Treatment of tuberculosis in renal disease
Guideline, Version 4.0 July 2021
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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-existing 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

<table>
<thead>
<tr>
<th>Antimycobacterial agent and normal dose</th>
<th>Dosage adjustment according to established degree of renal function</th>
<th>Comments and recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated creatinine clearance (CrCL)</td>
<td>Intermittent haemodialysis (IHD)</td>
</tr>
<tr>
<td></td>
<td>30–60 mL/min</td>
<td>10–29 mL/min</td>
</tr>
<tr>
<td>Rifampicin 10mg/kg/day up to 600mg</td>
<td>No dose adjustment required</td>
<td>No dose adjustment required</td>
</tr>
</tbody>
</table>

- 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 |

- 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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Information</th>
<th>Dose Adjustment Required</th>
<th>Administration</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| Pyrazinamide | 30–40mg/kg/day     | No dose adjustment       | 30–40mg/kg     | 30–40mg/kg 3 times weekly after dialysis sessions | 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. |
|              | 1.5g for <50kg     |                          | 1.5g           |                                                                         |
|              | 2g for >50kg       |                          | 2g             |                                                                         |
|              |                    |                          | 30–40mg/kg     | 3 times weekly after dialysis sessions                               |
| Ethambutol   | 15mg/kg/day        | No dose adjustment       | 7.5–15mg/kg    | 15mg/kg 3 times weekly after dialysis sessions | 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. |
|              |                    |                          | q48h           | 15mg/kg g q48h                                                        |
| Moxifloxacin | 400mg/day          | No dose adjustment       | No dose        | 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 |
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose Adjustment</th>
<th>Use and TDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>No dose adjustment</td>
<td>Use with caution and consider TDM</td>
</tr>
<tr>
<td>400mg daily for 2 weeks; 200mg thrice weekly thereafter</td>
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<td></td>
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<tr>
<td>Clofazamine</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
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<tr>
<td>100 mg daily</td>
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<tr>
<td>Linezolid</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
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<tr>
<td>600mg/day</td>
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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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>15mg/kg individual doses with interval between doses adjusted to achieve undetectable plasma trough levels</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15mg/kg individual doses with interval between doses adjusted to achieve undetectable plasma trough levels</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15mg/kg individual doses with interval between doses adjusted to achieve undetectable plasma trough levels</td>
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</table>

**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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose</th>
<th>Dosage Schedule</th>
<th>Monitoring</th>
<th>Notes</th>
</tr>
</thead>
</table>
| 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.  
No dose adjustment required |  |
| 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.
References


Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. Thorax, 65 (6), 557-570.


Document approval details

Revision history

<table>
<thead>
<tr>
<th>Version number</th>
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<th>Date of next revision</th>
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Document custodian

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Chief Health Officer and Deputy Director-General Prevention Division Queensland Health

Approving group

Tuberculosis Expert Advisory Group