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

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Current guidelines advocate screening hemodialysis patients for latent tuberculosis infection; however, the tuberculin skin test (TST) is believed to be insensitive in this population. This study compared the diagnostic utility of the TST with that of an IFN-γ assay (T-SPOT.*TB*) and the clinical consensus of an expert physician panel. A total of 203 patients with ESRD were evaluated for latent tuberculosis infection with the TST, T-SPOT.*TB* test, and an expert physician panel. Test results were compared with respect to their association with established tuberculosis risk factors. Tuberculosis infection, as estimated by the tuberculin test, T-SPOT.*TB* test, and expert physician panel, was detected in 12.8%, 35.5, and 26.1 of patients respectively. Among patients with a history of active tuberculosis and radiographic markers of previous infection, 78.6 and 72.7% had positive T.SPOT.*TB* results, compared with 21.4 and 18.2% who had positive tuberculin tests. The physician panel unanimously declared infection in these two groups. On multivariate analysis, a positive T-SPOT.*TB* test was associated with a history of active tuberculosis, radiographic markers of previous infection, and birth in an endemic country, whereas a physician panel diagnosis also was associated with a history of previous tuberculosis contact. The TST is insensitive in hemodialysis patients and is not recommended to be used in isolation to diagnose latent tuberculosis infection. It is suggested that a combination of T-SPOT.*TB* testing and medical assessment may be the most accurate screening method.

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Since its development more than a century ago, the tuberculin skin test (TST) has become the most widely used test to diagnose latent tuberculosis infection (LTBI). In immunocompetent individuals, the TST is highly sensitive (1); however, in immunocompromised populations, sensitivity declines in parallel with decreasing cellular immune system function. Ironically, immunocompromised patients who are at elevated risk for reactivation of LTBI are encouraged to undergo screening with the TST (2).

Patients who have chronic renal failure and receive hemodialysis are an example of a population that typically manifests cutaneous anergy to skin test antigens yet are at high risk for developing active tuberculosis (TB) (3–6). These patients have roughly a 10- to 25-fold increased risk for reactivating LTBI when compared with the general population (7–9). Moreover, hemodialysis units themselves have been shown to be important centers for the spread of infectious TB (10). Different strategies to improve the sensitivity of the TST in this population have been advocated including two-step tuberculin skin testing, however this likely increases test sensitivity at the expense of specificity (11). Antigen panels have been used in an attempt to identify false negative results, however this technique has been abandoned in other immunocompromised populations due to the phenomenon of selective anergy, inconsistent results, and poor predictive value for the subsequent development of active TB (12,13).

A more sensitive screening test would be of great value in detecting LTBI in patients with ESRD or other immunocompromised states. The latest generation of IFN-γ assays such as the T-SPOT.*TB* (Oxford Immunotec, Oxford, UK) and QuantiFERON TB-Gold tests (Cellestis, Melbourne, Australia) have shown considerable promise in diagnosing LTBI in immunocompetent individuals, largely through improved specificity when compared with the TST (14–18). However, published data assessing the utility of these tests in immunocompromised populations remains limited. Given that IFN-γ–based assays also require intact cellular immune function, it has been suggested that immunologic anergy also may be their "Achilles heel," as it is for the TST (19).

In practice, when clinicians assess anergic patients for LTBI, they must consider information other than TST results, such as chest radiographic findings and historical risk factors for TB infection. Although imperfect, assessing the probability of LTBI on a case-by-case basis represents the current clinical practice

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standard when TST results are unreliable. Herein, we conducted a head-to-head analysis that compared the diagnostic utility of the T-SPOT.*TB* test, the TST, and an expert panel of physicians in identifying LTBI in a population of hemodialysis patients.

Materials and Methods

Participants

Study participants were hemodialysis patients who were recruited prospectively from the outpatient hemodialysis unit at the Toronto General Hospital site of the University Health Network (UHN). All patients who attended this unit between January 15 and April 15, 2005, were considered eligible for entry into the study, provided that they did not exhibit signs or symptoms of active TB. Of 286 eligible patients, a total of 203 (71.0%) consented and participated in an epidemiologic survey and underwent tuberculin skin testing, T-SPOT.*TB* testing, and chest radiography. The UHN research ethics board approved the study.

T-SPOT.TB *Testing*

All participants underwent T-SPOT.*TB* testing in accordance with the manufacturer's instructions. In brief, two 8-ml blood samples were obtained from patients during a hemodialysis session. The blood samples were centrifuged to enable the quantification of peripheral blood mononuclear cells before incubating them with ESAT-6 and CFP-10 antigens in an enzyme-linked immunosorbent spot assay. For 14 patients who had indeterminate test results upon initial T-SPOT.*TB* testing, four consented to retesting, three of whom had measurable results. T-SPOT.*TB* testing was performed at the UHN Infection Prevention and Control Research Laboratory by a trained medical laboratory technologist. The assays were read manually by a technologist who was blinded to patient clinical information and test results.

Tuberculin Skin Testing

Tuberculin skin testing was performed by hemodialysis nursing staff who were trained by a nurse practitioner who specialized in the area of TB. Participants were administered the TST (5 IU PPD-S, Tubersol; Sanofi Pasteur, Toronto, ON, Canada) *via* intradermal injection on the volar aspect of the forearm contralateral to patient's vascular access. Tests were administered and interpreted as per existing national guidelines (1). Patients with <10 mm of induration on initial testing were administered a second TST 1 to 4 wk later to elicit a potential booster response. Results from two-step testing were used in all further analyses.

Epidemiologic Survey

An epidemiologic survey was administered to each participant by the study coordinator with the aid of an interpreter as needed. Survey questions focused on participants' country of birth, self-reported history of active TB, self-reported contact with an active case of TB, Bacille-Calmette-Guérin (BCG) vaccination status, and occupational history. Participants were defined as originating from a TB-endemic area when the annual incidence rate of active TB in their native country exceeded 20 cases per 100,000 people. Participants were considered recipients of the BCG vaccine when they self-reported a history of vaccination, whereas individuals who denied vaccination or were uncertain about their vaccination status were considered nonrecipients. Participants were defined as having a high-risk occupation when they were ever employed in a health care setting, a medical laboratory, a homeless shelter, or a refugee camp setting.

Chest Radiography

Chest radiography was requested of all participants who had not had a chest radiograph within 6 mo before study enrollment. For 33 participants who did not have recent films and refused chest radiography as part of the study protocol, the most current film available was used (range 7 to 27 mo before study enrollment). All radiograph reports were reviewed for findings consistent with previous TB infection, including upper lobe fibronodular disease, granulomata, calcified mediastinal lymph nodes, pleural thickening, and any other changes consistent with "prior granulomatous disease" or "prior tuberculosis," as stated in the radiologist's final report.

Expert Physician Panel

Five physicians who were experienced in the management of TB independently evaluated information from each participant's epidemiologic survey (country of birth, self-reported history of active TB, self-reported contact with an active case of TB, BCG vaccination status, and occupational history), in addition to results from participants' TST and chest radiograph. Each physician then was asked to integrate this information clinically and determine to the best of their ability whether the participant had ever been infected with *Mycobacterium tuberculosis*. Physicians were forced to provide a definitive answer and were blinded to the determinations of one another and T-SPOT.*TB* test results. The majority decision that was made by the physician panel (three or more in agreement) was used to determine whether participants were or were not infected with TB.

Statistical Analyses

The primary outcome of this study was defined by evidence of current or previous infection with *M. tuberculosis*. Results across the three primary modalities in the analysis (T-SPOT.*TB*, TST, and expert physician panel) were compared using the χ^2 test. Agreement among various diagnostic modalities was evaluated using the κ statistic. Agreement among the five-member expert physician panel was measured using the first-order agreement coefficient (AC1 statistic). Multivariate logistic regression analysis was used to determine which factors were associated with TB infection as determined by the T-SPOT.*TB*, TST, and expert physician panel. For each of the three multivariate regression models in our analysis, age, self-reported history of TB, and chest radiograph consistent with previous TB infection were forced into the final model on the basis of an *a priori* decision. All other variables were entered into the final multivariate model using stepwise selection. All analyses were performed using SAS (version 8.2; SAS Institute, Cary, NC).

Results

Of the 203 participants in our analysis, 72 (35.5%) had a positive T-SPOT.*TB* test and 19 (9.4%) had a positive TST on initial testing, with an additional seven positive tests upon two-step testing (12.8% of total). If a 5-mm threshold were used, then an additional 11 participants would have been deemed TST positive (18.2% of total). Of note, 159 (78.3%) of the 203 participants had 0 mm of induration on two-step testing, including three patients with evidence of fibronodular disease on chest radiograph. Overall, the expert panel affirmed that 53 (26.1%) participants had evidence of current or past infection with TB.

The first run of the T-SPOT.*TB* test produced 14 indeterminate results, and four patients consented to retesting. Of these, two were nonreactive (included in 131 nonreactive T-SPOT.*TB* results), one was reactive (included in the 72 reactive T-SPOT.*TB*

results), and one remained indeterminate (included in 11 invalid T-SPOT.*TB* results). Of the 11 remaining indeterminate results, one patient had 17 mm of induration on TST, two had 5 mm of induration, and the remainder had 0 mm of induration.

The proportion of positive results for each of the three primary outcomes of our analysis is shown in Figure 1. For participants for whom historical or clinical information was suggestive of current or past infection with TB (self-reported history of active TB, radiographic findings consistent with previous TB infection, and a TST of ≥10 mm induration), the T-SPOT.*TB* was positive in 78.6, 72.7, and 73.1% of cases, respectively. Conversely, the TST was positive in 21.4% of participants with a self-reported history of active TB and in 18.2% of participants with radiographic findings consistent with previous TB infection. Of note, the expert physician panel was unanimous in diagnosing TB infection among participants with a self-reported history of active TB, radiographic findings consistent with previous TB infection, or at least 10 mm of induration on TST. Interphysician agreement decreased, however, as the risk factors for TB infection became less compelling (see Figure 1).

Table 1 shows results from three logistic regression analyses. On multivariate analysis, a positive T-SPOT.*TB* was strongly associated with a self-reported history of active TB (odds ratio [OR] 7.24; 95% confidence interval [CI] 1.70 to 30.8; $P = 0.007$), chest radiograph findings consistent with previous TB infection (OR 5.48; 95% CI 1.20 to 25.1; $P = 0.03$), and birth in a TB-endemic country (OR 5.45; 95% CI 2.72 to 10.9; $P < 0.0001$). The only factor that was associated with a positive TST on multivariate analysis was previous vaccination with BCG (OR 2.90; 95% CI 1.22 to 6.92; $P = 0.02$). Because the expert physician panel was unanimous in diagnosing TB infection among participants with a history of TB, a suggestive chest radiograph, or a positive TST, these variables could not be included in a logistic regression model. In addition to these three variables,

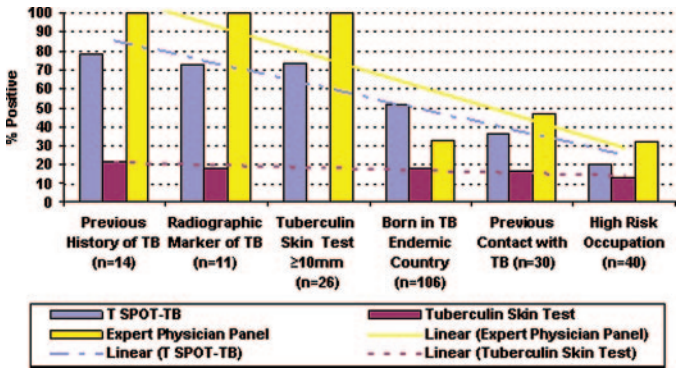

Figure 1. Diagnosis of current or previous tuberculosis (TB) infection by the T-SPOT.*TB* test, tuberculin skin test, and expert physician panel. Agreement among the five physicians in the expert panel was measured using the first-order agreement coefficient (AC1 statistic) for each of the six variables: History of TB (AC1 0.96), radiographic markers of TB (AC1 0.79), tuberculin skin test with at least 10 mm of induration (AC1 1.00), birth in a TB-endemic country (AC1 0.54), previous contact with TB (AC1 0.40), and high-risk occupation (AC1 0.61). All patients (AC1 0.67).

the expert physician panel's assessment of TB infection was associated with birth in a TB-endemic country (OR 2.64; 95% CI 1.31 to 5.29; $P = 0.007$) as well as self-reported history of contact with an active TB case (OR 3.81; 95% CI 1.63 to 8.92, $P = 0.002$).

Agreement between each of the three diagnostic modalities is shown in the Appendix. In particular, the level of agreement between the T-SPOT.*TB* test and the expert physician panel was relatively poor ($\kappa = 0.37$; 95% CI 0.24 to 0.50). Inspection of the discordant pairs revealed that the expert physician panel was positive in 18 patients when the T-SPOT.*TB* test was negative and was negative in 37 patients when the T-SPOT.*TB* test was positive.

Discussion

Our study compares three diagnostic modalities for current or previous TB infection in a population that generally is considered to be at high risk for cutaneous anergy. Consistent with past experience (3–6), we found that the TST was highly insensitive in our cohort of hemodialysis patients, missing nearly four of every five patients with compelling risk factors for TB infection (*e.g.*, those with a self-reported history of active TB or radiographic markers consistent with previous TB infection). Conversely, the T-SPOT.*TB* test was positive in approximately three of every four patients with the same risk factors. Therefore, if one assumes that these factors provide evidence of previous disease, then the sensitivity of the T SPOT.*TB* test in hemodialysis patients would be on the order of approximately 75%. In support of this assumption, our expert physician panel unanimously diagnosed TB infection in these patients. It is of interest to note that the percentage of positive results for both the T-SPOT.*TB* and the expert physician panel decline as the "strength" of the risk factors for TB infection decline (see Figure 1, trend lines). The results of the TST, however, varied minimally across all risk factors.

Given our inability to determine definitively which patients did *not* have TB infection, we were unable to estimate the specificity of each diagnostic modality. Previous studies have shown IFN-γ assays to be more specific than the TST (20). With respect to the expert panel, it is possible that they may have minimized false-negative results at the expense of false-positive results as the physicians were unanimous in diagnosing TB infection in patients with a positive TST. We know from previous studies, however, that previous vaccination with BCG and/or exposure to nontuberculous mycobacteria can be associated with false-positive results (21,22). This supposition is consistent with findings on multivariate analysis in which previous vaccination with BCG was the only factor that was significantly associated with a positive TST.

In situations in which only circumstantial evidence of TB infection was available (birth in a TB-endemic country, previous contact with an active TB case, and high-risk occupation), it remains unclear whether the judgment of the expert physician panel or the results from the T-SPOT.*TB* were more accurate. Our analysis demonstrates that physicians were more likely to declare patients with a contact history or high-risk occupation to have TB infection than the T-SPOT.*TB*. We believe that this finding is consistent with the risk-averse position that has been

Table 1. Logistic regression analysis: Factors associated with a positive T-SPOT.*TB* test, TST, and expert physician panel diagnosis of current or past tuberculosis infection[a]

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P*	OR (95% CI)	*P*
T-SPOT.*TB*[b]				
age (yr)	1.01 (0.99 to 1.03)	0.21	1.01 (0.99 to 1.03)	0.52
history of TB	7.69 (2.07 to 28.6)	0.002	7.24 (1.70 to 30.8)	0.007
radiographic markers of TB[c]	5.33 (1.37 to 20.8)	0.02	5.48 (1.20 to 25.1)	0.03
born in TB-endemic country[d]	5.08 (2.66 to 9.70)	<0.0001	5.45 (2.72 to 10.9)	<0.0001
previous contact with TB	1.06 (0.48 to 2.38)	0.88	—	—
high-risk occupation[e]	0.39 (0.17 to 0.89)	0.03	—	—
history of BCG vaccination	1.90 (1.05 to 3.42)	0.03	—	—
TST[b]				
age (yr)	0.99 (0.97 to 1.02)	0.75	0.99 (0.97 to 1.02)	0.59
history of TB	1.97 (0.51 to 7.56)	0.33	2.73 (0.65 to 11.5)	0.17
radiographic markers of TB[c]	1.56 (0.32 to 7.63)	0.59	1.21 (0.24 to 6.21)	0.82
born in TB-endemic country[d]	2.81 (1.12 to 7.01)	0.03	—	—
previous contact with TB	1.45 (0.50 to 4.19)	0.50	—	—
high-risk occupation[e]	0.97 (0.34 to 2.74)	0.95	—	—
history of BCG vaccination	2.59 (1.12 to 5.99)	0.03	2.90 (1.22 to 6.92)	0.02
Expert panel[f]				
age (yr)	1.00 (0.98 to 1.02)	0.78	1.00 (0.98 to 1.02)	0.98
born in TB-endemic country[d]	2.16 (1.13 to 4.16)	0.02	2.64 (1.31 to 5.29)	0.007
previous contact with TB	3.01 (1.35 to 6.70)	0.007	3.81 (1.63 to 8.92)	0.002
high-risk occupation[e]	1.48 (0.70 to 3.14)	0.31	—	—
history of BCG vaccination	1.73 (0.92 to 3.28)	0.09	—	—

[a]BCG, Bacille-Calmette-Guérin; CI, confidence interval; OR, odds ratio; TB, tuberculosis; TST, tuberculin skin test.
[b]Age, history of TB, and radiographic markers of TB were forced into the final multivariate model; other variables were entered or eliminated from using stepwise selection.
[c]Includes evidence of fibronodular disease, mediastinal calcifications, or pleural fibrosis or calcification.
[d]Refers to countries with an annual incidence rate exceeding 20 cases per 100,000 people.
[e]Defined as current or former occupation in health care, laboratory, homeless shelter, or refugee camp settings.
[e]History of TB and radiographic markers of TB were removed because of a lack of variability in these parameters (*i.e.*, physician panel always considered these individuals to have current or past TB infection).

adopted by physicians who may feel uncomfortable with discounting these "softer" risk factors. It is interesting that the physician panel was less likely to declare patients who originated from endemic countries to have TB infection than the T-SPOT.*TB*. Given the lack of an established gold standard for TB infection, however, resolving the discordance between these two diagnostic modalities remains problematic.

In our analysis, 5.1% of patients had indeterminate results. In theory, the T-SPOT.*TB* may be less prone to indeterminate results than the QuantiFERON Gold test because, as an enzyme-linked immunosorbent spot test, it requires the enumeration of T cells before measurement of IFN-γ release so that conditions that result in low T cell counts are controlled for (19). In a study that involved a head-to-head comparison of the T SPOT.*TB* test and the QuantiFERON Gold test, 11.2% of QuantiFERON test results were indeterminate compared with 3.1% with the T SPOT.*TB* test (23). However, immunosuppression was strongly associated with indeterminate results for each of the two commercially available assays (23). A relationship between indeterminate QuantiFERON test results and declining CD4 cell counts in a large HIV-infected cohort was reported recently (24). However, another study reported that the T-SPOT.*TB* test gave interpretable results in all HIV-infected patients with CD4 counts <200 cells/μl, although there were only 11 patients in this subgroup (25). We are unaware of studies that have examined the use of the QuantiFERON Gold test specifically in hemodialysis patients.

Our study has certain limitations that warrant discussion. Foremost, it suffers from the same problem as previous studies that have examined IFN-γ–based assays in LTBI: Namely, we were unable to determine definitively the sensitivity and the specificity of each diagnostic modality given the lack of an established gold standard. We were restricted by limitations in patient recall when conducting our epidemiologic survey. Also, our analysis incorporated "softer" epidemiologic risk factors such as any *lifetime* self-reported history of TB contact or any *lifetime* high-risk occupation. These variables are less stringent than parallel measures in studies of known TB outbreaks or people who were currently employed in high-risk settings, where IFN-γ–based assays have been shown previously to correlate highly with exposure risk (14,15,17,18,26). We chose to include these variables in our analysis because patients rarely

have conclusive historical or radiographic evidence of TB infection, yet the clinician is forced to make a definitive diagnosis.

Our data strongly support the notion that screening for LTBI in this patient population and potentially in other groups in which cutaneous anergy likely is present should not be performed using the TST alone. Although it generally is assumed that screening for LTBI should include a thorough assessment of epidemiologic risk factors for TB infection, it is our belief that this may not always occur. The recent report of TST-negative patients who developed active TB after receiving infliximab supports this belief: 11 of 12 patients who developed active TB had risk factors for infection, yet preinfliximab determination of these risk factors was elucidated in only three cases (27). In these patients, as with our population, anergy was believed to play an important role in causing false-negative TST (27). It is of interest to note that 6 mo after the completion of this study, one of our patients who was found to be positive by both the T-SPOT.*TB* and the expert physician panel yet negative on the TST developed reactivated multidrug-resistant TB.

Conclusion

We suggest that the TST should not be used to screen dialysis patients for LTBI without the accompaniment of medical assessment, because it is highly insensitive in detecting those who are at high risk for LTBI. Furthermore, because the TST has been shown in previous studies to be less specific than the T-SPOT.*TB*, we suggest that a combination of T-SPOT.*TB* testing and medical assessment may be the most accurate screening method.

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Appendix 1. Disagreement between the three diagnostic methods[a]

		Expert Physician Panel	
		Negative	Positive
T-SPOT.*TB* test	Negative	113	18
	Positive	37	35
		TST ≥10 mm	
T-SPOT.*TB* test		Negative	Positive
	Negative	124	7
	Positive	53	19
		TST ≥10 mm	
Expert physician panel		Negative	Positive
	Negative	150	0
	Positive	27	26

[a]T-SPOT.*TB versus* expert physician panel: $\kappa = 0.37$, 95% CI 0.24 to 0.50. T-SPOT.*TB versus* TST ≥10 mm: $\kappa = 0.25$, 95% CI 0.12 to 0.37). Expert physician panel *versus* TST ≥10 mm: $\kappa = 0.59$, 95% CI 0.46 to 0.72.

Disclosures

None.

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