Tests for latent tuberculosis in people with end stage kidney disease: a systematic review

Thomas E. Rogerson, BSc[12], Sharon Chen, MBBS, PhD[3], Jen Kok MBBS[3], Andrew Hayen, BA MM(Biostat), PhD[2], Jonathan C. Craig, MBBS, PhD[12], Kamal Sud, MBBS[3] Kathy Kable BASci, MN[3], Angela C Webster, MBBS MM(Clin Epid), PhD[123]

1 The Centre for Kidney Research, Children's Hospital at Westmead,

2 Sydney School of Public Health, The University of Sydney

3 Centre for Infectious Diseases and Microbiology, Westmead Hospital

Corresponding author and request for reprints

Angela C. Webster

Address: Sydney School of Public Health (A27), The University of Sydney, NSW, 2006, Australia

Email: angela.webster@sydney.edu.au

Running head

Tests for latent TB in ESKD

Word count (excluding abstract, acknowledgements, figure legends, and references)

3662

Number of tables and figures

6

Keywords

Latent tuberculosis, tuberculin skin test, QuantiFERON, T-SPOT.TB, end stage kidney disease, systematic review, dialysis, transplantation

1

Conflict of interest notification

The authors have no conflicts of interest to report.

Funding notification

Acknowledgements

Abstract

Background: The relative diagnostic accuracy of interferon gamma release assays (IGRAs; QuantiFERON®-TB Gold In-Tube [QFT] and T-SPOT®.*TB*) and the tuberculin skin test (TST) for latent tuberculosis (TB) infection in people with end stage kidney disease (ESKD) is uncertain and national guidelines for their use are inconsistent.

Study design: Systematic review.

Selection criteria for studies: Evaluated performance of tests for latent TB with clinical risk factor assessment.

Setting and population: People with ESKD (chronic kidney disease stage five [eGFR < 30] or kidney transplant recipients). No limits on setting.

Index tests: QFT, TSPOT.TB, TST, MycoDot, Determiner TBGL Antibody and flow cytometry.

Outcomes: Odds of test positivity with clinical risk factor for latent TB, expressed as Odds Ratios (OR, with CI 95%). Relative Odds Ratios (ROR, with CI 95%).

Results: Forty-seven studies (6828 participants) were included, but only 30 studies (4546 participants) contained sufficient data to contribute to meta-analysis. Studies were predominately in the dialysis population (23/30, 3700 participants) in countries with low to high TB prevalence (4.7-258.0 cases/10^5 persons). BCG vaccination rate was variable (2.7-100.0%). Nine studies compared IGRAs with the TST directly, 17 studies evaluated the TST only, and the remaining four studies evaluated other tests. Compared to a positive TST, a positive QFT was more strongly associated with radiological evidence of past TB (ROR 4.29, CI95% 1.83-10.3, p=0.001), and contact with active TB (ROR 3.36, 95%CI 1.61-7.01, p=0.001). Compared to a negative TST, a negative QFT was more strongly associated with BCG vaccination (ROR 0.30, 95%CI 0.14-0.63, p=0.002). There was insufficient data to compare performance of the TSPOT.TB with the TST or QFT.

Limitations: Seventeen of 47 included studies (36.2%) did not contain sufficient data to contribute to meta-analysis.

Conclusion: Compared to the TST, the QFT assay was more strongly associated with risk factors for latent TB in ESKD.

Introduction

Uraemia in end stage kidney disease (ESKD) contributes to generalised immune dysfunction which results in increased susceptibility to infectious diseases, including tuberculosis[1,2]. Individuals with ESKD are up to 50 times more likely to develop active TB than the general population and mortality is high, between 17 and 75%[3]. A recent study in Australia reported an incidence of active TB in people on dialysis of 66.8 per 100000 persons/ year and an adjusted relative risk of 7.87 when compared with the general population[4]. Accurate and timely diagnosis and treatment of latent TB is key to preventing active disease, but is hampered by limitations in 'gold-standard' diagnostic tests for determining true latent TB status[5]. Whilst prophylaxis with anti-TB medications is effective in preventing active disease, anti-TB medications are also associated with hepatitis, neurotoxicity and significant drug-drug interactions[6-9]. Screening patients for latent TB can be used to target prophylaxis to patients at highest risk of developing active TB, whilst avoiding unnecessary complications of treatment in low risk individuals.

Until recently, the detection of latent TB has relied on the tuberculin skin test (TST). The utility of the TST in clinical practice is limited by poor sensitivity in immunocompromised people and poor specificity in Bacillus Calmette Guerin (BCG) vaccinated people[10]. An alternative to the TST are interferon gamma release assays (IGRAs), including the QuantiFERON®-TB Gold (QFT; Cellestis, www.cellestis.com) and T-SPOT®.*TB* (Oxford Immunotec, www.oxfordimmunotec.com). These tests are *in-vitro* T-cell based assays that measure the response of sensitized T-cells to mycobacterial antigens (early secretory antigenic target 6 [ESAT6] and culture filtrate protein 10 [CFP10]) in whole blood.

National guidelines for the diagnosis of latent TB are inconsistent[11,12]. Some guidelines offer no specific recommendation for test use[13], some propose that IGRAs should be used following a negative TST[14,15], whilst others recommend that IGRAs replace TST. No specific guidelines exist for the ESKD population, however current recommendations from the United Kingdom indicate the

use of IGRAs with or without a TST in people with chronic kidney disease[16]. The few guidelines that exist for immunosuppressed populations (excluding HIV) are also conflicting. Canadian guidelines for immunosuppressed persons recommend using the TST with or without a supplementary IGRA[14], whilst the United Kingdom and Switzerland recommend replacing the TST with an IGRA[17,18].

Determining the diagnostic accuracy of IGRAs in ESKD using epidemiological first principles is problematic because the existing standard test (TST) performs poorly and therefore makes direct comparison invalid. Previous systematic reviews of IGRA test performance are limited to the general population and most use two separate populations of people to estimate sensitivity (a population including only active TB cases) and specificity (a population of healthy low risk people)[19-21]. An alternative approach is to measure the association of test positivity with medical evidence of TB infection and epidemiological risk factors[22]. A pre-test clinical risk assessment encompassing a person's risk of exposure, other co-morbidities and radiological imaging may help to interpret the validity of a positive or negative result. A test that is both sensitive and specific for latent TB should have test positivity closely associated with risk factors such as old TB on chest x-ray, previous treatment for active TB, contact with an active case of TB, high risk nationality and immunosuppression (other than uraemic related).

Given the paucity of evidence based guidance for clinical decision making, we aimed to systematically review all studies which assessed the association of TST or IGRA test results with clinical risk factors for latent TB in people with ESKD.

Methods

Inclusion/exclusion criteria

We included all studies in any language that reported the performance of any diagnostic test for latent TB in conjunction with either medical evidence or clinical risk factors, in adults or children with ESKD. We excluded studies that included ESKD patients with active TB at the time of testing when data could not be separated from patients without active TB.

Search strategy

We searched MEDLINE and EMBASE from inception to October 2010. Articles were located using a search strategy composed of three filters, the first for test terms, the second for people with ESKD or CKD IV, and the third for TB terms. The full search strategy is available in *Supplementary Table 1*. We also searched conference proceedings, including: Australian Society for Microbiology 2005-10, Australian Society for Infectious Diseases 2007-10, Infectious Diseases Society of America 2007-10, Interscience Conference on Antimicrobial Agents and Chemotherapy 2005-10, European Congress of Clinical Microbiology and Infectious Diseases 2005-10, American Society for Microbiology 2010 and International Congress on Infectious Diseases 2008-10. The search was conducted by hand, or where electronic copies were available, we searched on the following text terms: *tuberculosis, interferon, QuantiFERON, QFT, TSPOT.TB, ELISPOT, tuberculin skin test, TST, haemodialysis* and *hemodialysis.*

Data abstraction

Data was abstracted from studies by three investigators working independently, using standardised data abstraction forms. We collected data on study setting and design, participant characteristics, risk factors for latent TB, test details and test results. We investigated both medical and epidemiological risk factors for latent TB *(Supplementary Table 2)*. Medical risk factors included a

positive chest radiograph for past TB, previous active TB or prophylactic treatment for TB and any iatrogenic or disease related immunosuppression (other than uraemia related). Epidemiological risk factors included nationality and contact with a person with active TB (documented by a healthcare professional or self-reported). We also investigated BCG vaccination status as a protective factor. Study quality was assessed with an adapted version of the QUAlity assessment of Diagnostic Accuracy Studies (QUADAS) tool, see *Supplementary Table 3*[23]. The QUADAS tool consists of 14 methodological items which assess study validity in terms of appropriateness of patient spectrum and reference standard, bias, test execution, loss to follow up and indeterminate results.

Statistical analysis

The study setting, patient characteristics and the QUADAS tool data were summarised descriptively. Where sufficient data were available, we constructed 2x2 tables and calculated odds ratios (OR) (with 95% confidence intervals) for test positivity with each risk factor. When all patients in a study had a risk factor, or all patients with a risk factor had the same result, we added 0.5 to each cell of the 2x2 table to calculate the OR[24]. In studies that assessed two or more tests in the same population, we compared the association of test positivity with risk factor between tests as a relative diagnostic odds ratio (ROR, with 95% confidence intervals). Variance was calculated using a previously published method which assumes a correlation between tests of 0.5, producing conservative estimates[22]. Statistical significance was tested with a Wald test and reported as a p-value. Forest plots and summary estimates for ORs and RORs were generated in STATA 11.2 (Statacorp, USA) using a random effects model weighted by inverse variance. Heterogeneity between was assessed using the I^2 statistic, which reports the percentage of variation across studies that is due to true heterogeneity rather than chance.

Sensitivity analysis

To test the robustness of our results against inter-study heterogeneity, we conducted sensitivity analyses using random effects meta-regression. Specifically, we compared studies of dialysis patients alone versus transplant/mixed populations of dialysis and transplant patients, studies that used blinding of test interpretation to other test results versus those that did not use blinded interpretation, studies that used a TST cut-off of 5mm versus 10mm and studies that used second generation versus third generation QFT tests.

Results

Our search identified 949 potential citations. Nine hundred and thirty seven citations where identified in electronic databases, nine citations where identified in conference proceedings, one citation came from reference list searches and one citation came from an expert in the field *(Figure 1)*. In total 47 studies (6828 participants) were included, however only 30 studies (4546 participants) contained sufficient data to contribute to meta-analysis.

The characteristics of included studies that contributed to meta-analysis are listed in *Table 1*. In general, studies were mostly conducted in dialysis patients (23/30 [76.7%]) and in countries with low (≤ 5 cases/100000) to moderate (≤ 50 cases/100000) TB prevalence[25]. The study setting was primarily outpatient dialysis clinics and all studies were prospective. Two studies (306 participants) were conducted as contact investigations in response to possible TB exposure[26,27]. Seventeen studies (2903 participants) evaluated TST only, nine studies (1126 participants) directly compared an IGRA with TST, and the remaining four studies (517 participants) evaluated flow cytometry or antibody detection kits.

Table 1: Characteristics of included studies

Study	Test evaluation	Country	N	Males (%)	Age (years ± SD)	ESKD treatment (months ± SD)	BCG vaccinated (%)	TB prevalence† case/10^5 persons (95% CI)
Dialysis population								
Inoue 2009[28]	TST vs QFT	Japan	154	97 (59.9)	65.4 ± 65	42.4 ± n/s	n/s‡	74.6 (8.3-46.0)
Lee 2010[29,30]	TST vs QFT	Taiwan	93	35 (37.6)	58.3 ± 14.9	72.0	61.3	137.0 (56.0-225.0)*
Seyhan 2010[31]	TST vs QFT	Turkey	100	47 (47.0)	56.2 ± 15.3	n/s	67.0	41.0 (15.0-71.0)
Kim 2010[32,33]	TST vs TSPOT.TB	South Korea	209	78 (72.2)	n/s	n/s	n/s	115.0 (38.0-197.0)
Chung 2010[34]	TST vs QFT vs TSPOT.TB	South Korea	167	71 (42.5)	54.1 ± 14.4	60.8 ± 57.5	66.5	115.0 (38.0-197.0)
Triverio 2009[35]	TST vs QFT vs TSPOT.TB	Switzerland	62	46 (74.2)	65.0 ± 15.0	n/s	22.6	5.7 (1.9-9.8)
Lee 2009[36,37]	TST vs QFT vs TSPOT.TB	Taiwan	32	34 (54.8)	54.9 ± 10.1	n/s	71.9	137.0 (56.0-225.0)*
Eleftheriadis 2005[38]	TST vs Antibody detection	Greece	95	53 (55.8)	n/s	n/s	100.0	8.3 (2.8-14.0)
Yanai 2006[39]	TST vs Antibody detection	Japan	243	148 (60.9)	60.0 ± 11.0	86.0 ± 84.0	n/s	29.0 (9.2-49.0)
Wauters 2004[40]	TST	Belgium	224	130 (58.0)	n/s	n/s	2.7	15.0 (5.0-25.0)
Shankar 2005[41]	TST	India	108	78 (72.2)	37.75 ± 11.8	51.6 ± 31.2	70.4	258.0 (114.0-431.0)
Fang 2002[42]	TST	Taiwan	177	78 (44.1)	54.7 ± 17.3	40.0 ± 28.9	48.0	214.0 (99.0-315.0)*
Yildiz 1998[43,44]	TST	Turkey	29	17 (58.6)	30.9 ± 9.5	20.5 ± 17.4	n/s	75.0 (32.0-125.0)
Ates 2010[45,46]	TST	Turkey	779	381 (48.9)	51.2 ± 15.9	35.1 ± 33.4	53.9	41.0 (15.0-71.0)
Habesoglu 2007[47]	TST	Turkey	187	97 (51.9)	50.0 ± 15.9	53.1 ± 54.9	55.1	42.0 (14.0-73.0)
Taskapan 2000[48]	TST	Turkey	30	17 (56.7)	42.0 ± 12.0	27.8 ± 15.9	60.0	75.0 (32.0-125.0)

Dogan 2005[49]	TST	Turkey	124	56 (45.2)	45.3 ± 16.2	30.0 ± 17.0	90.3	46.0 (16.0-80.0)
Cengiz 2006[50]	TST	Turkey	106	47 (44.3)	49.9 ± 14.4	107.0 ± 54.8	100.0	42.0 (14.0-74.0)
Woeltje 1998[51]	TST	USA	307	129 (42.0)	58	3.7	0.0	7.9 (2.6-13.0)
Smirnoff 1998[52]	TST	USA	50	28 (56.0)	55	44.4	16.0	7.9 (2.6-13.0)
Hickstein 2007[27]	TST	USA	212	n/s	n/s	n/s	n/s	6.0 (2.1-10.0)
Linquist 2002[26]	TST	USA	94	n/s	n/s	n/s	n/s	7.9 (2.6-13.0)
Poduval 2003[53]	TST	USA	118	59 (50.0)	n/s	n/s	n/s	6.5 (2.2-11.0)
Transplant population								
Sester 2006[54]	TST vs Flow cytometry	Germany	117	n/s	53.1 ± 14.8	n/s	n/s	8.8 (2.9-15.0)
Sester 2009[55]	Flow cytometry	Germany	62	34 (54.8)	n/s	n/s	n/s	6.2 (2.0-11.0)
Mixed dialysis and transplant population								
Passalent 2007[56]	TST vs TSPOT.TB	Canada	209	78 (44.1)	n/s	n/s	78.0	6.1 (2.2-11.0)
Winthrop 2008[57]	TST vs QFT vs TSPOT.TB	USA	100	130 (58.0)	n/s	n/s	n/s	4.7 (1.3-8.0)
Kantarci 2006[58]	TST	Turkey	164	86 (52.4)	35.2 ± 10	43.0 ± 32	14.6	
Aydogan 2009[59]	TST	Turkey	150	72 (48.0)	48.1 ± 16.7	n/s	62.0	41.0 (15.0-71.0)
Basoglu 2006[60]	TST	Turkey	44	25 (56.8)	46.6 ± 15.6	n/s	90.9	42.0 (14.0-71.0)

†National **prevalence of TB in** in year of study publication, *TB prevalence in Taiwan estimated from data for China, ‡**Not specified**

The characteristics of included studies that did not provide sufficient data to contribute to meta-analysis are listed in *Supplementary Table 4*. Six studies directly compared the TST and an IGRA, seven studies evaluated TST only, three studies evaluated QFT only and one study evaluated flow cytometry. These studies included 2282 participants, of which 1258 were on dialysis, 820 were transplanted, and the remaining 204 were not specified. Age and time spent on treatment of participants was similar between studies that contributed to meta-analysis and those that did not. Data on BCG vaccination rate was limited.

Results of the study quality assessment are presented in *Figure 2*. Overall, the quality of studies included in the review was suboptimal and often insufficient detail was available to make a judgment about potential bias. The method of patient recruitment was unclear in most studies (46/47 [97.8%]). The blinding of test interpretation to other test results and to knowledge of clinical risk factors was also predominately unclear (20/47 [42.6%] and 45/48 [95.7%] respectively). Risk factor assessment and test procedures were generally described in sufficient detail to repeat the studies (30/47 [63.8%] and 41/47 [87.2%] respectively). The clinical risk assessment was considered comprehensive in 37/47 studies (78.7%). Few studies reported unexplainable indeterminate results or participant withdrawals. Study quality was poor but not different across studies that contributed to meta-analysis and those that did not; see *Supplementary Figure 1* for quality assessment of only studies that contributed to meta-analysis.

Association of test positivity with clinical risk factors

Overall, positive tests for latent TB as measured by QFT, TSPOT.TB and TST were significantly associated with a medical history of TB infection (QFT; OR 6.01 [95%CI 2.66-13.56, p=0.001], TSPOT.TB; OR 5.02 [95%CI 2.13-11.87, p=0.001], TST; OR 1.95 [95%CI 1.17-3.23, p=0.01]). A positive QFT test was strongly associated with radiological evidence of TB infection (OR 2.97 [95%CI 1.30-6.82, p=0.01]) and contact with a case of active TB (OR 3.52 [95%CI 1.69-7.31, p=0.001]). In contrast, there was insufficient evidence to determine the direction of association of a

13

positive TST with radiological evidence of TB infection (OR 0.79 [95%CI 0.9-3.25, p=0.7]) or contact with (OR 0.88 [95%CI 0.43-1.82, p=0.7]). The direction of association of a positive TSPOT.TB with radiological evidence of TB infection and contact with a case of active TB was also unclear (OR 1.88 [95%CI 0.43-8.22. p=0.4] and OR 1.42 [95%CI 0.80-2.52, p=0.2] respectively). There was insufficient evidence to determine the direction of association of test positivity with high-risk nationality, immunosuppression and BCG vaccination for all tests, see *Supplementary Figures 2-7*. Comparing studies that blinded test interpretation to information about clinical risk factors to those that did not or were unclear, we found no significant differences in association of test positivity for radiological evidence of TB, medical evidence of TB, contact with active TB, immunosuppression or nationality (p>0.5). The OR for the association of TST positivity with BCG vaccination was significantly higher in unblinded studies (2.04 [95%CI 1.18-3.53]) compared to blinded studies (0.63 [95%CI 0.27-1.46]), p=0.05. A significant difference was also found in the association of a positive TST with immunosuppression when studies were stratified by modality of ESKD treatment. The summary OR was higher in studies of dialysis patients (OR 1.38 [95%CI 0.98-1.94]) than transplant and mixed populations (OR 0.38 [95%CI 0.22-0.67]), p=0.004. There were no significant differences for other risk factors when studies were stratified by modality of ESKD treatment (p>0.1). Our findings also remained unchanged when we compared studies using a TST cut-off of 5mm versus 10mm (p>0.1) and studies that used second versus third generation QFT tests (p>0.4).

Relative association of QFT, TSPOT.TB and TST test positivity with clinical risk factors

Figures 3-5 show the direct comparison between IGRAs and TST for association of test positivity with clinical risk factors. From the findings of six studies, compared to a positive TST, a positive QFT test was more strongly associated with radiological evidence of past TB (ROR 4.29 [95%CI 1.83-10.03, p=0.001]) and contact history with active TB (ROR 3.36 [95%CI 1.61-7.01, p=0.001]) (*Figure 3*). Conversely, a positive QFT test was less strongly associated with BCG vaccination

14

compared to a positive TST (ROR 0.30 [95%CI 0.14-0.63, p=0.002]) (*Figure 3*). There was no evidence of a difference of association of test positivity with high-risk nationality (ROR 2.25 [95%CI 0.53-9.61, p=0.3]) or medical history of TB (ROR 2.68 [95%CI 0.97-7.43, p=0.06]) between the QFT and TST. Data from six studies comparing the performance of the TSPOT.TB and TST tests showed there was no evidence of a difference between the association of a positive TSPOT.TB or TST result for any of the risk factors (*Figure 4*).

Four studies compared the QFT and TSPOT.TB tests directly. One study reported a positive TSPOT.TB to be more strongly associated with radiological evidence of past TB than a positive QFT (ROR 0.11 [95%CI 0.02-0.77, p=0.03]). No evidence of a difference was found for any of the other risk factors, see *Figure 5*. These results were robust to heterogeneity in TST cut-off (p>0.3), QFT test generation (p>0.5) and modality of ESKD treatment (p>0.3).

Comparisons of other tests for latent TB

Two studies evaluated flow cytometry, one evaluated both ESAT-6 and TuberkulinGT-100 as stimulating antigens and the other evaluated only ESAT-6[38,39]. All transplant recipients were assumed to be immunosuppressed. There was no significant association between flow cytometry positivity (using TuberkulinGT-100 or ESAT-6 as the stimulating agent) and immunosuppression (OR 1.36 [95%CI 0.08-22.13, p=0.8] and OR 0.43 [95%CI 0.01-22.46, p=0.7] respectively), see *Supplementary Figure 6.* In one study TST was also evaluated, however no difference in association with immunosuppression was found between flow cytometry (using either ESAT-6 or TuberkulinGT-100) and TST (ROR 4.58 [95%CI 0.09-244.796, p=0.5] and ROR 1.80 [95%CI 0.033-98.112, p=0.8] respectively). Two studies evaluated antibody detection kits. In one study both the Mycodot and Determiner test positivity were significantly associated with radiological evidence of past TB (OR 3.47 [95%CI 1.33-9.07, p=0.01] and OR 2.18 [95%CI 1.04-4.59, p=0.04] respectively). The other study, which evaluated Mycodot only, showed no significant association of test positivity with BCG vaccination (OR 0.44 [95%CI 0.01-22.61, p=0.7]).

Discussion

Screening for latent TB in the ESKD population allows treatment to be targeted at persons with the highest risk of active TB and who will benefit most from prophylaxis. The key finding of this review is that compared to the TST, QFT test positivity was more strongly associated with clinical risk factors for latent TB, whilst less strongly associated with prior BCG vaccination. This suggests that QFT is both more sensitive and specific than the TST in the context of ESKD. Global guidelines for latent TB screening in immunocompromised populations currently recommend using an IGRA as a supplementary or replacement test to the TST[11]. The results of this review support the replacement of the TST with the QFT. Not enough data was available on the relative performance of TSPOT.TB with the TST, or TSPOT.TB with QFT to make any conclusions about the TSPOT.TB test.

The data analysed in the present study was largely restricted to the dialysis population (3700/4546 [81.4%]). Whilst this may be considered a limitation, the performance of tests for latent TB in the dialysis population is most clinically relevant because assessment for latent TB generally occurs prior to commencing dialysis or during clinical evaluation leading up to kidney transplantation[61].

Compared to both the TST and TSPOT.TB tests the QFT assay demonstrated the strongest overall association with clinical risk for latent TB, including radiological evidence of past TB (OR 2.97, *Supplementary Figure 2,* medical evidence of past TB (OR 6.01, *Supplementary Figure 3)* and contact with a person with active TB (OR 3.52, *Supplementary Figure 4)*. Data was less conclusive for the utility of the TSPOT.TB test, although positive results from this assay were associated with a medical evidence of past TB (OR 5.02, *Supplementary Figure 3*). We found no association between nationality and test positivity for any of the tests, however in these analyses data was limited to studies conducted in countries with low to moderate TB burden. The clinical value of IGRAs for detecting latent TB in different patient populations in high prevalence regions warrants study.

Studies that met the inclusion criteria but did not provide sufficient data to contribute to meta-analysis represent a potential source of bias in this review. These studies accounted for 36.2% (17/47) of included studies and 33.4% (2282/6828) of all participants. Due to missing data on study design and patient characteristics it was not possible to formally compare differences between studies that contributed to meta-analysis and those that did not, see *Table 1* and *Supplementary Table 4.* The available data suggest that patient characteristics within the dialysis and transplant populations are similar between studies that contributed to meta-analysis and those that did not, but there appear to be proportionately more transplant recipients in the studies that did not contribute to meta-analysis.

Another key finding of the present study is that based on best available evidence, the preferred IGRA for diagnosing latent TB is the QFT assay, even though comparison of either the QFT or TSPOT-TB assays with the TST and each other was limited by the small number of evaluable studies (n=<10 for each comparison; *Figure 3-5*). Data from six studies indicate that compared to the TST, QFT positivity was more strongly associated with clinical risk factors for latent TB, whilst comparing TSPOT.TB and TST no statistical differences were observed in ROR for any clinical risk factors [32,34-36,56,57]. Only a single study out of four comparing the performance of TSPOT.TB and QFT in ESKD showed that the former was more strongly associated with radiological evidence of past TB than the QFT assay[35].

Although the utility of assays other than the QFT, TST and TSPOT.TB have been studied in the context of diagnosing of latent TB, neither serological detection of antibody to *M. tuberculosis* or flow cytometry studies have been shown to be clinically useful and sensitivity analyses have been limited by the small number of reports[10,38,39,54,55]. Based on present available data, these assays cannot be recommended for assisting in the diagnosis of latent TB.

Systematic reviews are the preferred format for summarising evidence because they use explicit and reproducible methods to limit bias. We acknowledge that the validation of test results against

clinical risk factors has several limitations. Whilst this approach allows us to make inferences about the accuracy of tests in relative terms, it does not allow us to calculate absolute measures of test accuracy. To derive test accuracy characteristics, previous reviews in the general population have overcome the lack of a reference standard by using active TB and low risk individuals as surrogates for positive and negative latent TB status[19-21]. This method is dubious because active and latent TB are distinct disease states that elicit different responses from the host immune system and therefore it may be inappropriate to use active TB as an immunological model for latent TB[1,62]. Several studies have shown that responses to the TST and IGRAs diminish during untreated active TB infection, but rapidly increase after treatment, suggesting active TB may suppress the host immune response to these tests[63-66].

Another limitation of this review is that the implications of our results rely on the assumption that a high proportion of people with clinical risk factors for latent TB actually have latent TB. Although this assumption is difficult to prove, given the lack of a reference standard for latent TB, there is evidence that active TB is more likely to develop in dialysis patients with old TB on chest X-ray or immunosuppressive diseases including diabetes mellitus and HIV infection[67]. Risk factors for the transmission of latent TB may also be inaccurate and difficult to quantify and therefore a potential source of heterogeneity between studies[22]. For example, the studies included in this review assessed contact with active TB as a dichotomous risk factor only, whereas from epidemiological studies we know that the likelihood of transmission is determined by both time and proximity to a person with active TB[22]. Assessing nationality as a dichotomous risk factor is similarly problematic, because it assumes that all individuals from a country with high TB burden have the same risk of transmission, whereas in reality transmission requires and interplay of several factors, including socioeconomic status, time spent in the country and where that time was spent in the country.

Future research in this area should pursue three directions. Firstly, this review demonstrated a gap in evidence on the relative test performance of the QFT and TSPOT.TB. More studies are required

to assess the relative performance of these tests in the ESKD population. Secondly, a study assessing the active TB rate in patients after test directed treatment would be helpful to derive the relative clinical value of the TST, QFT and TSPOT.TB. Thirdly, a cost-effectiveness evaluation is needed to determine whether the reduction in false positive and negative results that occurs when QFT replaces the TST is worth the trade-off in any cost increase that may also occur.

In conclusion, we determined that compared to the TST, the QFT positivity was more strongly associated with risk factors for latent TB in ESKD and is therefore likely to be a more accurate diagnostic tool for latent TB in ESKD. This finding is consistent with previous systematic reviews conducted in the general population which showed that IGRA results correlate better with the intensity of TB exposure compared to the TST whilst remaining independent of BCG vaccination status[22], and that IGRAs are more sensitive and specific and thus the preferred tests[19-21]. On the basis of best available evidence, we propose that the QFT assay should be the test of choice for screening for latent TB, and a review clinical practice guidelines for managing latent TB in the ESKD population is warranted.

References

1.   Mack U, Migliori GB, Sester M, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. *Eur Respir J.* 2009;33(5):956-973.

2.   Cengiz K. Increased incidence of tuberculosis in patients undergoing hemodialysis. *Nephron.* 1996;73(3):421-424.

3.   Hussein MM, Mooij JM, Roujouleh H. Tuberculosis and chronic renal disease. *Semin Dial.* 2003;16(1):38-44.

4.   Dobler CC, McDonald SP, Marks GB. Risk of tuberculosis in dialysis patients: a nationwide cohort study. *PLoS ONE.* 2011;6(12):e29563.

5.   Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. *N Engl J Med.* 2002;347(23):1860-1866.

6.   Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med.* 2003;167(4):603-662.

7.   Sousa M, Pozniak A, Boffito M. Pharmacokinetics and pharmacodynamics of drug interactions involving rifampicin, rifabutin and antimalarial drugs. *J Antimicrob Chemother.* 2008;62(5):872-878.

8.   Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin : clinical relevance. *Clin Pharmacokinet.* 2003;42(9):819-850.

9.   Thompson NP, Caplin ME, Hamilton MI, et al. Anti-tuberculosis medication and the liver: dangers and recommendations in management. *Eur Respir J.* 1995;8(8):1384-1388.

10.   Sester M, Sester U, Clauer P, et al. Tuberculin skin testing underestimates a high prevalence of latent tuberculosis infection in hemodialysis patients. *Kidney Int.* 2004;65(5):1826-1834.

11.   Segall L, Covic A. Diagnosis of tuberculosis in dialysis patients: current strategy. *Clin J Am Soc Nephrol.* 2010;5(6):1114-1122.

12. Denkinger CM, Dheda K, Pai M. Guidelines on interferon-gamma release assays for tuberculosis infection: concordance, discordance or confusion? *Clin Microbiol Infect.* 2011;17(6):806-814.

13. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR.* 2010;59(RR-5):1-25.

14. Canadian Tuberculosis Committee. Updated recommendations on interferon gamma release assays for latent tuberculosis infection. An Advisory Committee Statement (ACS). *Canada Communicable Disease Report.* 2008;34(ACS-6):1-13.

15. National Institute for Health and Clinical Excellence. 2011. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. CG117. London: National Institute for Health and Clinical Excellence.

16. British Thoracic Society Standards of Care C, Joint Tuberculosis C, Milburn H, et al. Guidelines for the prevention and management of Mycobacterium tuberculosis infection and disease in adult patients with chronic kidney disease. *Thorax.* 2010;65(6):557-570.

17. Health Protection Agency. 2007. Health Protection Agency position statement on the use of Interferon Gamma Release Assay (IGRA) tests for tuberculosis (TB). London: Health Protection Agency.

18. Swiss Lung Association. 2011. Tuberculosis in Switzerland. Berne: Swiss Lung Association.

19. Pai M, Riley LW, Colford JM, Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. *Lancet Infect Dis.* 2004;4(12):761-776.

20. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med.* 2008;149(3):177-184.

21. Chang KC, Leung CC. Systematic review of interferon-gamma release assays in tuberculosis: focus on likelihood ratios. *Thorax.* 2010;65(3):271-276.

22. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess.* 2007;11(3):1-196.

23. Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol.* 2003;3:25.

24. Agresti A. *An introduction to categorical data analysis*. New York, United States of America: Wiley; 1996.

25. World Health Organization. 2010. WHO report 2010: Global Tuberculosis Control. Geneva: World Health Organization.

26. Linquist JA, Rosaia CM, Riemer B, Heckman K, Alvarez F. Tuberculosis exposure of patients and staff in an outpatient hemodialysis unit. *American Journal of Infection Control.* 2002;30(5):307-310.

27. Hickstein L, McPherson C, Kwalick D, et al. Tuberculosis transmission in a renal dialysis center--Nevada, 2003. *MMWR.* 2004;53(37):873-875.

28. Inoue T, Nakamura T, Katsuma A, et al. The value of QuantiFERON TB-Gold in the diagnosis of tuberculosis among dialysis patients. *Nephrol Dial Transplant.* 2009;24(7):2252-2257.

29. Lee SSJ, Chou KJ, Dou HY, et al. High prevalence of latent tuberculosis infection in dialysis patients using the interferon- release assay and tuberculin skin test. *Clinical Journal of the American Society of Nephrology.* 2010;5(8):1451-1457.

30. Lee S, Y. C, Su I, et al. High Prevalence of Latent Tuberculosis Infection in End-Stage Renal Disease Patients on Hemodialysis Using QuantiFERON-GOLD In-Tube Test and Tuberculin Skin Test. Paper presented at: The 49th Interscience Conference on Antimicrobial Chemotherapy; Sept 12-15, 2009 San Francisco, CA.

31. Seyhan EC, Sokucu S, Altin S, et al. Comparison of the QuantiFERON-TB Gold In-Tube test with the tuberculin skin test for detecting latent tuberculosis infection in hemodialysis patients. *Transplant Infectious Disease.* 2010;12(2):98-105.

32. Kim SH, Lee SO, Park IA, et al. Diagnostic usefulness of a T cell-based assay for latent tuberculosis infection in kidney transplant candidates before transplantation. *Transplant Infectious Disease.* 2010;12(2):113-119.

33. Kim S, Lee S, Park I, et al. A Prospective Longitudinal Study of Usefulness of a T Cell-Based Assay for Latent Tuberculosis Infection (LTBI) in Renal Transplant Recipients. Paper presented at: The 48th Meeting of the Infectious Diseases Society of America; Oct 21-24, 2010 Vacouver, BC.

34. Chung WK, Zheng ZL, Kim H-S, et al. Serial testing of interferon-gamma-release assays for the diagnosis of latent tuberculosis in hemodialysis patients. *J Infect.* 2010;61(2):144-149.

35. Triverio P-A, Bridevaux P-O, Roux-Lombard P, et al. Interferon-gamma release assays versus tuberculin skin testing for detection of latent tuberculosis in chronic haemodialysis patients. *Nephrol Dial Transplant.* 2009;24(6):1952-1956.

36. Lee SSJ, Chou KJ, Su IJ, et al. High prevalence of latent tuberculosis infection in patients in end-stage renal disease on hemodialysis: Comparison of QuantiFERON-TB GOLD, ELISPOT, and tuberculin skin test. *Infection.* 2009;37(2):96-102.

37. Lee S, Ni Y, Huang T, et al. QuantiFERON-TB GOLD for Diagnosis of Latent Tuberculosis Infection in Patients with End-Stage Renal Disease in Taiwan. Paper presented at: The 46th Interscience Conference on Antimicrobial Chemotherapy; Sept 27-30, 2006; San Francisco, CA.

38. Eleftheriadis T, Tsiaga P, Antoniadi G, et al. The value of serum antilipoarabinomannan antibody detection in the diagnosis of latent tuberculosis in hemodialysis patients. *American Journal of Kidney Diseases.* 2005;46(4):706-712.

39. Yanai M, Uehara Y, Takeuchi M, et al. Evaluation of serological diagnosis tests for tuberculosis in hemodialysis patients. *Therapeutic Apheresis & Dialysis.* 2006;10(3):278-281.

40. Wauters A, Peetermans WE, Van den Brande P, et al. The value of tuberculin skin testing in haemodialysis patients. *Nephrol Dial Transplant.* 2004;19(2):433-438.

41. Shankar MSR, Aravindan AN, Sohal PM, et al. The prevalence of tuberculin sensitivity and anergy in chronic renal failure in an endemic area: tuberculin test and the risk of post-transplant tuberculosis. *Nephrol Dial Transplant.* 2005;20(12):2720-2724.

42. Fang HC, Chou KJ, Chen CL, et al. Tuberculin skin test and anergy in dialysis patients of a tuberculosis-endemic area. *Nephron.* 2002;91(4):682-687.

43. Yildiz A, Akkaya V, Turk S, Sever MS, Ark E, Yildiz P. Tuberculin responsiveness in hemodialysis patients. *Chest.* 1998;114(3):947-948.

44. Yildiz A, Sever MS, Yildiz P, et al. Tuberculin (PPD) reactivity in hemodiaylsis patients (HDp). *Nephrology DialysisTransplant.* 1997 12(9):A148.

45. Ates G, Yildiz T, Danis R, et al. Incidence of tuberculosis disease and latent tuberculosis infection in patients with end stage renal disease in an endemic region. *Ren Fail.* 2010;32(1):91-95.

46. Ates G, Ozekinci T, Yildiz A, Danis R. Comparison of interferon-gamma release assay versus tuberculin skin test for latent tuberculosis screening in hemodialysis patients. *Biotechnology & Biotechnological Equipment.* 2009;23(2):1242-1246.

47. Habesoglu MA, Torun D, Demiroglu YZ, et al. Value of the tuberculin skin test in screening for tuberculosis in dialysis patients. *Transplant Proc.* 2007;39(4):883-886.

48. Taskapan H, Oymak O, Utas C. Tuberculin and anergy testing in CAPD patients. *Peritoneal Dialysis International.* 2000;20(6):807-809.

49. Dogan E, Erkoc R, Sayarlioglu H, Uzun K. Tuberculin skin test results and the booster phenomenon in two-step tuberculin skin testing in hemodialysis patients. *Ren Fail.* 2005;27(4):425-428.

50. Cengiz K, Seker A. Boosted tuberculin skin testing in hemodialysis patients. *American Journal of Infection Control.* 2006;34(6):383-387.

51. Woeltje KF, Mathew A, Rothstein M, Seiler S, Fraser VJ. Tuberculosis infection and anergy in hemodialysis patients. *American Journal of Kidney Diseases.* 1998;31(5):848-852.

52. Smirnoff M, Patt C, Seckler B, Adler JJ. Tuberculin and anergy skin testing of patients receiving long-term hemodialysis. *Chest.* 1998;113(1):25-27.

53. Poduval RD, Hammes MS. Tuberculosis screening in dialysis patients - Is the tuberculin test effective? *Clinical Nephrology.* 2003;59(6):436-440.

54. Sester U, Junker H, Hodapp T, et al. Improved efficiency in detecting cellular immunity towards M. tuberculosis in patients receiving immunosuppressive drug therapy. *Nephrol Dial Transplant.* 2006;21(11):3258-3268.

55. Sester U, Wilkens H, Van Bentum K, et al. Impaired detection of Mycobacterium tuberculosis immunity in patients using high levels of immunosuppressive drugs. *Eur Respir J.* 2009;34(3):702-710.

56. Passalent L, Khan K, Richardson R, Wang J, Dedier H, Gardam M. Detecting latent tuberculosis infection in hemodialysis patients: a head-to-head comparison of the T-SPOT.TB test, tuberculin skin test, and an expert physician panel. *Clin J Am Soc Nephrol.* 2007;2(1):68-73.

57. Winthrop KL, Nyendak M, Calvet H, et al. Interferon-gamma release assays for diagnosing mycobacterium tuberculosis infection in renal dialysis patients. *Clin J Am Soc Nephrol.* 2008;3(5):1357-1363.

58. Kantarci G, Altinoz H, Sahin S, Manga G, Tasan G. Tuberculin positivity: A serious problem before transplantation in Turkey. *Transplant Proc.* 2006;38(2):646-648.

59. Aydogan O, Gurgun A, Basoglu OK, et al. [Tuberculin skin test reactivity in patients with chronic renal failure]. *Tuberkuloz ve Toraks.* 2009;57(3):268-276.

60. Basoglu OK, Atasever A, Gunduz Telli C, et al. [T-lymphocyte subgroups and tuberculin skin test reactivity in patients with chronic renal failure]. *Tuberkuloz ve Toraks.* 2006;54(1):5-10.

61. Mycobacterium tuberculosis. *Am J Transplant.* 2004;4:37-41. doi: 10.1111/j.1600-6135.2004.00724.x

62. Rothel JS, Radford AJ. Comparison of tuberculosis tests: finding truth or confirming prejudice? *Clin Infect Dis.* 2003;36(9):1206-1207.

63. Pathan AA, Wilkinson KA, Klenerman P, et al. Direct ex vivo analysis of antigen-specific IFN-gamma-secreting CD4 T cells in Mycobacterium tuberculosis-infected individuals: associations with clinical disease state and effect of treatment. *J Immunol.* 2001;167(9):5217-5225.

64. Shams H, Wizel B, Weis SE, Samten B, Barnes PF. Contribution of CD8(+) T cells to gamma interferon production in human tuberculosis. *Infect Immun.* 2001;69(5):3497-3501.

65. Rooney JJ, Jr., Crocco JA, Kramer S, Lyons HA. Further observations on tuberculin reactions in active tuberculosis. *Am J Med.* 1976;60(4):517-522.

66. Hirsch CS, Toossi Z, Othieno C, et al. Depressed T-cell interferon-gamma responses in pulmonary tuberculosis: analysis of underlying mechanisms and modulation with therapy. *J Infect Dis.* 1999;180(6):2069-2073.

67. Christopoulos AI, Diamantopoulos AA, Dimopoulos PA, Goumenos DS, Barbalias GA. Risk factors for tuberculosis in dialysis patients: a prospective multi-center clinical trial. *BMC Nephrol.* 2009;10:36.

Figure 1: Results of literature search for studies reporting test performance and risk factor assessment for latent TB in people with end stage kidney disease
*TST = Tuberculin skin test, QFT = QuantiFERON
†See *Supplementary Table 4* for study details

Figure 2: Methodological quality of studies included in review

QUADAS 1: Generalisability of test results to ESKD population (spectrum bias), QUADAS 2: Participant selection method adequate (selection bias), QUADAS 3: Comprehensive risk factor assessment (verification bias), QUADAS 4: Acceptable delay between testing and risk factor assessment (disease progression bias), QUADAS 5: All patients had all tests (partial verification bias), QUADAS 6: All patients had the same tests (differential verification bias), QUADAS 7: Risk factor assessment independent from tests (incorporation bias), QUADAS 8: Tests described in sufficient detail to repeat (repeatability), QUADAS 9: Risk factor assessment described in sufficient detail to repeat (repeatability), QUADAS 10: Tests interpretation conducted without knowledge other test results(blinding), QUADAS 11: Risk factor assessment conducted without knowledge of test results (blinding), QUADAS 12: Normal clinical information available during risk factor assessment and test interpretation (information bias), QUADAS 13: Reasons for indeterminate results provided, QUADAS 14: Reasons for withdrawals provided (intention to treat bias), * See *supplementary figure 1* for quality of studies contributing to meta-analysis

Figure 3: TST versus QFT: relative association of a positive test with risk factors for latent TB

Figure 4: TST versus TSPOT.TB: relative association of a positive test with risk factors for latent TB

Figure 5: TSPOT.TB versus QFT: relative association of a positive test with risk factors for latent TB

Appendices

Supplementary figure 1: Methodological quality of studies contributing to meta-analysis
White: Low risk (good quality), Black: high risk (poor quality): Grey: unclear, QUADAS 1: Generalisability of test results to ESKD population (spectrum bias), QUADAS 2: Participant selection method adequate (selection bias), QUADAS 3: Comprehensive risk factor assessment (verification bias), QUADAS 4: Acceptable delay between testing and risk factor assessment (disease progression bias), QUADAS 5: All patients had all tests (partial verification bias), QUADAS 6: All patients had the same tests (differential verification bias), QUADAS 7: Risk factor assessment independent from tests (incorporation bias), QUADAS 8: Tests described in sufficient detail to repeat (repeatability), QUADAS 9: Risk factor assessment described in sufficient detail to repeat (repeatability), QUADAS 10: Tests interpretation conducted without knowledge other test results(blinding), QUADAS 11: Risk factor assessment conducted without knowledge of test results (blinding), QUADAS 12: Normal clinical information available during risk factor assessment and test interpretation (information bias), QUADAS 13: Reasons for indeterminate results provided, QUADAS 14: Reasons for withdrawals provided (intention to treat bias)

Supplementary figure 2: Association of test positivity with radiological evidence of past TB

Supplementary figure 3: Association of test positivity with medical evidence of past TB

Supplementary figure 4: Association of test positivity with active TB contact

Supplementary figure 5: Association of test positivity with BCG vaccination

Supplementary figure 6: Association of test positivity with immunosuppression

Supplementary figure 7: Association of test positivity with high-risk nationality

Supplementary table 1: Electronic search strategy for MEDLINE and EMBASE (06/10/2010)

Supplementary table 2: Standard definitions of risk factors

Supplementary table 3: QUADAS working definitions