Interferon-γ Release Assays for Diagnosing Mycobacterium tuberculosis Infection in Renal Dialysis Patients

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Background and objectives: End-stage renal disease (ESRD) patients are at high risk for tuberculosis (TB). IFN-γ release assays that assess immune responses to specific TB antigens offer potential advantages over tuberculin skin testing (TST) in screening such patients for Mycobacterium tuberculosis infection. This study sought to determine whether IFN-γ release assay results are more closely associated with recent TB exposure than TST results.

Design, setting, participants, and measures: Prospective cohort investigation of patients at a hemodialysis center with a smear-positive case of TB. Patients without a history of TB underwent initial and repeat testing with TST, and with the IFN-γ assays QuantiFERON-TB Gold® (QFT-G) and ELISPOT test. Outcome measures included the prevalence of positive test results, identification of factors associated with positive results, and test result discordance.

Results: A total of 100 (47% foreign born; median age, 55 yr; age range, 18 to 83 yr) of 124 eligible patients were enrolled. Twenty-six persons had positive TST results, 21 had positive QFT-G results, and 27 had positive ELISPOT results. Patients with TB case contact were likely to have a positive QFT-G result (P = 0.02) and ELISPOT results (P = 0.04), whereas TB case contact was not associated with positive TST results (P = 0.7). Positive TST results were associated with foreign birth (P = 0.04) and having had a TST in the previous year (P = 0.04).

Conclusions: Positive IFN-γ assay results were more closely associated with recent TB exposure than were positive TST results. QFT-G and ELISPOT might offer a better method for detecting TB infection in ESRD patients.


More than 300,000 persons in the United States with end-stage renal disease (ESRD) currently require renal replacement therapy (1). These patients are at increased risk for a variety of infections. The basis for their underlying immune dysfunction is not completely understood but thought to be mediated by uremia (2). Renal failure patients are at 8 to 25 times higher risk for tuberculosis (TB) than the general population (3–5). TB disease in these patients can be difficult to diagnose, as it is frequently extrapulmonary and insidious in onset (6). Recommendations for screening dialysis patients for latent Mycobacterium tuberculosis infection (LTBI) exist to decrease transmission of TB in this setting of highly susceptible patients (7).

Despite such recommendations, screening dialysis patients for latent TB infection can be difficult. Their underlying immune suppression raises the likelihood of false-negative TB skin test (TST) results and makes interpretation of negative results unreliable. Dialysis patients have been shown to have significant rates of cutaneous anergy to antigens, such as Candida, mumps, or tetanus (8,9). Furthermore, as in immunocompetent populations, the TST can be falsely positive in persons with a history of previous nontuberculous mycobacterium infection or vaccination with bacillus Calmette-Guerin (BCG) (10).

 Newly developed blood tests might offer improved ways of screening ESRD patients for LTBI. The QuantiFERON-TB Gold® test (QFT-G) measures production of IFN-γ by sensitized lymphocytes after whole blood is stimulated with specific TB antigens. It became commercially available in the United States following approval by the Federal Drug Administration in May 2005. The enzyme-linked immuno-spot assay (ELISPOT) is a diagnostic platform that enumerates the number of reactive T lymphocytes releasing IFN-γ in the presence of TB antigens. Both of these technologies can be used to assess immune response to Culture Filtrate Protein 10 (CFP-10) and Early Secretary Antigen 6 (ESAT-6). These antigens are encoded on the RD-1 portion of the M. tuberculosis genome, and are not found in BCG strains or most nontuberculous mycobacterium. Ac-
Accordingly, these tests are more specific for LTBI than the TST, which relies on purified protein derivative (11). To date, there has been limited evaluation of QFT-G and ELISPOT in screening immunosuppressed populations for TB, including those with ESKD.

In October 2003, we were notified of a TB case in a dialysis center in southern California. We evaluated patients at the dialysis center and assessed the utility of using the IFN-γ assays during a TB-contact investigation. We compared the results of IFN-γ assays and TST and identified factors associated with positive test results and test result discordance.

**Materials and Methods**

This study was part of a multisite study conducted by the U.S. Centers for Disease Control and Prevention (CDC) to evaluate new tests for LTBI. The study protocol was approved by the institutional review boards of CDC, California Department of Health Services, and other participating study sites.

For this investigation, we toured the dialysis center and interviewed patients and staff. We reviewed the TB case-patients’ charts for clinical details and dialysis history. Dialysis logs were reviewed for patients’ dialysis weekly schedules, seating arrangements, and history of TST results. The amount of daily dialysis time shared between the TB case-patient and each other patient was calculated in 15-min intervals in 1- and 3-mo periods before he was removed from the dialysis center. Overlapping time periods of less than 15 min were not counted. The patient had no pulmonary symptoms until developing a cough during the last week before his exit from the center. During that week he dialyzed daily (Monday through Friday). Before this week, and for the 3 mo before his exit, he dialyzed three times weekly (Monday/Wednesday/Friday). Accordingly, and a priori, we decided that any patient who shared dialysis time with him during his final and symptomatic week was a “contact.” These turned out to be patients who had a shared Monday/Wednesday/Friday dialysis schedule in the month before his departure, as well as patients with Tuesday/Thursday/Saturday schedules who dialyzed with him on the Tuesday and Thursday of his last week. All other patients were considered “noncontacts.”

The center had a large open floor divided in half by a 4-ft median, with dialysis stations positioned on either side (Figure 1). We also attempted to assess the infectious risk of TB case-patient contact with a trichotomyous exposure variable “proximity.” Noncontacts were considered “A”, contacts seated on the opposite side of the room as the case-patient were “B”, and contacts seated on the same side as the case-patient were “C.” There was one station on the case’s side of the room (Figure 1, bottom, right station on diagram) that was located farther away than the closest station on the other half of the room. Accordingly, this station was considered “B” for the purposes of this analysis. This variable was analyzed as a categorical variable in logistic regression. Similar proximity analysis using A (no contact), B (seated ≥15 ft from case), or C (seated ≤15 ft from case) produced similar results and is therefore not presented. Air flow in the facility was not assessed.

Patients had laboratory work performed monthly as part of their routine renal care. We collected patients’ most recent predialysis blood urea nitrogen, hemoglobin concentration, and serum creatinine and albumin levels (all labs had been drawn 1 to 3 d before enrollment).

We became aware of the situation nearly 10 wks after the TB case-patient was removed from the center. At 11 wks, we arrived at the center and asked all patients there to participate. Patients were excluded from the study if they had a documented history of a positive TST result ≥10 mm or a history of prior treatment for LTBI or TB disease. After obtaining consent, we drew 30 ml of blood before the subject was connected to the hemodialysis machine. Blood was transported to the Long Beach Public Health Laboratory (Long Beach, CA) at room temperature where QFT-G was performed and interpreted as described previously (12). For the ELISPOT assay, blood was collected in a BD Vacutainer CPT cell preparation tube with sodium citrate and centrifuged for 20 min according to the manufacturer’s instructions (BD Biosciences, Franklin Lakes, NJ) and shipped overnight to the laboratory in Portland, OR, where the peripheral blood mononuclear cells were prepared and cryopreserved for future analysis. ELISPOT was performed according to published methods (13,14). After venipuncture, patients underwent routine Mantoux TST with 0.1 ml (5 TU) of tuberculin purified protein derivative (Tubersol, Connaught Laboratories Limited, Toronto, Ontario, Canada). TSTs were read 48 to 72 h later by study personnel. Induration of ≥5 mm was considered a positive TST result. Positive QFT-G assay results were defined per QuantiFERON-GOLD® test-kit manufacturer’s instructions (15). Positive ELISPOT results were determined in the following fashion. First, to determine the frequency of antigen specific responses, 250,000 peripheral blood mononuclear cells were incubated with both ESAT-6 and CFP-10 antigens. These antigens were comprised of pooled peptides reflecting the entire gene. Each peptide pool was comprised of 15 amino acid peptides, and each peptide overlapped by an 11-amino acid segment with the adjacent peptide (5 μg/peptide per ml; Genemed Synthesis, South San Francisco, CA). Controls included media (nil) and phytohemagglutinin 10 μg/ml (Sigma-Aldrich, St. Louis, MO). All determinations were performed in duplicate. For the ELISPOT assay, spots were counted by an automated ELISPOT reader (Zeiss). Lab personnel were blinded to clinical and epidemiologic data. For a response to be considered evaluable, the mean number of spots (reactive lymphocytes) had to be 3 SD greater than the media control well. If evaluable, then the response of the media control well was subtracted from the antigen specific response. A result greater than 10 spots was considered positive.

To assess the reproducibility of the blood tests, we returned at 16 wk after exposure to draw more blood for QFT-G and ELISPOT. TST was also repeated at this time if the initial TST response was <5 mm. Consistent with the principles of TB contact investigation, patients were...
defined as “TST positive” if they had positive TST results on either initial or repeat assessment. Similarly, persons with a positive result on either the initial or repeat blood testing were considered “positive” by IFN-γ assay.

All data were entered into Epi-Info (version 3.4.1, CDC, Atlanta, GA). Univariate logistic regression was used to assess the association of various patient characteristics with the outcome of skin or blood test results. Multivariate models were constructed using variables that, in univariate analysis, were associated with a test result with a \( P \leq 0.20 \). Because of significant differences in age between contacts and noncontacts, age was included in all multivariate models. Stepwise backward logistic regression was then performed using Fisher exact \( P \) values (\( P \) values ≤0.05 were considered statistically significant).

**Results**

The index patient was a 64-yr-old foreign-born man. In the month before his diagnosis, he routinely dialyzed on a Monday/Wednesday/Friday schedule in the first of three shifts (5 a.m. to 9 a.m.) offered on those days (there were 4 daily shifts on Tuesday and Thursday). Approximately 1 mo before TB diagnosis, he developed ascites. One week before his TB diagnosis, he developed a productive cough. Because of worsening ascites, he attended dialysis every day (Monday through Friday) in the last week before being removed from the center, admitted to the hospital, and diagnosed with TB disease. At that time, his sputum was smear-positive for acid-fast bacilli. His chest radiograph showed pleural effusion and parenchymal infiltrate. *M. tuberculosis* was isolated from sputum and from peritoneal fluid. The isolate was sensitive to all first-line anti-tuberculosis drugs tested.

We attempted to enroll all dialysis patients from the first three 4-h dialysis shifts (5 a.m. to 9 a.m., 9 a.m. to 1 p.m., 1 p.m. to 5 p.m.) of each day (\( n = 124 \)), and 100 were enrolled. Twelve declined and 12 were excluded because of prior positive TST results or previous LTBI treatment. During our statistical analysis, 6 additional patients were excluded from QFT-G analysis because of improper blood specimen labeling (\( n = 4 \)), or indeterminate results (\( n = 2 \)). Three patients were excluded from ELISPOT analysis for having only indeterminate ELISPOT results. The total number of patients with evaluable results for each test were: TST (\( n = 100 \)), QFT-G (\( n = 94 \)), and ELISPOT (\( n = 97 \)). The median age of patients was 55 yr (range, 18 to 90 yr), 47 (47%) were born outside the United States or Canada, and 55 (55%) were male. The most common countries of origin for foreign-born patients were: Mexico (\( n = 19 \)), Philippines (\( n = 12 \)), and Cambodia (\( n = 5 \)). Seven were from American Samoa. Fifty-eight (58%) patients were considered contacts. In the month before his diagnosis, contacts had an average of 18 h of exposure (range, 1 to 52 h) to the case, whereas noncontacts had less than 0.5 h of exposure (range, 0 to 6 h) and no contact during the index case’s symptomatic week. Contacts were similar to noncontacts with regard to sex and foreign birth, but they were significantly younger than noncontacts (Table 1).

**TST**

Twenty-six persons (26%) were positive by TST, of whom 24 had induration ≥10 mm. Six persons with negative TST results on initial assessment became positive on repeat testing, three of whom were contacts. Among foreign-born persons, 11 (36%) contacts had positive results compared with 7 (44%) noncontacts. Among U.S.-born, 5 (19%) contacts had positive results compared with 3 (12%) noncontacts. In univariate analysis, persons with a positive TST result were likely to be foreign-born (\( P = 0.01 \)) and to have had a TST performed in the prior year (\( P = 0.02 \)). Neither age nor TB case-patient contact was associated with a positive TST result. In multivariate analysis, both foreign birth (\( P = 0.04 \)) and a recent previous TST (\( P = 0.04 \)) remained significantly associated with a positive TST result (Table 2).

**QFT-G Assay**

Twenty-one (22%) persons were positive by QFT-G assay. Four persons with negative results on initial assessment became positive on repeat testing; all were contacts. An equal number of patients (\( n = 4 \)) with positive initial results reverted

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**Table 1. Baseline characteristics of dialysis patients**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Contacts (( n = 58 ))</th>
<th>Noncontacts (( n = 42 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [median (range)]</td>
<td>52 (18-83)</td>
<td>60 (19-90)</td>
<td>0.04</td>
</tr>
<tr>
<td>Male sex, no. (%)</td>
<td>33 (57)</td>
<td>22 (53)</td>
<td>0.99</td>
</tr>
<tr>
<td>Foreign birth, no. (%)</td>
<td>31 (53)</td>
<td>16 (38)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

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**Table 2. Risk factors for positive TST results among dialysis patients**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. (%) of Subjects With Positive TST Result</th>
<th>OR (95% CI)(^a)</th>
<th>( P )(^a)</th>
<th>Adjusted ( P )(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin</td>
<td>18/47 (38)</td>
<td>2.4 (0.7–8.5)</td>
<td>0.19</td>
<td>NA</td>
</tr>
<tr>
<td>Foreign birth</td>
<td>16/58 (28)</td>
<td>3.5 (1.3–9.1)</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Contact</td>
<td>10/59 (17)</td>
<td>2.0 (0.5–5.9)</td>
<td>0.67</td>
<td>NA</td>
</tr>
<tr>
<td>Age</td>
<td>—</td>
<td>1.0 (0.98–1.03)</td>
<td>0.91</td>
<td>NA</td>
</tr>
<tr>
<td>Recent TST(^c)</td>
<td>20/58 (35)</td>
<td>3.8 (1.3–11.2)</td>
<td>0.02</td>
<td>0.04</td>
</tr>
</tbody>
</table>

\(^a\)From univariate analysis.

\(^b\)From a multivariate model incorporating all univariate risk factors with \( P \) values ≤0.20 and age; only foreign birth and recent TST remain statistically significant.

\(^c\)TST performed previously in the study year.
to negative on repeat testing, two of whom were contacts. In univariate analysis, a positive result was most closely associated with foreign birth \((P = 0.07)\), increasing age \((P = 0.05)\), and TB case-patient contact \((P = 0.07)\). Among foreign-born persons, 10 (32%) contacts had positive results compared with 4 (27%) noncontacts. Among U.S.-born, 6 (25%) contacts had positive results compared with 1 (4%) of noncontacts. In multivariate analysis, patients with a positive QFT-G result were significantly more likely to be TB case-patient contacts \((P = 0.02)\) and to be older \((P = 0.01)\) as compared with patients with negative results (Table 3).

**ELISPOT Assay**

Twenty-seven (28%) persons were positive by ELISPOT assay. Six persons with negative results on initial assessment became positive on repeat testing, 4 of whom were contacts. Eight patients with positive initial results reverted to negative on repeat testing, 6 of whom were contacts. In univariate analysis, a positive result was significantly associated only with TB case-patient contact \((P = 0.05)\). Among foreign-born persons, 13 (42%) contacts had a positive result compared with 1 (4%) of noncontacts. Among U.S.-born patients, 7 (28%) contacts had a positive result compared with 3 (12%) noncontacts. Unlike QFT-G, positive results were not associated with increasing age. In multivariate analysis controlling for age, foreign birth, and other factors, patients with a positive ELISPOT result were significantly more likely to have TB case-patient contact than those with negative results \((P = 0.04)\). (Table 4)

**Results Considering Proximity of Exposure**

Substituting the variable “proximity” into a multivariate model in place of the variable “TB case-contact” did not change final model results. Compared with noncontacts, dialysis patients sitting closer to the TB case were more likely to have a positive QFT-G result \((\text{OR} = 5.4; 95\% \text{ CI}, 1.2 \text{ to } 24.3; \text{ adjusted } P = 0.03)\), whereas a trend was noted for those contacts sitting less closely to the case \((\text{OR} = 3.5; 95\% \text{ CI}, 0.94 \text{ to } 13.3; \text{ adjusted } P = 0.06)\). As compared with noncontacts, more proximal contacts were likely to have positive ELISPOT results \((\text{OR} = 4.9; 95\% \text{ CI}, 1.4 \text{ to } 16.6; \text{ adjusted } P = 0.01)\), whereas less proximal contacts did not \((\text{OR} = 1.8; 95\% \text{ CI}, 0.6 \text{ to } 5.4; \text{ adjusted } P = 0.29)\). For TST results, in multivariate analysis, neither contacts sitting closely \((\text{OR} = 2.6; 95\% \text{ CI}, 0.7 \text{ to } 9.1; \text{ adjusted } P = 0.14)\), nor those sitting farther away \((\text{OR} = 0.5; 95\% \text{ CI}, 0.2 \text{ to } 1.7 \text{ from the case, } P = 0.27)\), were more likely to have positive test results.

**Test Concordance and Reproducibility**

The reproducibility (concordance) of the QFT-G assay between initial and repeat testing was 85% \((\text{kappa} = 0.57; 95\% \text{ CI}, 0.37 \text{ to } 0.78)\). Reproducibility with ELISPOT was similar with concordance of 83% \((\text{kappa} = 0.61; 95\% \text{ CI}, 0.45 \text{ to } 0.77)\). Concordance between results from different testing methodologies

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**Table 3. Risk factors for positive QFT-G results among dialysis patients**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. (%) of Subjects With Positive QFT-G Result</th>
<th>OR (95% CI)(^a)</th>
<th>(P^b)</th>
<th>Adjusted (P^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin</td>
<td>14/46 (30)</td>
<td>1.8 (0.5–6.9)</td>
<td>0.40</td>
<td>NA</td>
</tr>
<tr>
<td>Foreign birth</td>
<td>16/55 (29)</td>
<td>2.6 (0.9–7.1)</td>
<td>0.07</td>
<td>NA</td>
</tr>
<tr>
<td>Contact</td>
<td>14/53 (26)</td>
<td>2.8 (0.9–8.4)</td>
<td>0.07</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>—</td>
<td>1.03 (0.99–1.07)</td>
<td>0.05</td>
<td>0.01</td>
</tr>
<tr>
<td>Recent TST(^c)</td>
<td></td>
<td>2.0 (0.7–5.9)</td>
<td>0.19</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable as variable was not included in final model.
\(^a\)From univariate analysis.
\(^b\)From multivariate model incorporating all univariate risk factors with \(P\) values \(\leq 0.20\); only TB case-contact remains statistically significant.
\(^c\)TST performed previously in the study year.

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**Table 4. Risk factors for positive ELISPOT results among dialysis patients**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. (%) of Subjects With Positive ELISPOT Result</th>
<th>OR (95% CI)(^a)</th>
<th>(P^b)</th>
<th>Adjusted (P^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin</td>
<td>17/47 (36)</td>
<td>2.2 (0.6–7.5)</td>
<td>0.24</td>
<td>NA</td>
</tr>
<tr>
<td>Foreign birth</td>
<td>20/56 (36)</td>
<td>2.3 (0.9–5.6)</td>
<td>0.08</td>
<td>NA</td>
</tr>
<tr>
<td>Contact</td>
<td>20/56 (36)</td>
<td>2.7 (1.0–7.2)</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Age</td>
<td>—</td>
<td>1.00 (0.98–1.03)</td>
<td>0.86</td>
<td>NA</td>
</tr>
<tr>
<td>Recent TST(^c)</td>
<td></td>
<td>1.9 (0.7–4.9)</td>
<td>0.19</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable as variable was not included in final model.
\(^a\)From univariate analysis.
\(^b\)From multivariate model incorporating all univariate risk factors with \(P\) values \(\leq 0.20\); only TB case-contact remains statistically significant.
\(^c\)TST performed previously in the study year.
ranged from 71% (TST versus ELISPOT) to 79% (TST versus QFT-G), to 87% (QFT-G versus ELISPOT results).

Univariate analysis of TST-positive/QFT-G-negative discordant test subjects revealed a trend for these persons (n = 12) to be foreign born (OR = 3.1; 95% CI, 0.8 to 11.4; P = 0.09) compared with persons who were negative by both TST and QFT-G assay. No other factors were found to be associated with this discordant outcome. Conversely, there were 8 test subjects with TST-negative/QFT-G-positive assay results. Relationships between this discordant outcome with other variables were also explored in univariate and multivariate fashion. When compared with those testing negative by both methodologies, in a multivariate model using exact methods, these persons were significantly more likely to have had TB case-patient contact (OR = 15.6; 95% CI, 1.2 to 195.3, adjusted P = 0.03) and to be older (OR for each year of increased age = 1.09; 95% CI, 1.01 to 1.17; adjusted P = 0.02).

Similar discordance analyses were performed for those persons with discordant TST and ELISPOT results. Patients with TST-positive/ELISPOT-negative discordant results, compared with patients who tested negative by both methodologies, were more likely to have had a recent TST performed (OR = 3.4; 95% CI, 0.9 to 13.9; P = 0.08), although this association did not reach statistical significance. Conversely, 15 persons had TST-negative/ELISPOT-positive results, and in univariate analysis, no patient characteristics were found to be closely associated with this outcome.

**Contact Follow-up**

All persons with positive TST results (n = 26) were advised to obtain chest radiographs. One patient was reported to have a radiograph consistent with TB disease. He was symptomatic with cough, underwent sputum evaluation, and was diagnosed with *Mycobacterium avium*. Although radiographs from a handful of other patients were reportedly negative, we were unable to systematically obtain radiograph reports or follow-up these results. At 24 mo after the investigation, both the dialysis center and the local health authority reported no further TB cases involving dialysis center patients.

**Discussion**

We compared two whole-blood based IFN-γ assays with tuberculin skin testing in ESRD patients during a TB contact investigation at a hemodialysis center. A high percentage of persons were found to be positive regardless of the test used. IFN-γ assay, but not TST, results was correlated with contact to the TB case-patient in the facility. Similar results from both of these assays suggested the possibility of TB transmission between the TB case-patient and contacts. Our data suggested that TST results were influenced by “boosting” and that TST might not be as useful as IFN-γ assays in evaluating hemodialysis patients with recent exposure to TB.

QFT-G and ELISPOT results were most closely associated with TB case-contact. Results were similar when we analyzed the risk of positive tests results according to proximity of seating between contacts and the case-patient. These associations between positive test results and TB case-patient contact were independent of other TB risk factors and suggested the possibility that TB transmission occurred in the dialysis facility. Conversely, analysis of TST results did not suggest TB transmission. A possible explanation for this finding is that the IFN-γ assays are more sensitive and/or specific for recent TB infection than the TST in this study population.

Previous studies have suggested high rates of anergy to TST among ESRD patients (8,9). This is the first study, to our knowledge, that has assessed the ability of IFN-γ assays to detect recent TB infection in renal dialysis patients. Without a gold standard for TB infection, it is impossible to determine which test is more accurate and less influenced by the immune suppression of ESRD. Interestingly, individuals in our study with a positive QFT-G assay result and negative TST result were significantly more likely to be TB case-patient contacts than those persons with discordant negative test results. One possible explanation is that the QFT-G assay might be more sensitive in detecting recent infection in this population. Such improved sensitivity could be the result of a number of factors, including the possibility that in vitro testing of IFN-γ response is less affected by uremic immune suppression or malnutrition than in vivo assessment with the TST. This has been shown previously with immune responses to purified protein derivative (PPD). Sester et al. (16) compared ESRD patient immune response to PPD using both in vivo (the TST) and in vitro methods (flow-cytometric quantification of PPD-specific reactive T cells). They found that a large percentage of persons who had reactive in vitro assays lacked positive TST results, suggesting a high rate of cutaneous anergy to the TST in their dialysis population (16). Furthermore, several studies in immunocompetent persons suggest that blood-based IFN-γ assays using certain RD-1 antigens are better correlated with recent TB exposure than TST, and therefore, possibly more sensitive in detecting recent TB infection (17,18).

The use of highly specific antigens for *M. tuberculosis* in the IFN-γ assays provides the theoretical basis for a more specific test for LTBI compared with the PPD-based TST. This has been suggested in a number of studies of immunocompetent subjects using the same QFT-G assay used in our study (11,19–21) and similar RD-1 antigens in an ELISPOT platform (16,22). Only one published study compared TST with either the QFT-G or T-SPOT (a commercialized ELISPOT assay) in ESRD patients. In that study, there was no defined TB exposure, so they were limited in their ability to assess which test result was more likely to represent TB infection (23). Although limited by low study numbers, our analysis of patients with discordant TST and QFT-G results supports the possibility that TST was less specific for detecting recent TB infection in the dialysis center. Persons with positive TST and negative QFT-G results were more likely (although not quite statistically significant) to have been foreign born than those with discordant negative TST and QFT-G results. In some of these persons, BCG vaccination might have caused false-positive TST results. BCG has been shown to strongly influence TST results up to 10 mm of induration in patients older than 40 yr (10). In previous studies comparing INF-γ assay and TST results, similar discordance has been associated with previous BCG vaccination or non-tu-
berculous mycobacterium exposure (11). Although we attempted to collect BCG vaccination histories from the patients in this study, because of language barriers, old age, recall bias, and other medical comorbidities, most patients were not able to tell us if they had been vaccinated before.

Finally, logistical issues might favor the use of an IFN-γ assay in evaluating ESRD patients for TB infection. Many ESRD patients have distorted forearm architecture and skin atrophy due to disease, medical interventions (graft or shunt placement), and age. Placing and reading a TST can be challenging in these conditions. On the contrary, obtaining blood specimens is easy given the permanent vascular access in such patients. Furthermore, IFN-γ assays have obvious advantages over the TST: they can be performed in a single patient visit, they eliminate the technical difficulties with placement of a TST and the subjectivity involved in interpreting the TST, and there is no “boosting” of the immune system like that which can take place with repeated TST assessments. In our study, boosting was suggested by the fact that persons with positive TST results were more likely to have had recent previous tuberculin skin testing. No such association was observed for those with positive IFN-γ assay results.

Our data suggest that IFN-γ assays are useful in the detection of latent TB infection among renal dialysis patients. Our experience suggests they might be more sensitive and specific than the time-honored TST in diagnosing recent latent TB infection. Our study is the first to assess this technology in ESRD patients recently exposed to TB, and further studies should be undertaken. Our findings suggest that clinicians could consider using IFN-γ assays instead of TST to screen renal dialysis patients for TB infection.

Acknowledgments

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Disclosures

None.

References


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