Tuberculosis in Chronic Kidney Disease

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Despite global efforts to eliminate TB, it continues to be a major burden in both high- and low-income countries.¹ In 2017, globally, 6.4 million new cases of TB were reported to WHO and it is regarded as one of the top ten causes of death. Worldwide, more than one in three individuals is infected with TB. This disease affects all countries and age groups. Overall, the best estimates for 2017 were that 90% of cases were adults (aged ≥15 years), 64% were male, 9% were people living with HIV (72% of them in Africa) while two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). Only 6% of cases were in the WHO European Region and the WHO Region of the Americas, each of which had 3% of cases.² Thus, it remains as an important cause of morbidity and mortality in several countries including India.³ Killing two persons every three minutes, nearly 1000 every day, India bears a large burden of the world’s TB rates.⁴ It is a cause for concern as India stands first in terms of absolute number of cases. In India, the incidence of TB has reduced from 289/lakh/year in 2000 to 217/lakh/year in 2015, and the mortality related to TB has reduced from 56/lakh/year in 2000 to 36/lakh/year in 2015 per the TB India annual report 2017. Given the fact that the current rate of annual decline of TB cases globally being 1.5%, India is lagging behind in its national decline rate.³ With the majority of the TB related deaths being preventable and the accessibility of the treatment regimens, their number is disappointingly large.⁴

**Chronic Kidney Disease**

CKD refers to abnormal kidney function and/or structure. The NICE guidelines for “Chronic kidney disease in adults: assessment and management” defines CKD as abnormalities of kidney function or structure present for more than 3 months, with implications for health. This is inclusive of all individuals with renal damage markers and those with a glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m² on at least 2 occasions separated by a period of at least 90 days (with or without markers of kidney damage).⁵ Thus, CKD is a general term designated for heterogeneous disorders affecting kidney structure and function with variable clinical presentation, in part related to cause, severity and the rate of progression. The various stages of CKD form a continuum and are classified as follows⁶ (Table 1).

With high prevalence, morbidity and mortality rates, CKD is a crucial public health issue.⁷ A wide geographic variation in the cause of kidney disease has been observed. Hypertension and diabetes are the most common causes of CKD, especially in the elderly population in developed countries. It can be challenging to differentiate CKD due to hypertension and diabetes from CKD due to other disorders in populations with a high prevalence of diabetes and hypertension. United Nations Children’s Emergency Fund data show that 28% of children are <2.5 kg at birth; hypovitaminosis A and other nutritional issues during pregnancy may result in smaller kidney volume at birth and a lower eGFR. There is increased risk of congenital anomalies of the kidney and urinary tract and obstructive or reflux nephropathy due to consanguinity and genetic inbreeding.⁸ Many factors contribute to high prevalence of CKD in India such as poverty, poor sanitation, pollutants, water contamination, overcrowding, and known and unknown nephrotoxins (including heavy metals and plant toxins in indigenous remedies) may also result in glomerular and interstitial kidney diseases. There is considerable variation in etiological presentation of CKD throughout India. Parts of the states of Andhra Pradesh, Odisha, and Goa have high levels of CKD of unknown etiology (CKDu), which is a chronic interstitial nephropathy with insidious onset and slow progression. CKD may also result from Poly cystic kidney diseases, Renal vascular diseases, other known causes, like prolonged obstruction of the urinary tract, nephrolithiasis, vesicoureteral reflux, leading to recurrent kidney infections/ pyelonephritis, not to forget injudicious use of drugs like non-steroidal anti inflammatory drugs and aminoglycosides for various infections. Furthermore, due to the difficulties in access to care, over 50% of patients with advanced CKD are first diagnosed when the eGFR is <15 ml/min per 1.73 m². The prevalence of CKD in different regions varies from <1% to 13%, and lately, a prevalence of 17% was reported by the International Society of Nephrology’s Kidney Disease Data Center Study.⁹

**TB and CKD Association**

As compared to the general population, patients with chronic kidney disease (CKD), have a greater possibility of developing TB. Diagnosis of TB in dialysis patient can be complex and challenging due to the increased frequency of extra-pulmonary involvement, atypical manifestations and non-specific symptoms. The relationship between active TB and CKD was first reported in 1974, in a case series including dialysis patients.⁹ An increased risk (6.9- to 52.5-fold) of TB in patients with chronic renal failure and

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**Table 1: Grades of renal impairment in CKD**

<table>
<thead>
<tr>
<th>Grades of Renal Impairment in CKD</th>
<th>Stage 1 CKD</th>
<th>Stage 2 CKD</th>
<th>Stage 3 CKD</th>
<th>Stage 4 CKD</th>
<th>Stage 5 CKD</th>
</tr>
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<tbody>
<tr>
<td>Normal creatinine clearance and function but urinary tract abnormality, e.g., polycystic kidney, structural abnormality</td>
<td>Creatinine clearance 60–90 ml/min</td>
<td>Creatinine clearance 30–60 ml/min</td>
<td>Creatinine clearance 15–30 ml/min</td>
<td>Creatinine clearance &lt; 15 ml/min with or without dialysis</td>
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on dialysis as compared to the general population is observed as host resistance to infection is primarily mediated by cellular immunity which is deficient in chronic renal failure patients. Also, deterioration of immune status of the patient is one of the leading causes of reactivation of latent TB. The reported prevalence of TB in patients under maintenance dialysis is 10.5% in India. Additionally, comorbidities such as diabetes or other autoimmune diseases further impair immunity, rendering CKD patients susceptible hosts to such infections. Socioeconomic and demographic factors further increase the possibility of developing TB. Furthermore, TB patients have a significantly higher risk of developing CKD than the general population. The use of immunosuppressive medications in kidney transplant recipients explains much of the increased risk of active TB in this category of patients. Renal insufficiency can be caused by longstanding TB infection itself or previous use of aminoglycosides.

As per the National Institute for Health and Care Excellence guidelines, the relative risk for developing active TB is 10% to 25% in patients at any stage of CKD. It has been also reported that patients on continuous ambulatory peritoneal dialysis (PD) are at high risk of peritoneal TB. The symptomatology in renal patients is often insidious and atypical, simulating uremic symptoms resulting in delayed diagnosis. Uraemia and post-renal transplant states are acquired immunodeficiency states that increase the risk of developing TB. It is crucial to note that cough and hemoptysis, classic symptoms of TB in the general population, are less frequently reported in dialysis patients. It can be complicated and challenging because of the high frequency of extra-pulmonary involvement. The treating physician or nephrologist should be vigilant regarding the varied and unusual clinical TB presentation in CKD patients. It is important to therefore include TB in the differential diagnosis of any patient presenting with nonspecific symptoms such as anorexia, fever and weight loss. Despite the fact that the uncomplicated pulmonary TB management is well established in patients with intact renal function, evidence for management of this disease in patients with CKD, on dialysis or following renal transplantation, is meagre and often inconsistent.

Pharmacological and Therapeutic Considerations

The basic principles of antitubercular chemotherapy remain the same; however, in presence of chronic renal failure either the drugs or the regimes have to be adjusted. Either the dosage of the drug is reduced as per creatinine clearance or the dose interval is increased.

The pharmacokinetics of anti-TB drugs are changed as some are excreted by the kidneys and/or removed via hemodialysis thereby mandating dose adjustment in patients with renal insufficiency or end stage renal disease (ESRD). There is lowered peak serum drug concentrations and compromised treatment efficacy when the dose is decreased. The interval between drug doses in patients with a creatinine clearance of 30 mL/min or less is suggested. In these individuals, standard doses may be used, but measurement of serum concentrations 2 and 6 hours post timed administration could be deployed to assist with optimizing drug dosages.

The commonly administered antitubercular drugs in patients of chronic renal failure (CRF), Maintenance Haemodialysis (MHD) and renal transplantation (RT) are isoniazid (INH), rifampicin (RIF), ethambutol (EMB), pyrazinamide (PZA), aminoglycosides and fluoroquinolones. Rif and INH are metabolized by the biliary route, and conventional dosing could be administered in renal insufficiency cases. These drugs may be thus considered safe in normal dosages in chronic renal failure (CRF) patients. Rifampin has been shown to lead to acute interstitial nephritis in few cases and can result in deterioration of renal function. Therefore patients on this drug should be observed for this possible complication. Pyridoxine supplementation should be administered with isoniazid to prevent the occurrence of peripheral neuropathy.

Until a few years ago, the effect of chronic kidney disease (CKD) on Pyrazinamide (Z) kinetics was not fully studied and various authors
had recommended either to avoid Z in CKD or to use it in reduced dosage of 12–20 mg/kg/day or 40–60 mg/kg/thrice or twice a week. Now most of the guidelines, including the WHO recommendations, approve usual dosage of Z in CKD patients.

EMB is excreted predominantly by the kidneys and may accumulate in patients with renal insufficiency. Specialists suggest a longer interval between doses (ie, thrice weekly) for EMB. With hemodialysis, PZA and, probably, its metabolites are cleared to a significant degree, while INH and EMB are cleared to some degree, and RIF is not cleared by hemodialysis. On the basis of creatinine clearance rates, EMB should be used in decreased dosages of 5–10 mg per kg per day or 25 mg per kg, thrice or twice a week. Approximately 50% dose reduction is suggested in patients with creatinine clearance of less than 10 ml/min. Ocular toxicity of the drug has been found to be dose dependent and must be noted during chemotherapy. Dosages of quinolones should also be decreased in CRF patients. Aminoglycosides are infrequently used in the management of TB nowadays owing to its nephrotoxicity and other side effects. If the drug has to be used, its dose must be adjusted based on the degree of renal failure. It is recommended that 0.75 g to 0.5 g should be given twice or thrice weekly during first two months of therapy. It can be given in reduced dosages in hospitals where close monitoring of renal parameters is possible. The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America published guidelines for the management of drug-susceptible TB and recommended dose and frequency of anti-TB antimicrobials in patients with creatinine clearance <30 mL/min, or patients undergoing hemodialysis (Table 2).

It is crucial to remember that all anti-TB agents should be given post dialysis for the prevention of premature clearance of the drug and to ensure directly observed therapy.

Drug Interactions with Immunosuppressive Drugs

TB remains a complex opportunistic infection in the solid organ transplant recipients. Development of TB has been reported in over 50% of renal transplant population within the first year of transplant. Risk of TB in solid organ transplant recipients is about 20–74 times higher than the general population with a mortality rate of up to 30%. Given the elevated risk of graft rejection, solid organ transplant recipients need to be monitored closely for drug interactions with immunosuppressive regimens. Rifampicin is the most likely to interact with immunosuppressive regimens by induction of a number of liver enzymes. Doses of other drugs such as mycophenolate mofetil, tacrolimus, and cyclosporine may need adjustment and their levels should be monitored regularly. There is clinical evidence suggestive of its interacting with mycophenolate mofetil by induction of hepatic, renal and gastrointestinal uridine diphosphate glucuronosyltransferases and organic anion transporters. Per experts, the daily corticosteroid dose should be doubled in patients on rifampicin. Once rifampicin therapy has been discontinued, liver enzyme induction usually takes two weeks to return to normalcy.

Rifampicin is a potent inducer of cytochrome p450 enzymes and decreases serum levels of commonly used antihypertensive drugs – amlodipine, metoprolol, and prazosin. This interaction is of significant clinical importance in hypertensive CKD 5D patients initiated on rifampicin-based antitubercular treatment. They experience significant lowering of anti-HT drug levels and corresponding worsening of hypertension. Given the clinical impact of this findings and ease of applicability, it would be prudent to monitor patients closely for worsening of hypertension after initiation of rifampicin or use an alternative antitubercular drug in place of rifampicin or change the antihypertensive drugs as the case may be.

Other drug interactions that need to be noted are: INH may increase corticosteroid levels and its adverse effects, streptomycin with cyclosporine and sirolimus may cause additive nephrotoxicity, fluoroquinolones can further increase risk of tendon rupture with concomitant corticosteroids, and corticosteroids may decrease INH levels.

Study by Dr. Mahesh Kumar Lal and group from VMMC and Safdarjung Hospital, New Delhi in this issue of JAPI beautifully narrates that TB is more common in patients of CKD and patients of CKD need to be screened for TB more so due to their overlapping signs and symptoms. They have studied 160 patients of CKD for pulmonary and extra pulmonary tuberculosis. They have not included renal transplant recipient patients and also patients with co-existing HIV and patients on steroids or other Immuno suppressive therapies. They have found prevalence of 13.7% active TB in CKD patients with significant patients having extra pulmonary TB, also they observed more tuberculosis in patients of CRF on dialysis than those who were not on dialysis, meaning more advanced CKD more the chances of active tuberculosis.

Conclusion

Despite consistent evidence demonstrating a link between these two diseases, this association remains poorly understood. There is an urgent requirement for further research on the association between CKD and TB. A globally focused and coordinated response from the nephrology and TB communities is the need of the hour.

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