCL)			Intermittent haemodialyist (IHD)	Peritoneal dialysis (PD)	
	30–60 mL/min	10–29 mL/min	<10 mL/min			
Rifampicin 10mg/kg/day up to 600mg	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	• Can be used safely in renal disease. • Main route of clearance is hepatobiliary. • Exercise caution with concomitant drugs due to potential for significant drug-drug interactions, e.g. renal transplant patients on Tacrolimus or Cyclosporin.
Isoniazid 5mg/kg/day up to 300mg	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	• Can be used in renal disease. • Main route of clearance is hepatic. • Increased risk of neurotoxicity in patients with renal disease and supplemental pyridoxine (25mg/day) should be co-prescribed.

Pyrazinamide 30–40mg/kg/day 1.5g for <50kg 2g for >50kg	No dose adjustment required	30–40mg/kg q48h	30–40mg/kg 3 times weekly	30–40mg/kg 3 times weekly after dialysis sessions	No dose adjustment required	• Can be used safely in renal disease. • Main route of clearance is hepatic with active metabolites undergoing some renal clearance. • Monitor LFTs for hepatotoxicity. • Monitor uric acid levels.
Ethambutol 15mg/kg/day	No dose adjustment required	7.5–15mg/kg q48h	15mg/kg g q48h	15mg/kg 3 times weekly after dialysis sessions	15mg/kg q48h	• **AVOID** use unless essential in renal disease with CrCl <30mL/min. • Main route of clearance is renal. • Ocular toxicity is a significant concern in patients with renal disease and regular ophthalmological reviews are essential.
Moxifloxacin 400mg/day	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	• Can be used with caution in renal disease. • Main route of clearance is hepatobiliary with some renal clearance. • Higher risk of adverse effects in patients with renal disease including neurotoxicity and tendonopathies. Concomitant corticosteroid use further increases risk. • Co-administration with antacids, phosphate binders or supplements containing, calcium, iron, magnesium

						or aluminium must be avoided due to markedly reduced absorption of fluoroquinolones. Dose at bedtime, or 2 hours before or after other medications, to achieve separation.
Bedaquiline 400mg daily for 2 weeks; 200mg thrice weekly thereafter	No dose adjustment required	Use with caution and consider TDM	Use with caution and consider TDM	Use with caution and consider TDM	Use with caution and consider TDM	• Bedaquiline has a long half life (5.5 months) and is predominantly excreted in faeces with minimal renal excretion. • No dose adjustment is recommended for mild to moderate renal impairment but caution is recommended in more severe renal failure.
Clofazamine 100 mg daily	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	• Can be used safely in renal disease.
Linezolid 600mg/day	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	• Can be used with caution in renal disease. • Main route of clearance is hepatic with some renal clearance. • Increased risk of haematological toxicity and peripheral neuropathy in patients with renal disease. • TDM can be considered to optimize dosing and minimize risk of toxicity

Streptomycin 15mg/kg/day	15mg/kg individual doses with interval between doses adjusted to achieve undetectable plasma trough levels	Aminoglycosides & Capreomycin • Can be used with significant caution in renal disease. • Main route of clearance is renal. • Dose adjustment and therapeutic drug monitoring required due to toxicity risk and changes in drug clearance over time. • Dosing intervals should be extended to allow for clearance of drug between doses. Intervals should be extended to achieve an undetectable plasma trough level prior to each dose. • For haemodialysis patients, doses can be administered intravenously at the end of the dialysis session, but dosing may not be required for each session. • Monitoring should include regular U&Es to assess renal function along with clinical assessment, audiometry +/- dynamic visual acuity testing (where feasible) to assess oto/vestibulotoxicity.
Amikacin 15mg/kg/day	15mg/kg individual doses with interval between doses adjusted to achieve undetectable plasma trough levels	
Capreomycin 15mg/kg/day	15mg/kg individual doses with interval between doses adjusted to achieve undetectable plasma trough levels	

Prothionamide 15–20mg/kg/day in divided doses	No dose adjustment required	No dose adjustment required	250mg q12h	250mg q12h	250mg q12h	• Can be used in renal disease. • Main route of clearance is hepatic. • Monitor for neuropathy and hepatotoxicity.
Cycloserine 10–15mg/kg/day in divided doses	250mg q12h	250mg q24h	250mg q24h	250mg q24h given after dialysis	250mg q24h	• **AVOID** if possible in renal disease. • Main route of clearance is renal. • Increased risk of significant neurotoxicity in patients with renal disease. • Plasma level monitoring recommended but currently unavailable in Queensland.
Para-aminosalicylic Acid (PAS) 8-12g/day in divided doses	No dose adjustment required	4g q12h	4g q12h	4g q12h	4g q12h	• Use with significant caution in renal disease. • Main route of clearance is renal. • Increased risk of acidosis and gastrointestinal side effects.

* When daily doses are due on haemodialysis days, it is advisable to administer drugs after the dialysis session – afternoon or evening – to minimise the removal of the active drug by dialysis.

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