REVIEW ARTICLE

Treatment of Tuberculosis in Renal Insufficiency

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Received: 31 December 2025; *Accepted:* 04 May 2026

Abstract

Tuberculosis (TB) is a significant global health challenge, particularly in patients with renal insufficiency, where both the disease and its treatment are complicated by altered pharmacokinetics, immunosuppression, and increased risk of drug toxicity. Management of TB in patients with renal insufficiency is complex and necessitates an individualized, multidisciplinary approach. Careful dose adjustments, regimen selection, management of comorbid conditions, regular monitoring, and adherence to current guidelines can optimize outcomes while minimizing adverse effects. This article reviews current strategies and evidence-based approaches for the treatment of TB in patients with renal insufficiency, with a focus on drug selection, dose adjustment, and monitoring for toxicity and efficacy.

Journal of The Association of Physicians of India (2026): 10.59556/japi.74.1527

Introduction

Treatment of tuberculosis (TB) in renal insufficiency poses a difficult clinical problem because various anti-TB medications are cleared by the kidney.[1] On the one hand, it raises concerns about drug-induced toxicity because of impaired excretion by sick kidneys; on the other hand, it raises concerns about undertreating TB. Adequate peak serum concentrations in subsequent situations are typically low and of no therapeutic value. The therapeutic dose of antitubercular medications in hemodialysis patients with end-stage renal failure is another cause for concern because certain medications are cleared more readily than others.

Pathophysiology of Tuberculosis in Renal Insufficiency

The pathophysiology of TB in renal disease involves numerous interactions between the physiological changes of chronic kidney disease (CKD), immunological changes, and altered pharmacokinetics. Renal dysfunction decreases the host's ability to fight infections, increasing patients' risk of TB, and influences how the illness develops and manifests.[2] Altered immune function in CKD—cellular immunity plays a vital role in reducing *Mycobacterium tuberculosis* infection. T cells, macrophages, and cytokines like interferon-gamma (IFN-γ) play an important role in the immune response. In CKD, there is reduced T-cell activation and multiplication. Impaired macrophage function leads to decreased production of pro-inflammatory cytokines like IFN-γ and tumor necrosis factor-alpha (TNF-α), which are crucial for the development of granulomas. Chronic inflammation and uremia suppress innate and adaptive immune responses, leading to increased latent TB reactivation and new infections. *M. tuberculosis* often remains dormant within granulomas in immunocompetent individuals. Immune dysfunction due to CKD disrupts the granuloma structure, leading to reactivation of dormant bacilli and causing active infection. Systemic inflammation due to uremic toxin accumulation, oxidative stress, and a pro-inflammatory cytokine milieu are the hallmarks of CKD. Reduced pathogen clearance results from immune homeostasis being disrupted by chronic inflammation. Additionally, the uremic state lowers the expression of important receptors called toll-like receptors (TLRs), which makes it harder for the innate immune system to recognize and combat *M. tuberculosis*. Granulomas, which serve as a physical and immunological barrier to contain the germs, are the pathognomonic indication of TB. Granuloma formation and maintenance are impaired in CKD due to decreased production of TNF-α and IFN-γ. Reactivation or systemic spread of TB is caused by T-cell and macrophage dysfunction.

Chronic kidney disease leads to decreased renal excretion of TB medications, resulting in drug accumulation and potential toxicity.[3] The effectiveness of anti-TB medications is impacted by CKD-related edema and hypoalbuminemia, which change drug distribution and protein binding. Frequent hospital exposure, repeated use of vascular access points, and malnutrition in hemodialysis patients lead to increased risk of TB. Water-soluble drugs are removed during dialysis, leading to altered drug pharmacokinetics. Cautious timing of medicine delivery is important for optimal therapeutic drug levels. CKD is often associated with malnutrition, which causes immune dysfunction and increases the risk of TB. Repeated blood transfusions or treatment of anemia leads to iron overload, which promotes bacterial growth, as *M. tuberculosis* utilizes iron for replication. Hematogenous spread during primary TB or reactivation can lead to *M. tuberculosis* infection of the kidneys. The bacteria typically reside in the renal cortex, leading to granulomatous inflammation, tissue destruction, and cavitation. Renal TB presents with hematuria, sterile pyuria, and progressive renal damage, which may exacerbate preexisting CKD. Advanced renal TB can develop fibrosis, strictures, or calcification, decreasing renal function and complicating management. Together, TB and CKD produce a "vicious cycle" of disease progression. The systemic inflammatory state is made worse by active TB, which may hasten the development of CKD. Reduced drug clearance and toxicity risk make treatment less effective and raise the possibility of resistance or treatment failure. A thorough understanding of these pathophysiological processes is necessary to enhance patient outcomes and tailor TB treatment in renal insufficiency.

Dosing Recommendation for Adult Patients

Dosing of antitubercular drugs for renal insufficiency patients should be done according to creatinine clearance.[4] It is done with the help of the following formula, which is different for males and females, respectively. For males, it is calculated as ideal body weight (kg) × (140 – age)/72 × serum creatinine (mg/dL). For females, it is

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How to cite this article: Gupta N, Rani H, Kacker R, *et al.* Treatment of Tuberculosis in Renal Insufficiency. J Assoc Physicians India 2026;74(6):85–87.

calculated as 0.85 × ideal body weight (kg) × (140 – age)/72 × serum creatinine (mg/dL).

The British Thoracic Society advocates dose reduction for drugs that are excreted by renal route, while the American Thoracic Society prefers increasing the dosing interval instead of decreasing the dose. Administration of drugs that are excreted by kidney should be changed by increasing the dosing interval if creatinine clearance falls below 30 mL/minute (Table 1). There is a paucity of data to guide the dosing recommendation if creatinine clearance is above 30 mL/minute, when standard doses should be prescribed. Rifampicin and isoniazid are eliminated by the liver, and they could be given in usual dose. Patients with slow hepatic acetylation of isoniazid could be given supplemental pyridoxine to prevent peripheral neuropathy. Alteration in dose of ethambutol, which is 80% excreted by kidney, should be made if creatinine clearance falls below 70 mL/minute, to lowest possible dose, but if it falls below 30 mL/minute, it should be given intermittently as three times a week in dose of 15–20 mg/kg body weight. Pyrazinamide is metabolized in liver, but its metabolites, pyrazinoic acid and 5-hydroxypyrazinoic acid, are excreted by kidney; thus, the drug should be given three times a week, in dose of 25–35 mg/kg body weight, to avoid toxicity if creatinine clearance falls below 30 mL/minute (Table 1). Apart from this, the risk of developing hyperuricemia with pyrazinamide is increased in cases of renal insufficiency. Since streptomycin is predominantly excreted by renal route and removed by hemodialysis to a significant extent (about 40%), it should be administered three times a week in dose of 12–15 mg/kg body weight (Table 1) in patients with renal insufficiency with creatinine clearance below 30 mL/minute, and those on hemodialysis. Since the pharmacokinetics of other aminoglycosides is similar to streptomycin, they need similar modification of dose. Renal clearance of fluoroquinolones varies from drug to drug. It is greater for levofloxacin than moxifloxacin. Dose adjustment for fluoroquinolones is recommended if creatinine clearance is <30 mL/minute (750–1000 mg three times a week). Ethionamide needs no or little alteration of administration as it is not excreted by kidney. The dose of cycloserine should be modified if creatinine clearance falls below 30 mL/minute or the patient is on hemodialysis. It should be changed to 500 mg thrice a week or 250 mg daily (Table 1); evidence for safety of 250 mg daily dose of cycloserine is not yet established with regard to neuropathy,

Table 1: Dosing recommendation for adult patients with renal insufficiency or undergoing hemodialysis

Drug	*Change in frequency*	*Dose and frequency in patients with creatinine clearance <30 mL/minute or those on hemodialysis*
Isoniazid	No change needed	300 mg daily
Rifampicin	No change needed	600 mg daily
Pyrazinamide	Yes	25–35 mg/kg per dose three times a week
Ethambutol	Yes	15–25 mg/kg per dose three times a week
Rifabutin	No	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity
Rifapentine	No	No adjustment necessary
Levofloxacin	Yes	750–1000 mg per dose three times a week
Moxifloxacin	No	No adjustment necessary
Gatifloxacin	No	400 mg three times a week
Ofloxacin	Yes	600–800 mg per dose three times per week
Cycloserine	Yes	250 mg daily or 500 mg/dose three times per week
Terizidone		Recommendations not available
Ethionamide	No change needed	1 gm daily
PAS	No change needed	4 g/dose, twice daily maximum dose
Streptomycin	Yes	12–15 mg/kg/dose twice or three times a week
Capreomycin	Yes	12–15 mg/kg/dose twice or three times a week
Kanamycin	Yes	12–15 mg/kg/dose twice or three times a week
Amikacin	Yes	12–15 mg/kg/dose twice or three times a week
Linezolid	No change needed	Usual dose is 600 mg twice daily but can be reduced to 600 mg once daily after 4–6 weeks
Clofazimine	No	No dose adjustment required
Amoxicillin and clavulanic acid	Yes	Dose used is 625 mg twice daily; 1000 mg should not be used
Bedaquiline	No	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment; use with caution)
Delamanid	No	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment; use with caution)
Imipenem/cilastatin	Yes	For creatinine clearance 20–40 mL/minute: dose 500 mg every 8 hours; for creatinine clearance <20 mL/minute: dose 500 mg every 12 hours
Meropenem	Yes	For creatinine clearance 20–40 mL/minute: dose 750 mg every 12 hours; for creatinine clearance <20 mL/minute: dose 500 mg every 12 hours
High-dose isoniazid		Recommendations not available
Pretomanid	No	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment; use with caution)

and 500 mg three times a week is preferred in this regard. Serum concentrations of drug should be monitored. PAS is not safe in renal disease and should only be given if no other alternatives are available, as it may aggravate metabolic acidosis. If it is to be given, it should be given at dose of 4 g/dose, twice daily. Since thioacetazone is excreted in urine, it should not be given to patients with renal disease. The pharmacokinetics of the parent drug, linezolid, are not altered in patients with any degree of renal insufficiency, but the metabolites of linezolid may accumulate in patients with renal insufficiency, with the amount of accumulation increasing with the severity of renal dysfunction. Therefore, no dose adjustment is recommended for patients with renal insufficiency. However, given the absence of information on the clinical significance of accumulation of the primary metabolites, use of linezolid in patients with renal insufficiency should be weighed against the potential risks of accumulation of these metabolites. Clofazimine is safe in patients having renal disease as excretion is mainly through biliary route. Imipenem is highly nephrotoxic, but the addition of cilastatin lessens its toxicity. No dosage adjustment is required in patients with mild to moderate renal impairment with bedaquiline (dosing not established in severe renal impairment; use with caution). No dosage adjustment is required in patients with mild to moderate renal impairment with delamanid. Dosing is not established in severe renal impairment; use with caution and only when the benefits outweigh the risks.

Hemodialysis eliminates the medication prior to its therapeutic impact, although much less medication is expected to be eliminated if the medication is given enough time prior to hemodialysis to allow for its distribution throughout the body.[5] Drug administration following hemodialysis will, on the one hand, prevent early drug removal and, on the other, enable directly observed treatment short course (DOTS). Premature removal of second-line drugs by hemodialysis may further aggravate the problem of drug resistance by exposing the tubercle bacillus to subtherapeutic drug concentration.

Hemodialysis eliminates pyrazinamide to a considerable degree while removing rifampicin, isoniazid, and ethambutol to negligible degrees. Therefore, in patients with end-stage renal disease receiving hemodialysis, a further dose of isoniazid, rifampicin, and ethambutol is not required. Similar to streptomycin, if medications like kanamycin, amikacin, and capreomycin are administered right before hemodialysis, approximately 40% of them are eliminated from the blood. Since hemodialysis does not remove ethionamide or fluoroquinolones, their dosage does not need to be changed in this case. If medication is used following hemodialysis, there are typically no major complications.

Ideally, it is important to monitor serum concentrations of drugs in persons with renal failure who are taking aminoglycosides, cycloserine, or ethambutol to provide effective therapeutic drug concentration and also to minimize dose-related toxicity.[6] Patients with renal failure may have other comorbid conditions, like diabetes mellitus and gastroparesis, which may further complicate the pharmacokinetics of drugs.[7] Presently, there are no data to guide administration of antitubercular drug use in patients undergoing peritoneal dialysis, and for this subset of patients, recommendations for hemodialysis are applicable. The safest regimen that is being advised in patients diagnosed as new cases of TB with renal insufficiency is rifampicin, isoniazid, and pyrazinamide for 2 months followed by rifampicin and isoniazid for the next four months.

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