The link between chronic kidney disease (CKD) and tuberculosis (TB) has been known for more than 40 years, but the interaction between these 2 diseases is still poorly understood. Dialysis and renal transplant patients appear to be at a higher risk of TB, in part related to immunosuppression along with socioeconomic, demographic, and comorbid factors. Meanwhile, TB screening and diagnostic test performance is suboptimal in the CKD population, and there is limited evidence to guide protocols. Given the increasing prevalence of CKD in TB endemic areas, a merging of CKD and TB epidemics could have significant public health implications, especially in low- to middle-income countries such as India and China, that are experiencing rapid increases in CKD prevalence and account for more than one-third of global TB prevalence. For this review, unless otherwise specified, the term CKD broadly refers to patients with end-stage kidney disease (i.e., glomerular filtration rate <15 ml/min per 1.73 m²) and/or receiving maintenance dialysis (either hemodialysis or peritoneal dialysis) as well as those with earlier stages of nondialysis-requiring CKD.

With CKD emerging as an important public health issue in low- and middle-income countries, we believe that the relationship between TB and CKD deserves closer scrutiny. Numerous publications, particularly from high-income countries, have reported on TB in CKD populations. These publications tend to focus on the risk of TB, treatment outcomes, and screening test performance in dialysis and kidney transplant populations, whereas few have noted the epidemiologic impact of the CKD as a whole on global TB epidemiology. Based on what we understand about these conditions, we can reasonably expect that as CKD incidence and consequent dialysis and kidney transplant use increase in low- and middle-income countries with high TB prevalence, TB-CKD will become a more significant clinical and public health issue in coming years. In this mini review, we examine the epidemiologic relationship between these 2 conditions and review the current evidence and guidelines addressing TB screening and treatment in the kidney transplant, dialysis, and nondialysis-requiring CKD populations.

**Global CKD epidemiology**

The prevalence of CKD is estimated to be between 8% and 16% worldwide and appears to have increased in recent years. Between 1990 and 2010, CKD rose from 27th to 18th
on the list of causes of global deaths, second only to HIV in rank increase during this period. These estimates of prevalence and mortality, however, may not accurately reflect true global CKD burden as they rely on variable CKD definitions and limited epidemiologic information, particularly in low- and middle-income countries (Figure 1b). CKD appears to disproportionately affect impoverished and marginalized populations with limited access to health care. This may be due to the direct impact of poverty on CKD or indirectly to the increased health-care burden linked to poverty-associated comorbidities such as HIV, diabetes, and hypertension.

In its most severe form, CKD progresses to ESKD, which requires renal replacement therapy (RRT) in the form of dialysis or renal transplantation. The number of ESKD patients receiving RRT is estimated at >2.6 million worldwide, with >80% of ESKD patients living in high-income countries. A lack of registries in many low- and middle-income countries makes the accurate estimation of ESKD prevalence challenging. At present, the prevalence of treated ESKD patients appears to be highest in Taiwan, Japan, and the United States, with rates at 2902, 2365, and 1976 per million population, respectively. The global average of 430...
per million population suggests that access to treatment is limited in many countries and that many people with ESKD do not receive life-saving RRT.15

Over the next decade, the global ESKD prevalence is predicted to rise sharply. The fastest growth is expected in low- and middle-income countries with growing economies, such as India and China, where elderly populations are expanding, health-care expenditure is increasing, and disease burden is shifting toward noncommunicable conditions such as diabetes and hypertension.9,13 Liyanage et al.13 estimated that by 2030, 5.4 million people worldwide will be receiving RRT, with the largest increase in RRT prevalence projected in Asia, increasing from 1.0 million in 2010 to 2.2 million by 2030, followed by Africa and Latin America. In 2010, Zuo et al.16 estimated that the RRT population in China was increasing by 53% per year. It appears that the number of patients with ESKD vastly underestimates global CKD burden as prevalence of earlier, nondialysis-requiring CKD stages exceeds ESKD prevalence by as much as 50 times.17

Global TB epidemiology

TB continues to be a leading cause of infectious morbidity and mortality worldwide, with the disease developing in an estimated 9.0 million people 2013.18 Since 1990, TB mortality and prevalence have decreased by 45% and 41%, respectively, but much work still needs to be done to eliminate this largely preventable and curable disease.18 To accelerate decreases in TB incidence, the World Health Organization launched the Global EndTB strategy in 2015, which aims for fewer than 100 TB cases per million population by 2035.19 For low TB incidence regions (usually high-income countries), the World Health Organization has set lower targets, aiming for TB elimination at lower than 1 case per million population by 2035. Because trends in low TB incidence regions are primarily driven by migration dynamics, these ambitious targets will only be achieved if TB diagnosis, treatment, and prevention strategies are scaled up globally, and particular attention is given to those populations at highest risk of TB.

Pathophysiology of TB-CKD. Immune deficiency associated with CKD appears to be multifactorial in etiology.16 Advanced CKD is associated with oxidative stress and inflammation, 25-hydroxyvitamin D deficiency, and malnutrition, with evidence of functional abnormalities in a variety of immune cells including B and T cells, neutrophils, monocytes, and natural killer cells. Changes in immunity begin as early as stage 3 CKD (defined as a glomerular filtration rate <60 ml/min per 1.73 m²) and worsen in later stages as kidney function deteriorates and waste products accumulate.20 A state of impaired cell-mediated immunity persists in dialysis and leaves patients susceptible to infectious complications. Active TB is an infectious complication that may develop and results from progression of Mycobacterium tuberculosis infection after recent exposure or reactivation of latent TB infection (LTBI) from a distant exposure, often years before the disease develops (Figure 2). Transplant recipients are also at high risk of active TB, related in part to postransplantation immunosuppressive medications that specifically target T cell–mediated immunity, which is critical to maintaining latency in patients with M tuberculosis infection.6,21

TB risk in dialysis patients. Numerous hospital-based cohorts and regional registry studies have reported an increased TB risk in patients on hemodialysis and peritoneal dialysis.3 High-quality epidemiologic studies estimate that TB risk is increased 3- to 25-fold, whereas a recent meta-analysis estimated that dialysis populations have a pooled unadjusted rate ratio of 7.7 (95% confidence interval 5.9–10.0) for active TB compared with the general population. This increased risk appears to be related, in part, to the demographic characteristics of dialysis patients rather than the dialysis state itself; in the same meta-analysis, after adjusting for demographic variables such as country of birth and age, the pooled rate ratio for active TB risk decreased to 3.6 (95% confidence interval 1.8–7.3).3

Country of birth appears to be a particularly important TB risk factor in dialysis populations. In a recent national registry study from Australia, TB incidence was estimated at 18 per

Figure 2 | Hypothesized relationship between CKD stage and risk of the development of TB. (a) Impaired cell-mediated immunity in late-stage CKD leaves patient susceptible to infectious complications, such as active TB. (b) Pathophysiology of CKD-related immunodeficiency suggests early stage CKD patients may also be susceptible to TB. CKD, chronic kidney disease; TB, tuberculosis.
100,000 per year in dialysis patients born in low TB incidence countries and 698 per 100,000 per year in those born in the highest TB incidence countries. This is consistent with the notion that active TB results from reactivation of LTBI acquired before dialysis initiation rather than from recent exposure and infection. That said, hemodialysis patients with active TB do pose a substantial risk to other patients and health care workers in hemodialysis units, particularly given the frequency and proximity of shared air space. Without effective screening and active TB case detection, dialysis and renal units can serve as means of ongoing TB transmission.

**TB risk in kidney transplant recipients.** Transplant recipients also have an increased TB risk ranging from 3 to 24 times that of the general population. In a meta-analysis, the pooled unadjusted rate ratio for TB in renal transplant recipients was 11.4 (95% confidence interval 3.0–43.4) compared with the general population. Like dialysis patients, most cases of TB in transplant recipients appear to be from LTBI reactivation. However, cases of transmission from donor organs as well as nosocomial transmission in renal transplant programs have been reported.

**TB risk in nondialysis-requiring CKD.** The pathophysiology of CKD-related immunodeficiency would suggest that early-stage CKD could also be a risk factor for TB. To our knowledge, however, no study has examined TB risk in populations with nondialysis-requiring CKD. In a cohort examined by Fried et al., infectious disease death appeared to increase incrementally as the glomerular filtration rate decreased, with an estimated glomerular filtration rate <60.2 ml/min per 1.73 m² associated with the highest mortality. Unfortunately, this study did not specifically record TB-related mortality, and it would be difficult to apply these findings to TB risk given the unique relationship between TB and host immunity.

Understanding the relationship between CKD stage and TB risk would have a significant impact on our understanding of global TB epidemiology and would also inform LTBI screening and preventive treatment strategies in CKD. Investigating this relationship, however, would require rigorous epidemiologic analysis. The relationship between CKD and TB is confounded by many variables including diabetes, HIV, immunosuppressive drugs, lifestyle, and socioeconomic factors. Diabetes is of particular importance because it triples an individual’s risk of TB and is currently responsible for ~15% of global TB cases. Socioeconomic status is also an important confounder because both CKD and TB disproportionately affect impoverished individuals with limited access to health care resources.

**Clinical presentation of TB in dialysis and kidney transplant patients.** The clinical presentation of TB in dialysis and kidney transplant patients is often insidious and atypical. Patients frequently present with systemic symptoms, such as fever, anorexia, and weight loss. These symptoms may mimic uremia and can result in a delay of diagnosis. Patients may present with extrapulmonary disease in as many as 60% to 80% of cases, with presentation including disseminated disease. Those patients receiving peritoneal dialysis in whom TB peritonitis develops typically present with fever, abdominal pain, and cloudy dialysate. Laboratory findings in TB peritonitis are similarly nonspecific and TB peritonitis may be associated with either lymphocyte or polymorphonuclear neutrophil predominance on peritoneal dialysis fluid cytology testing. These factors, combined with the occasionally insidious onset of TB peritonitis, frequently result in a significant delay in diagnosis.

In particular, TB peritonitis should be considered in all cases of culture-negative peritonitis or culture-positive peritonitis that is refractory to appropriate antibiotic treatment, even in the absence of other clinical symptoms or signs suggestive of TB. Physicians should be mindful of the potential for unusual presentation and localization of TB in CKD patients and should consider TB in patients presenting with nonspecific systemic symptoms. The atypical clinical presentation, delays in diagnosis, and hence appropriate anti-TB therapy likely contribute to the high mortality rates seen in these populations, ranging from 17% to 75% in different treatment cohorts.

**Screening for TB in CKD patients**

TB screening in the ESKD population serves the following 2 purposes: screening can detect asymptomatic or minimally symptomatic active TB early in the disease course, thus limiting patient morbidity, mortality, and potential for TB spread; screening may also detect LTBI, enabling the initiation of LTBI preventive therapy for patients at the highest risk of the development of active disease while avoiding unnecessary complications of treatment in low-risk individuals. In ESKD patients, a thorough TB screening process should rely on a combination of history and physical examination, immune assays, and chest radiography. All aspects of this screening process are essential for accurate diagnoses of active TB and LTBI, particularly in this population in which serological testing is unreliable, chest radiography is frequently abnormal, and patients often report respiratory and constitutional symptoms that are nonspecific and could be compatible with active TB.

The backbone of LTBI screening is the immune assay, which includes the traditional tuberculin skin test (TST) and the newer interferon gamma release assays (IGRAs). The TST is an inexpensive test with a robust evidence base but is complicated by significantly higher rates of false-negative results in the ESKD population than in the general population. Another limitation of the TST is false-positive TST results in the context of previous bacillus Calmette-Guérin vaccination. More recently, IGRAs were developed to measure an antigen-specific immune response to *M tuberculosis* infection. Two commercial IGRAs, the TSPOT (Oxford Immunutec, Abingdon, United Kingdom) and the QuantiFERON Gold in Tube (Qiagen, Chadstone Centre, Victoria, Australia), show promise in TB diagnostics, with evidence of enhanced sensitivity and specificity in many populations with suspected LTBI. Compared with the TST, the major
disadvantages of IGRAs are the high per-test cost and limited longitudinal evidence to support their use. Because significant costs can stem from active TB treatment and contact tracing, the higher diagnostic sensitivity and specificity seen with IGRAs could potentially result in cost savings in the long term by reducing the future burden of active TB in some populations. However, comprehensive, cost-effective analyses of appropriate screening strategies are limited for CKD-TB populations.

Unfortunately, both the TST and commercial IGRAs have important limitations and poor predictive value for active TB in patients with advanced CKD. Several cross-sectional studies have evaluated the diagnostic accuracy of the TST and IGRAs by examining the association between test result positivity and clinical risk factors for LTBI. In these studies, IGRAs appeared to be associated more strongly with clinical risk factors for LTBI infection, but sensitivity was still sub-optimal. More recently, a large multicenter European study tested both the IGRA and the TST in dialysis patients and evaluated each test’s ability to predict active TB on follow-up. Despite a high proportion of patients with a positive TST and/or IGRA result, no cases of active TB were observed during short-term follow-up, meaning that both the TST and IGRAs do not appear to have high positive predictive value in this population.

Pharmacological issues in the comanagement of CKD and TB

Treatment of LTBI. Large-scale, randomized, controlled trials of chemoprophylaxis with isoniazid have shown to be effective in reducing the development of TB by 60% to 90% in immunocompetent individuals. However, the optimal LTBI treatment in those with advanced CKD (including ESKD) or after kidney transplantation is unclear, as such patients are presumably at higher risk of complications given their numerous comorbidities and advanced age. The findings of a recent review support the use of isoniazid chemoprophylaxis in the kidney transplant population. However, firm conclusions are difficult to draw due to a lack of robust evidence. In many renal units in high TB incidence regions, current practice is to give isoniazid chemoprophylaxis to all transplant recipients without assessment of risk; whether this practice has any advantages over screening and targeted treatment remains unclear and requires further investigation.

Many preventive treatment protocols are in use for the kidney transplant population; however, there is a lack of sufficient data on the efficacy for this group as well as for the broader ESKD population that includes dialysis patients, and more substantial evidence is needed. A related issue is that for potential live kidney donors with evidence of LTBI, delay of transplantation is appropriate until treatment is completed, but in endemic areas, it may be difficult to avoid the use of infected donors.

**Treatment of active TB.** In all CKD patients with unexplained systemic or system-specific symptoms such as fever, weight loss, and a chronic cough, active TB should be considered and excluded by the appropriate diagnostic investigation. If suspected, all efforts should be made to isolate an organism for susceptibility testing. In the general population, first-line therapy for fully susceptible TB includes isoniazid, rifampin, pyrazinamide, and ethambutol. The standard quadruple therapy regimen is recommended in patients with CKD or a kidney transplant, but the regimen poses a special problem for those with more advanced CKD.

### Table 1 | Tuberculosis screening guidance for chronic kidney disease populations

<table>
<thead>
<tr>
<th>Society</th>
<th>Year</th>
<th>CKD</th>
<th>Dialysis</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Thoracic Society</td>
<td>2000</td>
<td>—</td>
<td>TST for immune compromised. No specific recommendations for dialysis</td>
<td>TST for immune compromised. No specific recommendations for transplant candidates</td>
</tr>
<tr>
<td>American Transplant Society (donor)</td>
<td>2012</td>
<td>—</td>
<td>—</td>
<td>All living donors should be screened with a TST or IGRA</td>
</tr>
<tr>
<td>American Transplant Society (recipient)</td>
<td>2011</td>
<td>—</td>
<td>—</td>
<td>All transplant candidates should be screened with TSS or IGRA</td>
</tr>
<tr>
<td>British Thoracic Society</td>
<td>2010</td>
<td>CKD patients should receive a TB risk assessment and if appropriate an IGRA</td>
<td>All dialysis patients should receive a TB risk assessment and, if appropriate, an IGRA</td>
<td>All transplant candidates should be screened with an IGRA</td>
</tr>
<tr>
<td>Canadian Thoracic Society</td>
<td>2014</td>
<td>—</td>
<td>TST or IGRA recommended for immune compromised. No specific recommendations for dialysis</td>
<td>TST or IGRA recommended for immune compromised. No specific recommendations for transplant candidates</td>
</tr>
<tr>
<td>Canadian Transplant Society</td>
<td>2005</td>
<td>—</td>
<td>—</td>
<td>All transplant candidates should be screened with TST</td>
</tr>
<tr>
<td>European Centre for Disease Prevention and Control</td>
<td>2011</td>
<td>—</td>
<td>IGRA with concurrent TST for immune compromised. No specific recommendations for dialysis patients</td>
<td>IGRA with concurrent TST for immune compromised. No specific recommendations for transplant candidates</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence</td>
<td>2011</td>
<td>—</td>
<td>IGRA or IGRA and concurrent TST for immune compromised. No specific recommendations for dialysis</td>
<td>IGRA or IGRA and concurrent TST for immune compromised. No specific recommendations given for transplant candidates</td>
</tr>
<tr>
<td>World Health Organization</td>
<td>2015</td>
<td>—</td>
<td>Screen all dialysis patients with TST or IGRA</td>
<td>Screen all transplant candidates with TST or IGRA</td>
</tr>
</tbody>
</table>

CKD, chronic kidney disease; IGRA, interferon gamma release assay; TST, tuberculin skin test.
(including ESKD) or significant graft dysfunction as both ethambutol and pyrazinamide are cleared through renal excretion and require renal-adjusted dosing.29 Meanwhile, rifampin often interacts with antihypertensive, diabetes, and immunosuppressive medications.34 Dose adjustment of concomitant medications may be required, or rifampin can be replaced with rifabutin to minimize drug interactions. Regardless, rifamycin derivatives are an essential component of a TB treatment, and every effort should be made to include them in the drug regimen for this population with appropriate monitoring and management of side effects and drug-drug interactions.29

Of note, rare cases of drug-induced acute interstitial nephritis have been reported with TB therapy, mainly during retreatment with an intermittent rifampicin-containing regimen as opposed to primary treatment.35 Despite the therapeutic safety of this drug, clinicians must be aware of this renal complication, which, if detected early and treated appropriately, is usually reversible.

Current TB-CKD guidance
The rationale for a global initiative to address the issue of TB-CKD is clear; both diseases affect impoverished populations with significant rates of comorbid disease and high health care needs and people with TB who require dialysis or kidney transplantation have worse outcomes than those with each condition. Yet, the potential public health importance of this relationship seems to be largely overlooked. Only recently did international bodies recommend systematic testing of dialysis and transplant recipients.36 Meanwhile, due to limited available evidence of the timing of screening and preferred modality, screening recommendations from different health care societies are often ambiguous and conflict with one another.29,36–43 (Table 1). The British Thoracic guidelines currently offer the most specific and comprehensive guidance for CKD-TB patients, recommending that all CKD and dialysis patients receive a TB risk assessment, clinical examination, chest X-ray, and IGRA if risk is identified. These guidelines also recommend screening patients on the waiting list for renal transplantation. Even so, these guidelines acknowledge the paucity of evidence for guiding screening recommendations.

There is a need for clear and consistent guidance, appropriate for regional epidemiology, to facilitate suitable protocols for screening, diagnosis, and treatment of TB in CKD patients. Rigorously developed, evidence-based guidelines have been shown to reduce the variability of care, improve patient outcomes, and upgrade deficiencies in health care delivery in CKD patients.44 Without such guidelines, TB will continue to afflict CKD populations and will likely become an increasingly important driver of TB spread in vulnerable populations.

Future directions
We believe that there is an urgent need for research on the relationship between CKD and TB. Despite consistent evidence demonstrating a link between these 2 diseases, this relationship is still poorly understood. Moreover, both diseases are strongly associated with poverty and the comorbidities of poverty, so this syndemic is likely to afflict the most marginalized and vulnerable members of our communities. New research to guide policy is greatly needed, this includes robust studies of the association of both conditions, the effect of CKD stage on the performance of TB screening modalities, well-designed randomized, controlled trials examining preventive treatment regimens, and a cost-effectiveness analysis of TB screening in CKD populations. Without these advances in our understanding, strategies for prevention, detection, and treatment of TB-CKD cannot be refined.

The CKD epidemic will have a significant impact on regional and global TB epidemiology, particularly in low- and middle-income regions where CKD is increasing rapidly and TB remains endemic. We urge the nephrology and TB communities to initiate a globally focused and coordinated response.

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REFERENCES


