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CLINICAL PRACTICE

Clinical Medicine 2014 Vol 14, No 1: 26–9

Managing latent tuberculosis in UK renal transplant units: how does practice compare with published guidance?

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ABSTRACT

Renal transplantation significantly increases the risk of active tuberculosis (TB) in individuals with latent TB infection (LTBI). UK transplant recipients are often born in TB endemic areas. Using a self-completed questionnaire, we evaluated how the 23 UK renal transplant units' LTBI management compared with recently published national guidance. Three-quarters had a management protocol, but only one-third of these were in line with the guidance. Interferon-gamma release assays were rarely used to confirm LTBI. Almost half of the units prescribed LTBI treatment at the wrong dose or duration. We conclude that units should develop local protocols in line with evidence-based guidance. This must be in a format that enables national audit programmes and quality improvement to be routinely performed.

KEYWORDS: Guideline adherence, renal transplantation, tuberculosis

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Introduction

People from tuberculosis (TB) endemic countries have both a high prevalence of latent TB infection (LTBI) and chronic kidney disease.[1] Immunosuppressive regimens used during renal transplantation can promote LTBI reactivation to symptomatic (active) TB disease. As a result, the incidence of active tuberculosis in renal transplant patients is estimated to

be 20–70 times higher than in the general population.[2] The sites affected are often extrapulmonary, the presentation may be atypical and it can be associated with other infections, making diagnosis more difficult in the transplant population.[3] Induction of liver enzymes by rifampicin reduces levels of cyclosporine and tacrolimus, meaning that anti-tuberculosis therapy using a rifampicin-containing regimen is not recommended by all authorities.[4] In cases where there is no alternative, the combination of rifampicin and cyclosporine can lead to a graft rejection rate of up to 25%.[3]

The UK has an ongoing problem with TB. Metropolitan areas, including Birmingham, Leicester and London, have rates of TB that are similar to those found in high burden parts of the world.[5,6] Data such as this prompted the Joint TB Committee (JTC) of the British Thoracic Society to develop guidelines in 2010 on the investigation and management of LTBI and active TB in patients with chronic kidney disease.[1] The JTC advised that:

- all patients on the renal transplant waiting list should h ave an individual risk assessment, including a history of TB or TB contact sought, previous TB treatment checked and a chest radiograph performed to assess for previous or current active infection
- testing with a TB interferon-gamma release assay (IGRA) should be performed if the risk is high
- in general, all black African and Asian patients born outside the UK should be tested and considered for preventive anti-TB therapy prior to, or after, transplantation
- recommended preventive therapy for LTBI is: 6 months of isoniazid 300 mg daily plus pyridoxine 10–25 mg daily, or isoniazid plus rifampicin (on a weight-adjusted basis) plus pyridoxine for 3 months.

The diagnosis of (asymptomatic) LTBI can be difficult, and the JTC guidelines acknowledge that the evidence underpinning recommendations to test with TB IGRAs is lacking. Evidence of previously active but untreated TB on a chest radiograph is often used as an indicator of latent infection. However, this is relatively rare. Tuberculin skin tests such as the Mantoux test can be helpful when positive, although false-negatives are common in immunocompromised patients. Studies have shown that the prevalence of anergy to the purified protein derivative (PPD) used in the skin test can reach 50% in the haemodialysis population.[7–9] Low efficacy is also reported after transplantation, with immunosuppressants affecting results.[4] Blood TB IGRAs have better diagnostic accuracy rates in the immunocompromised and are not affected by cross-reactivity with BCG vaccination and most environmental mycobacteria.[10] The sensitivity and specificity of IGRA in end-stage renal disease have been reported as 100% and 62.1%, respectively.[11]

However, the recommended dose and duration of preventive therapy was noted by the JTC to be based on high-grade evidence. A randomised controlled trial showed that 12 months of isoniazid prophylaxis at a dose of 300 mg daily in patients on haemodialysis led to a relative risk of developing tuberculosis of 0.4 compared with a control group.[12] There is an additional risk of hepatotoxicity associated with extending treatment from 6 to 12 months, with no significant reduction in the relative risk of tuberculosis.[13] Furthermore, a placebo-controlled clinical trial of 3 months of isoniazid plus rifampicin in patients with silicosis demonstrated a 50% reduction in risk of developing active TB in those on drug therapy.[1] Given the potential issues associated with rifampicin, isoniazid at a dose of 300 mg once a day for 6 months is the generally recommended regimen in renal transplantation.

The dissemination and adoption of guidance can be a slow process.[14] We wished to determine how UK renal transplant centres' management of LTBI compared with the guidance and the degree to which current practice may need review.

Method

An electronic internet-based questionnaire was sent to the leads of each UK renal transplant unit in October 2011. If the lead of the unit did not respond, a second person in the unit was telephoned personally in early 2012 to ask whether they were in a position to answer the questionnaire on behalf of the unit. The respondents could have been either surgeons or nephrologists, but all were members of the transplant unit. Data were requested on the number of transplants performed at each centre, an estimate of the number of active TB cases for the 5 years between 2006 and 2011 and the percentage of the transplant population born in a TB endemic country. This provided background information on the burden of tuberculosis in each centre. Further information was collected on whether the transplant centre had a current protocol for identifying patients at high risk of LTBI, whether this was based on specific professional body guidance, what it contained and how LTBI was treated. The results were compared with the JTC guidelines.[1] As this was an audit and service evaluation, ethical committee review was not required. The questionnaire has been included as supplemental content.

Results

All 23 renal transplant centres in the UK responded to the survey. A total of 74% (17/23) provided complete data. The median number of transplants performed per year was 100 (range 26–184). Seven (30%) centres reported that a high proportion (21–60%) of their transplant population had migrated to the UK from TB endemic areas.

Over the 5-year period, 70% (14 of 20 centres providing this information) had at least one case of TB in their renal transplant recipients, including all centres with high proportions of patients from TB endemic countries.

A total of 74% (14/19 respondents) of centres had a protocol to determine which patients should receive treatment for LTBI; 25% (4/14) were based on the JTC guidance (Table 1). Centres with high proportions of patients from TB endemic countries were no more likely to have a clear protocol. For example, one of the seven centres had a protocol in line with JTC guidance, three others did not, a further two had no protocol and one unit did not complete the question in full.

Tuberculosis and latent tuberculosis infection assessment in transplant recipients

Sixteen of 19 centres (84%) reported performing a clinical risk assessment for TB (Table 1). In 14 of 16, this included

Table 1. Relationship between local TB protocol and new JTC guidance for renal transplant units.

(a) Impact of local protocol on latent TB preventive therapy practice (n=19)

Local protocol	No preventive therapy used (% of centres) (n)	Clinical assessment only (% of centres) (n)	Clinical assessment + IGRA (% of centres) (n)	IGRA only (% of centres) (n)
Based on JTC guidance	–	21% (4)	–	–
Not based on JTC guidance	–	32% (6)	16% (3)	5% (1)
No protocol	11% (2)	16% (3)	–	–

(b) Impact of local protocol on isoniazid dose and duration (n=17)

Protocol	300 mg daily for 6 months	Duration >6 months	Dose <300 mg daily	Refer to specialist TB service	Details missing (eg duration)
Based on JTC guidance	6% (1)	6% (1)	–	–	12% (2)
Not based on JTC guidance	24% (4)	6% (1)	12% (2)	–	6% (1)
No protocol	–	12% (2)	6% (1)	6% (1)	6% (1)

IGRA = interferon-gamma release assay; JTC = Joint TB Committee; LTBI = latent TB infection; TB = tuberculosis.

determining whether a patient was born in a TB endemic country and whether there was any history of known TB contact. One centre considered only TB contact and previous TB infection to be relevant, whereas another regarded all patients of African and Asian descent, irrespective of place of birth, as high risk.

Blood IGRA was used by 4/19 centres (21%) as part of the patient evaluation for LTBI. Three of these combined the test with a clinical risk assessment, although none were as recommended by the JTC (Table 1).

Treatment of latent tuberculosis infection

A total of 74% (17/23) of centres gave details of their preventive therapy prescription practices (Table 1). The recommended treatment of 300 mg isoniazid daily for 6 months was reported by five centres (29%). Five others either did not state the dose or duration of treatment, or they referred the patient on to a specialist TB service. Another seven of 17 (41%) gave isoniazid preventive therapy for longer than recommended (one centre continued therapy indefinitely), or at a lower dose than recommended (one centre prescribed only 100 mg daily, whereas two prescribed 200 mg daily) (Table 1).

The management of patients with chest radiographic evidence of old TB and previously treated active TB was variable. A total of 63% (10/16) of centres gave isoniazid preventive therapy to the former, whereas 50% of centres indicated that they would offer LTBI treatment to those with a history of fully treated TB in the past. This approach differed from JTC guidance.

Testing donors for LTBI

The JTC guidelines do not deal specifically with the issue of testing donors for LTBI prior to transplantation. However, this has been discussed elsewhere[5] and was included in our survey. Seven of 17 (41%) centres screened live donors using chest radiographs to assess for possible TB. Three centres (3/17; 18%) routinely asked whether cadaveric donors were known to have had TB previously.

Discussion

The use of an evidence-based protocol to prevent TB following renal transplantation in UK transplant centres is patchy. Although protocols were in place in the majority of units, none were completely in line with the published JTC guidance. Clinical assessment was generally performed well and captured relevant information on personal TB risk. However, only 16% (3/19) combined the assessment with IGRA testing recommended by the JTC. Of note, transplant centres serving large communities at risk of TB seemed to be no better than those where active TB was less of an issue.

Prescribing practice was variable; almost half of the centres used either too low a dose or too long a duration of isoniazid preventive therapy. The former may result in lack of effect, false reassurance to the patient and clinician regarding future risk of active TB, and potentially lead to the development of drug resistance. The prolonged duration may increase the occurrence of adverse events. Many centres reported giving LTBI treatment to patients who had previously received a complete treatment course. This is likely to provide little extra benefit and again may cause drug toxicity.

Why does our survey show such variation in practice? One explanation may be the methodology we chose to use, which was a multiple-choice type format asking didactic questions. It is possible that if we had supplied clinical scenarios the responses would have been both more true to life and homogenous. In addition, the audit was carried out within 1 year of the JTC guidance being published. This may explain in part the discrepancy noted in our study between recommended guidance and clinical practice, as it can take time for guidance to be adopted.[14] Specific issues that appear to have been raised, such as the lack of IGRA employed, could result from poor local availability of the test or a perception regarding its (possibly low) sensitivity in this setting. Despite the survey being comprehensive (and hence lengthy), we did not ask about provision of tests.

Whatever underlies the national variability in practice, our study confirms the current need for clear, evidence-based guidance together with simple methods that maximise its use in clinical practice. Given the small number of units that undertake renal transplantation in the UK, a coordinated response to produce a standard management approach should be possible. Therefore, we propose the following:

- JTC guidance should be re-publicised to transplant units via the British Thoracic Society and the British Transplantation Society.
- There should be a nominated unit lead for TB responsible for protocol update, liaison with local TB services and networking with other transplant units.
- All units should adopt a standard protocol, even if the proportion of patients from a TB endemic country is relatively low.
- The protocol should discuss IGRA testing.
- The protocol should contain a section covering whom to contact for advice and joint management within local TB services.
- The correct dose and duration of isoniazid (300 mg daily for 6 months) plus pyridoxine, or isoniazid, rifampicin and pyridoxine for 3 months, should be highlighted.
- Thought should be given to IT solutions (including the use of mandatory data fields on electronic patient records or specific applications) that both encourage and simplify the assessment of individual patient risk for TB exposure.
- An annual national audit of practice and review of renal transplant case notes should be developed and supported by the relevant professional societies. Local action plans from the audit feedback can then assist in standardisation and practice improvement.
- This will also enable updated national guidance to reflect the needs of the transplant community, which we believe will encourage their ongoing use.

The direct effects of tuberculosis on graft function and drug interactions emphasises the importance of preventing transmission to the transplant population, especially in those parts of the country where TB rates are rising. Current national guidance promotes enhanced LTBI testing, more effective targeted preventive therapy and a reduction in subsequent cases of active TB. Their adoption enables national evaluation and audit (of outcome as well as process). Over time, this will include the impact of UK guidance on transplant-related TB.

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