An update on the management of latent tuberculosis infection and active disease in patients with chronic kidney disease

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ABSTRACT

In 2010, the British Thoracic Society published guidelines on the management of tuberculosis (TB) infection and disease in patients with chronic kidney disease (CKD), in response to physicians’ concerns about the challenges encountered in treating this complex patient group. Later, in 2010, we summarized the main messages from these guidelines for readers of this journal. The purpose of this review is an update on the current management of latent and active Mycobacterium tuberculosis infection in patients with CKD. Patients with CKD have an increased risk of both infection and disease with Mycobacterium tuberculosis, and practice varies between renal units. Since 2010, the majority of published data have focused on screening for TB infection in immunosuppressed patients, including those with CKD and transplant recipients. While there is currently no perfect screening test, the evidence suggests that we should be using the available interferon-γ release assays, with or without the tuberculin skin test, to try and reduce the undoubted risk of active TB in these patients. While we are not aware of any new evidence to change the recommended treatment regimens, we have reiterated some of the important recommendations outlined in the original guidelines.

KEY WORDS
chronic kidney disease, latent infection, tuberculosis

Introduction

The risk of tuberculosis (TB) is increased in patients with chronic kidney disease (CKD) when compared with those with normal renal function.¹ This is due to multiple factors, including coexistent immunodeficiency secondary to impaired cell-mediated immunity, diabetes, human immunodeficiency virus infection, or immunosuppressive therapies, particularly after transplant surgery. Patients from ethnic minorities are also at higher risk of both renal impairment and latent TB infection (LTBI), following migration from or travel to countries with a high incidence of TB.² Together, this means that patients with CKD are at significant risk for both de novo infection and reactivation of LTBI. Diagnosis can be a challenge due to nonspecific symptoms and a relatively high incidence of extrapulmonary TB, particularly peritoneal disease in patients receiving renal replacement therapy with continuous ambulatory peritoneal dialysis (CAPD).³ The British Thoracic Society (BTS) guidelines on the management of TB infection and disease in patients with CKD were published in 2010,⁴ and we later summarized the main messages from those guidelines for readers of this journal.⁵ This review provides an update on the current management of latent and active Mycobacterium tuberculosis infection in patients with CKD.

Until recently, most reports on the incidence of TB in patients with CKD came from countries with a high baseline incidence of TB. The original National Institute for Health and Clinical Excellence (NICE) guidelines⁶ reported an incidence of 10 to 25 times the background rate for patients with CKD or on dialysis, and 37 times for renal transplant recipients, based on a small case series.⁷ Although this figure is absent from the latest guidelines (2016).⁸ In a recently published series of patients from London, covering the period of 1994 to 2010, the cumulative incidence of TB in patients with CKD was found to be 85 times the background rate in patients on hemodialysis and 35 times in transplant recipients. The median time to diagnosis was 12 months following the diagnosis of CKD,
and 25% of patients with positive culture results had organisms resistant to at least one of the first-line drugs. This means that the diagnosis of both active disease and LTBI is crucial in patients with CKD. For example, in our unit alone in the years 2015 and 2016, we reported 2 cases of active TB (presumed reactivation from undiagnosed LTBI) in transplant recipients born in Africa and Asia, and 1 case in an indigenous patient with no history of prior exposure. This illustrates the importance of the attempts to find reliable screening tools for diagnosing LTBI in these patients as well as vigilance for active TB disease.

Since the publication of the 2010 BTS guidelines, the majority of research has centered around the performance of the interferon-γ release assays (IGRAs) and the tuberculin skin test (TST) as screening tests for LTBI in this patient group. This review summarizes the latest literature data.

**Screening for latent tuberculosis** Patients with CKD either on dialysis or following transplant have a significant risk of developing active TB. Lee et al reported a higher prevalence of LTBI in patients on hemodialysis than in healthy controls and a rate of active TB of 3.53 per 100 person-years. Where possible, we should seek to reduce the risk of active disease through effective management of latent disease. The diagnosis of LTBI can, however, be problematic. Both the 2010 BTS guidelines for the management of TB in patients with CKD and the 2016 NICE guidelines for the diagnosis and management of TB suggest that all patients with renal disease need a risk assessment based on the presence and severity of their immunocompromised state as well as risk factors for TB infection, including contact with infected persons and significant time spent in a country with medium-to-high background rates of TB. An assessment for possible active disease should also be made.

**Tuberculin skin test** In patients with renal failure, because of associated immunodeficiency, the reported rates of skin anergy to the TST vary but can be up to 50%, which translates to a low sensitivity for the test in this group. This is thought to be related to impaired cellular immunity associated with uremia. Therefore, a negative test result cannot be assumed to be true negative, while a positive test result should prompt further investigation in these patients.

**Interferon-γ release assays** The 2 commercially available IGRA tests (TSpot.TB, Oxford Diagnostic Laboratories, Oxford, United Kingdom and QuantiFERON-TB Gold In Tube (QFT) Cellestis, Australia) have advantages over the TST in that they have increased specificity with less cross-reactivity with the Bacillus Calmette–Guérin vaccine and the majority of environmental or non-tuberculous mycobacteria.

The IGRA response can be reduced in immunocompromised patients when compared with immunocompetent controls, but remains higher than the TST response. In a recent study of 95 patients with end-stage renal failure receiving hemodialysis, the QFT was reported to have a sensitivity of 100% and a specificity of 62% for active (as opposed to latent) TB and was superior to the TST, although the main use of these tests is to identify LTBI. A positive IGRA result is assumed to identify patients with the highest risk of progression to active TB. Most studies have included predominantly non-immunocompromised patients during contact tracing and have not compared any of the IGRAs with the TST. A meta-analysis of such studies investigating the positive and negative predictive values of the IGRAs and TST showed that the pooled positive predictive value for progression in at-risk groups with mixed etiologies was 6.8% (95% confidence interval [CI], 5.6%–8.3%) and 2.4% (95% CI, 1.9%–2.9%) for the IGRAs and the TST, respectively, and the negative predictive value for both IGRAs and the TST exceeded 99% with narrow CIs. Kim et al reported that 5.6% of untreated renal transplant recipients with a positive IGRA result developed active TB.

The pan-European TBNET trial, probably the most comprehensive cross-sectional prospective cohort study, involving 17 centers from 11 European countries, compared the 2 commercially available IGRAs and the TST. The risk of active TB in 5 different groups of immunocompromised patients and a group of immunocompetent controls was assessed. In 270 patients with CKD, the frequency of a positive test result ranged from 25.3% to 30.6%, while in 197 solid-organ transplant recipients, the frequency was both lower and more variable (9.0%–20%). The higher level of positive results in patients with CKD probably reflects the multifactorial nature of immunodeficiency in CKD, which is not primarily T-cell mediated, whereas immunodeficiency following transplantation is mainly due to drug-induced suppression of T-cell function. Up to 20% of immunocompromised patients had an indeterminate IGRA result compared with controls, with the highest rate found in those considered most immunodeficient, including transplant recipients, and a lower rate in patients with renal failure. Together with the higher percentage of positive test results, this suggests that immunodiagnostic assays are less affected by the underlying etiology of immunodeficiency in CKD compared with that after transplant, namely, the effects on T-cell function following transplantation and the required immunosuppressive therapy.

The performance of the TST and IGRAs undoubtedly differs among patients with various etiologies of immunodeficiency, and it is currently unclear which test is preferable for immunodiagnostic testing. The TBNET study revealed that the between-test agreement was higher between IGRAs, which also generally had a higher rate of
positive results and were more strongly associated with exposure to <i>Mycobacterium tuberculosis</i>. The percentage of those with positive results from all 3 assays or with positive results from the 2 IGRA's was the highest in cases with the greatest likelihood of exposure to TB, whereas positive results from only one test were less likely to be linked to exposure variables. While this could suggest false positive results, it may also be caused by variable effects of immunodeficiency on immune reactivity in vivo and in vitro. This also demonstrated that neither of the IGRA's nor the TST were adequately able to predict those at risk of later developing TB.

It must also be remembered that a negative test result is not always true negative, and the meaning of indeterminate results is unclear. Furthermore, once a patient has had active TB or LTBI with a positive TST or IGRA result, we do not know when, if ever, these test results return to normal.

How and when to screen? A recent survey in the United Kingdom (UK) revealed that only one-third of renal units follow the latest guidelines. IGRA testing is rarely used, and treatment schedules for latent disease were at an incorrect dose or schedule in nearly 50% of cases. There appears to be a lack of appetite in renal units to screen all patients on the transplant list, for example, as not all patients on that list will necessarily proceed to transplant (Ostermann M, personal communication). However, the figures from a large UK renal unit suggest that hemodialyzed patients at risk could well benefit from screening, whether or not they proceed to transplant surgery. In a recent study from Turkey, Sehan et al demonstrated that 6.2% of patients on hemodialysis with a positive QFT result progressed to active disease over a 5-year follow-up compared with 1.1% of healthy controls.

However, there is no perfect screening method and the increasing number of studies using IGRA's has highlighted their limitations and the difficulties in their clinical interpretation. The available screening tests need to be used with an appropriate risk assessment and a chest radiograph. Also, which patients with CKD should be screened for LTBI and active disease? We cannot assume that patients originating from countries with a high background risk of active disease as well as those with a clear history of TB contact should certainly be considered.

According to the 2012 TBNET consensus statement, pretransplant screening for LTBI should be performed with a TST or IGRA or both, although false negative or indeterminate results in patients with a high risk of exposure or profound underlying immunosuppression can be difficult to interpret. These patients should be evaluated carefully, both to determine the risk and to exclude active TB before initiating LTBI treatment. The advice for those with indeterminate results is usually to repeat the test.

While there is still no perfect test for LTBI, there is sufficient evidence that a positive result from either of the 2 commercially available IGRA's with or without the TST usually gives sufficient grounds for chemoprophylactic treatment in this significantly immunocompromised group. The difficulty arises with negative and indeterminate results, which cannot be assumed to be true negatives, so patients considered to be at particular risk should be monitored carefully.

Assessment for active disease All patients should be assessed for active disease. A detailed clinical history should be taken, including previous history of TB and contact with TB. Particular attention should be paid to symptoms of cough, sputum production, fever, night sweats, weight loss, and lymphadenopathy. However, it should be noted that from 30% to 50% of patients will present with extrapulmonary disease, and symptoms may not always be classic. In addition to this, patients on peritoneal dialysis who are at risk of intra-abdominal infection also require special consideration.

A chest radiograph should be performed as part of the workup of all renal patients to show any evidence of previous TB disease, but also so that future radiographs can be compared with previous studies, and any new infiltrates warrant further investigation. Further site-specific investigations such as abdominal ultrasound, computed tomography, or spinal magnetic resonance imaging should be considered based on symptoms.

Every attempt should be made to obtain samples for microscopy and culture. In suspected pulmonary disease, 3 sets of early-morning sputum samples (if available) should be sent for direct smear, culture, and sensitivity. If pulmonary disease is suspected based on chest radiograph but the patient has no productive cough, induced sputum or bronchoscopy could be considered. Intrathoracic lymphadenopathy can be investigated with endobronchial ultrasound and biopsy. If the disease site is extrapulmonary, an attempt should be made to obtain a tissue sample. This should be examined histologically for the appearance of granulomata, which are suggestive of disease, and stained for acid-fast bacilli. Biopsy specimens should also be sent for culture, and it is imperative that they are placed in a plain pot, and not in formalin, for a microbiological assessment.

Treatment of latent tuberculosis infection and active tuberculosis Appropriate treatment of <i>Mycobacterium tuberculosis</i> in renal patients remains...
Challenging. Patients with renal disease are at an increased risk of side effects, compared with those with normal renal function.

Given the high incidence of active TB in patients with CKD, particularly those due to undergoing transplantation, and the earlier paucity of evidence on the use of IGRA testing in these patients, one approach has been to treat all transplant recipients with chemoprophylaxis. This presents 2 difficulties: one is that this fails to identify patients with active disease and the second is that chemoprophylaxis is not without risk. Drug-induced hepatitis is the primary problem and may outweigh the risk of TB infection in those with low risk and without evidence of LTBI. Some centers limit the use of posttransplant chemoprophylaxis to patients with increased risks, but without a screening program, some with no perceived risks may still have LTBI that reactivates after transplant. In the UK, there is a marked discrepancy among renal units regarding chemoprophylaxis policy, with no clear association with regional incidence of TB and a broad variation in duration of chemoprophylaxis from none to lifelong. Unfortunately, guidelines do not appear to be followed and the evidence for appropriate chemoprophylaxis has failed to be put into clinical practice in some units.

Chemoprophylaxis There are 3 recommended treatment regimens for preventive therapy of LTBI using isoniazid or rifampicin or both. Both these drugs are metabolized by the liver, and poor renal function should not be problematic. However, patients with renal disease do seem to be more prone to peripheral neuropathy and central neurological disturbance sometimes associated with isoniazid; therefore, pyridoxine should be added to any isoniazid-containing regimen. The common regimens are: 6 (or 9) months of isoniazid, 300 mg/d, plus pyridoxine; 3 months of isoniazid and rifampicin based on weight (with pyridoxine); or 4 months of rifampicin alone, which seems to be better tolerated than isoniazid-containing regimens. There should be no problem with the use of rifampicin in patients on hemodialysis and CAPD, but most centers prefer to use isoniazid alone in transplant recipients because of the interactions between the rifamycins and immunosuppressive agents used to prevent rejection.

A Cochrane review including 11 trials with a total of 73,375 patients and investigating the risk of progression after chemoprophylaxis showed a risk ratio of 0.44 (95% CI, 0.27–0.73) for 6 months of using isoniazid alone and of 0.38 (95% CI, 0.28–0.50) for longer periods of up to 12 months. There was no additional benefit from the longer periods of chemoprophylactic treatment in preventing subsequent reactivation. Although a more recent detailed meta-analysis showed high efficacy following 9-month treatment with isoniazid alone, this was based on few data. Furthermore, the longer regimens are at the expense of increased side effects and poorer compliance; hepatotoxicity, for example, doubled with 12-month therapy (0.52% vs 0.26% for 6-month treatment). One randomized study, however, did not report a problem with hepatotoxicity in 181 patients who received a 1-year course of isoniazid after transplant in a high-incidence country. Of the patients treated, one later developed TB, as compared with 16 of the 207 patients who were not treated (P = 0.0003).

A 3-month treatment with isoniazid plus rifampicin or a 4-month treatment with rifampicin alone may be equally efficacious as the isoniazid-only regimens, and 12 weeks of isoniazid and rifapentine have been shown to have similar efficacy to 9 months of isoniazid alone. In a recent review and meta-analysis comparing different LTBI treatment regimens, those containing rifampicin for 3 months or more were potentially more efficacious in preventing active TB than isoniazid monotherapy. This would support the view that at-risk patients on dialysis should be screened for LTBI and treated appropriately, whether or not they then proceed to a transplant, as the rifamycins can generally be used with fewer problems in patients not yet on immunosuppression for graft protection. Indeed, a prospective randomized controlled trial of isoniazid chemoprophylaxis during hemodialysis in a high-incidence country showed a significantly lower incidence of TB in the treated dialysis group compared with controls, with a risk ratio of isoniazid versus controls for the development of TB of 0.40 (95% CI, 0.17–0.92; P = 0.032).

It is not necessary to complete chemoprophylaxis prior to transplantation, but all patients both before and after a transplant will require close monitoring for both drug toxicity and drug–drug interactions.

Patients who have completed chemoprophylaxis should have a considerably reduced risk of active TB unless they are reinfected. The sometimes indiscriminate use of chemoprophylaxis in all transplant recipients may account for the reduced incidence of active disease found in these patients compared with those on dialysis. A recent study from Saudi Arabia indeed demonstrated that expanded isoniazid chemoprophylaxis for deceased-donor kidney recipients was responsible for a significant reduction in post-transplant TB in a moderate-incidence country.

Treatment for active disease All patients with active TB should be treated with 4 agents as per the guidelines. The first-line treatment is with rifampicin, isoniazid, pyrazinamide, and either ethambutol or moxifloxacin with pyridoxine. As with rifampicin and isoniazid, pyrazinamide is likewise subject to hepatic metabolism, although in CKD stages 4 and 5 and on hemodialysis, excretion of metabolites may be impaired, resulting in uric acid retention and gout. Ethambutol is excreted by the kidneys in 80% and accumulates in renal failure, similarly to aminoglycosides.
ethambutol and aminoglycosides should be monitored, and moxifloxacin is often substituted for ethambutol in patients with CKD, those on dialysis, and transplant recipients. Note that moxifloxacin is only suitable for daily use and cannot be given 3 times a week. Since the introduction of the 2010 guidelines, there has been no evidence to suggest a change in the recommended regimen for active TB.4

**Special considerations in chronic kidney disease** Patients with renal disease have a higher incidence of adverse effects related to antituberculous drugs than patients with normal renal function, and should be managed by physicians experienced in the management of TB. Input from a renal pharmacist can also be helpful.

To avoid accumulation, changes to regimens that include pyrazinamide and ethambutol must be made for patients with advanced stages of CKD or on renal replacement therapy. However, dose adjustment can lead to decreased efficacy as these drugs exhibit concentration-dependent activity. In view of this, increasing the dose interval to 3 times weekly is recommended in stages 4 and 5 CKD and in patients on hemodialysis, as evidence suggests increased efficacy using this approach. Both rifampicin and isoniazid can be given at the normal daily dose. Moxifloxacin is frequently substituted for ethambutol but is only suitable for daily dosing.4

**Hemodialysis** The best approach to dosing for patients receiving hemodialysis is still being debated. Dosing 4 to 6 hours before dialysis has the advantage of reduced toxicity in regimens containing ethambutol and pyrazinamide, but at the risk of premature drug removal. This can be avoided by postdialysis dosing, which also potentially facilitates directly observed therapy and hence compliance, but this is balanced against the risk of increased drug levels between dialysis sessions. Monitoring of peak (1 hour after dosing) and trough (predose) levels of ethambutol and aminoglycosides is therefore mandatory.

**Peritoneal dialysis** Less is known about the pharmacokinetics of antituberculous drugs in patients undergoing CAPD. One study has shown that no adjustment in doses is needed for rifampicin, isoniazid, or pyrazinamide in patients on CAPD with pulmonary or systemic TB.31 However, rifampicin has a high molecular weight, lipid solubility, and protein-binding capacity, and only small amounts are found in the peritoneal dialysate, but drug levels of the other drugs appear to be variable. Therefore, the dose of rifampicin may need to be increased in patients with peritoneal TB. However, doses of isoniazid and pyrazinamide also need to be carefully monitored in these patients, and adjusted accordingly.

**Posttransplant drug interactions** After transplant, there is a potential problem with the use of rifamycins and concomitant immunosuppression. These drugs reduce the efficacy of steroids and other immunosuppressive agents such as mycophenolate mofetil, cyclosporine, and tacrolimus by the upregulation of cytochrome P450, and can result in an increased rate of graft rejection.32 As a general rule, steroid doses should be doubled, while the measurement of drug levels of other immunosuppressive drugs and appropriate dose adjustments should be made to protect the graft.3 Rifabutin demonstrates considerably less interaction with these drugs than rifampicin, as it is a weaker inducer of CYP450; therefore, rifabutin is being used more frequently after transplant.33 Care should also be taken with rifabutin if used in combination with the macrolides, as it increases the risk of uveitis.34 There have also been reports of rifabutin-induced neutropenia.34-38 In a multicenter study evaluating the tolerance and potential pharmacokinetic interactions between rifabutin and azithromycin, the incidence of neutropenia ranged from 10% to 26%; moreover, during the first 14 days of monotherapy with rifabutin, there was a significant decrease in the absolute neutrophil count.35 This suggests that significant neutropenia is not a rare side effect of rifabutin, and it is recommended that the white cell count be monitored for 1 week after initiation of therapy and at 2 to 4 weekly intervals thereafter.36

**Summary** Patients with CKD are at significantly increased risk of both latent infection and active disease with *Mycobacterium tuberculosis*. Current practice is variable and not always in accordance with the latest guidelines. A risk assessment should be performed for all patients with CKD in terms of their level of immunosuppression and risk of TB infection. At-risk patients should be screened, with the highest rate of detection being with concomitant TST and IGRA testing. This area has been the subject of most of the additional research since 2010 and, while none of the available screening tests is 100% reliable in this patient group, there have been numerous publications supporting the use of IGRA testing with or without the TST. Negative and indeterminate results should be considered in conjunction with a risk assessment and chest radiograph. The timing of screening is still being debated, but prior to transplantation, it would allow the use of rifamycins in chemoprophylactic regimens, and could also reduce the high rates of active TB seen in dialysis patients. It is crucial to exclude active disease and treat this if it is found at whatever stage of CKD, dialysis, or transplantation. We believe that there has been no substantial evidence published to support changing the treatment regimens recommended in the 2010 guidelines, but moxifloxacin is often used instead of ethambutol in severe renal disease, and rifabutin has become an increasingly popular alternative to rifampicin after transplant.
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REFERENCES


