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ORIGINAL ARTICLE

Detection and Management of Latent Tuberculosis in Liver Transplant Patients

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The optimal means for detecting and managing liver transplantation (LT) patients with latent tuberculosis (TB) are not well defined. Our study aims were to (1) determine the frequency and risk factors of latent TB in a large cohort of consecutive adult LT candidates and (2) determine the safety and efficacy of isoniazid treatment in LT recipients with latent TB. A review of patients assessed for latent TB by skin testing using purified protein derivative (PPD; January 2004 to September 2008) or with the interferon-γ release assay QuantiFERON-TB Gold (QFT; March 2008 to October 2009) was undertaken. The baseline clinical features and outcomes of subjects with latent TB and subjects without latent TB were compared. Twenty-five of 420 subjects (6.0%) were positive for PPD. In comparison, 11 of 119 subjects (9.2%) had a positive QFT assay, and 15 others (13%) had indeterminate results. Both PPD-positive and QFT-positive subjects were less likely to be Caucasian than subjects without latent TB ($p < 0.001$). The 3-year survival rate of the 25 LT recipients with latent TB was similar to that of the 296 LT recipients without latent TB (78.7% versus 74.6%, $P = 0.58$). Fifteen of the 25 latent TB patients received isoniazid at a mean of 0.67 months after LT. Although isoniazid was discontinued in 8 subjects because of possible side effects, none of the 25 latent TB patients developed TB reactivation after transplantation with a mean follow-up of 33 months. In conclusion, both QFT testing and PPD testing demonstrate similar rates of detecting latent TB infection in American LT candidates, but QFT testing also leads to a moderate rate of indeterminate test results. Early isoniazid chemoprophylaxis after LT is poorly tolerated and is frequently discontinued. ***Liver Transpl 17:306-314, 2011.*** © **2011 AASLD.**

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Nearly one-third of the world's population has been previously infected with *Mycobacterium tuberculosis* (MTB).[1] Because immunosuppression can lead to severe and life-threatening tuberculosis (TB) reactivation for solid organ transplant recipients, the identification of patients with latent TB is recommended before transplantation.[2] This recommendation is graded as level III on the basis of expert opinion and descriptive epidemiology.[2] However, there currently is no gold standard for diagnosing latent TB infection; detection is based on a patient's medical history, tuberculin skin testing using purified protein derivative (PPD), interferon-γ release assays, and chest X-ray findings. The sensitivity of PPD testing in transplant candidates is suboptimal because of the high rate of false-negative results in sick patients with anergy.[3] Currently, there are several interferon-γ release assays that are approved for the detection of the proliferative response of peripheral lymphocytes to specific MTB antigens.[4,5] All these assays, including the QuantiFERON-TB Gold (QFT) assay (Cellestis, Victoria, Australia), have sensitivity comparable to that of PPD testing. However, by distinguishing positive skin test results due to a previous Bacille Calmette-Guerin (BCG) vaccination or an infection with atypical mycobacteria from those due to a previous MTB infection, these assays have potentially improved specificity.[6,7] Although QFT testing for latent TB is positive in 0% to 3% of low-risk patient populations, the utility of QFT testing versus traditional PPD testing for latent TB in immunocompromised liver transplantation (LT) candidates is not well described.[7-11] The primary aim

Abbreviations: BCG, Bacille Calmette-Guerin; CFP-10, culture filtrate protein 10; CI, confidence interval; ESAT-6, early secreted antigenic target 6; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MTB, *Mycobacterium tuberculosis*; ND, not determined; NR, not reported; PPD, purified protein derivative; QFT, QuantiFERON-TB Gold; TB, tuberculosis.

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of our study was to determine the incidence, risk factors, and outcomes for consecutive adult LT candidates with or without latent TB as determined by PPD and QFT screening tests. Our secondary aim was to determine the safety and efficacy of isoniazid chemoprophylaxis in LT recipients with latent TB infection.

PATIENTS AND METHODS

Patient Population

A retrospective review of consecutive adult patients who were listed for LT between January 2004 and October 2009 at the University of Michigan and underwent testing for latent TB infection was undertaken. The medical records of these patients were searched after institutional review board approval was obtained for the following data fields: date of listing; age at listing; gender; ethnicity; liver diagnosis (eg, hepatitis C or alcohol); Model for End-Stage Liver Disease (MELD) score at listing; laboratory data at listing (including INR, bilirubin, creatinine, and white blood cell count); date of transplant, pretransplant death, or last available follow-up; results of pretransplant TB testing (PPD or QFT); preoperative chest imaging results; previous history of TB therapy; and history of BCG vaccination. In addition, recognized clinical risk factors for latent TB infection, including occupational exposure, residence in a high-prevalence country, and a history of imprisonment or known exposure to active MTB, were sought.[12]

For those with positive latent TB test results, the following data were also extracted: country of origin; dates and dosing of isoniazid therapy (total number of days); frequency and reasons for dose reduction; and serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin levels before, during, and after isoniazid treatment. In addition, immunosuppressive therapy while the patient was receiving isoniazid, evidence of TB reactivation, and survival after transplantation were determined. Immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisone initially and was tapered to tacrolimus monotherapy by 12 months whenever possible and particularly in patients with viral hepatitis. Basiliximab (Simulect, Genentech, Nutley, NJ) induction with a delay in tacrolimus use for 3 to 5 days was used in subjects with renal failure at the time of transplantation

Testing for Latent TB

A positive TB skin test result is defined as an induration of 5 mm or more in diameter 48 to 72 hours after the administration of 5 tuberculin units of intradermal PPD. The PPD test was administered at the initial evaluation appointment and before placement on the LT waiting list. The PPD test was interpreted by nursing staff or a physician either at the transplant center or locally, and results were reported as positive or negative. Repeat testing to assess for boosting was not routinely performed. *Candida* skin testing for anergy was not completed per the guidelines of the Centers for Disease Control and Prevention.[13] QFT testing (Cellestis, Valencia, CA) was performed at the University of Michigan Hospital laboratory; the results were reported as positive, indeterminate, or negative. This enzyme-linked immunosorbent assay evaluates the interferon-γ response of peripheral lymphocytes to 2 MTB-specific antigens: early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10).[14] The test consists of a negative control (a nil well: whole blood without antigens or mitogen), a positive control (a mitogen well: whole blood stimulated with the mitogen phytohemagglutinin), and 2 sample wells (whole blood stimulated with either ESAT-6 or CFP-10). The response to phytohemagglutinin is used as a positive control, and the test is considered positive if the concentration of interferon-γ in the sample, after stimulation with ESAT-6 and CFP-10, is greater than or equal to 0.35 IU/mL (regardless of the result of the positive control). The result of the test is considered indeterminate if both antigen-stimulated samples are negative and if the value of the positive control is less than 0.5 IU/mL.

Evidence of latent TB infection was defined as either a positive PPD skin test or a positive QFT test result. The absence of latent TB was defined as a PPD result <5 mm in maximal diameter or a QFT test that was negative. If subjects had an indeterminate QFT test, the results of all available follow-up studies, including the medical history, chest imaging, and PPD test results, were reviewed.

Treatment Protocol for Latent TB

Our treatment protocol for LT recipients with latent TB includes isoniazid (300 mg/day) and pyridoxine (50 mg/day). Treatment is to be initiated in the first year after transplantation once the patient is clinically stable, and the intended duration is 6 months with monthly laboratory monitoring and assessment for clinical symptoms of potential hepatotoxicity.

Statistical Analysis

Descriptive statistics of baseline clinical features were determined for subjects with or without evidence of latent TB. Kaplan-Meier survival curve analysis was undertaken to determine pretransplant survival censored at the time of LT or pretransplant death in latent TB–positive LT candidates versus latent TB–negative LT candidates. Kaplan-Meier survival curve analysis was also undertaken to determine posttransplant survival in latent TB–positive LT recipients versus latent TB–negative LT recipients. Baseline characteristics associated with posttransplant survival were determined with Cox regression analyses. All data analyses were performed with SPSS 10.0 (SPSS, College Station, TX)

TABLE 1. Baseline Characteristics of the 420 Adult LT Candidates Undergoing PPD Testing

Feature	PPD-Positive (n = 25)	PPD-Negative (n = 395)	*P* Value*
Age (years)	52.0 ± 6.6	52.5 ± 8.8	0.76
Male [n (%)]	14 (56)	243 (61)	0.58
Ethnicity [n (%)]			
Caucasian	14 (56)	331 (84)	0.00042
African American	6 (24)	25 (6.3)	0.0011
Asian American	1 (4)	6 (1.5)	0.35
Hispanic	3 (12)	15 (3.8)	0.049
Other	1 (4)	18 (4.5)	0.90
White blood count (1000 cells/mL)	5.3 ± 2.7	5.8 ± 3.4	0.70
Country of origin [n (%)]			
United States	23 (92)	381 (96.5)	0.26
Other	2 (8)	14 (3.5)	
Liver diagnosis [n (%)]			
Hepatitis C	15 (60)*	152 (38)	0.03
Alcohol	6 (24)	81 (21)	0.74
Primary sclerosing cholangitis	1 (4)	39 (9.9)	0.33
Hepatitis B	1 (4)	9 (2.3)	0.58
Cryptogenic	0 (0)	54 (13.7)	0.048
Other	2 (8)	60 (15.2)	0.33
Hepatocellular cancer [n (%)]	8 (32.0)	70 (17.7)	0.065
Laboratory MELD score at listing	15.8 ± 6.4	16.4 ± 6.6	0.68
Wait-list outcomes during follow-up [n (%)]			
Underwent transplantation	19 (76)	245 (62)	0.067
Died before LT	0 (0)	61 (15)	0.034
Still waiting	6 (24)	89 (23)	0.86
Mean follow-up before LT (months)	11 ± 18.7	12.3 ± 16.9	0.78

NOTE: Data are reported as numbers and percentages or means and standard deviations.
*PPD-positive versus PPD-negative.

RESULTS

Patient Population

From January 2004 to September 2008, 420 adult patients who were listed for LT underwent PPD testing; they represented more than 98% of the subjects listed for LT during that time. In March 2008, QFT testing became available and was implemented as the preferred test. The QFT test results from March 2008 to October 2009 for 119 adult LT candidates were available for review; they represented more than 99% of the patients listed during that time.

PPD Test Results

Of the 420 adult LT candidates undergoing PPD testing, 25 (6.0%) had a positive PPD result, and 395 (94.0%) had a negative result (Table 1). The mean age of the 25 PPD-positive patients was 52.0 ± 6.6 years; 14 (56%) were male; and there were 14 Caucasians (56%), 6 African Americans (24%), 3 Hispanics (12%), and 1 Asian American (4%). The primary liver diagnoses included hepatitis C (60%), alcohol (24%), and various other diagnoses (16%); 8 patients (32.0%) had hepatocellular carcinoma; and the mean MELD score at listing was 15.8 ± 6.4. During a mean follow-up of 41 months, 19 (76%) proceeded to LT, and 6 (24%) were still awaiting transplantation. The mean ages, percentages of males, MELD scores at listing, and proportions undergoing transplantation were similar for the PPD-positive subjects and the PPD-negative subjects. However, the PPD-positive subjects were significantly more likely to be non-Caucasian (44% versus 16.1%, $P = 0.00042$). Finally, the PPD-positive patients were significantly more likely to have hepatitis C versus the PPD-negative group (60% versus 38%, $P = 0.03$) and significantly less likely to have cryptogenic cirrhosis (0% versus 13.7%, $P = 0.048$).

Clinical risk factors for TB infection were identified during a retrospective chart review in only 6 (24%) of the PPD-positive patients, including 3 patients with a history of close personal contact with a known active TB patient, 2 patients with overseas military service in an endemic area, and 1 patient with a history of occupational exposure as a health care worker. In addition, only 2 (8%) of the PPD-positive patients had radiographic evidence of latent TB infection. None of the PPD-positive patients had been treated for active TB in the past, and 3 had received a course of isoniazid chemoprophylaxis.

QFT Test Results

From March 2008 to October 2009, 11 (9.2%) of the 119 tested LT candidates had a positive QFT result, 15 (12.6%) had an indeterminate result, and 93

TABLE 2. Baseline Characteristics of the 119 Adult LT Candidates Undergoing QFT Testing

Feature	QFT-Positive (n = 11)	QFT-Negative (n = 93)	QFT-Indeterminate (n = 15)	*P* Value*
Age (years)	54.0 ± 11.1	53.6 ± 8.4	45.6 ± 10.3	0.90
Male [n (%)]	7 (63.6)	59 (63.4)	5 (33.3)	0.84
Ethnicity [n (%)]				
Caucasian	4 (36.4)	74 (79.6)	9 (60.0)	0.00041
African American	3 (27.3)	8 (8.6)	3 (20.0)	0.057
Asian American	2 (18.2)	2 (2.2)	0 (0)	0.0086
Hispanic	1 (9.1)	2 (2.2)	2 (13.3)	<0.05
Other	1 (9.1)	7 (7.5)	1 (6.7)	0.85
White blood count (1000 cells/mL)	5.7 ± 2.3	5.9 ± 2.8	6.3 ± 2.4	0.13
Country of origin [n (%)]				
United States	10 (91)	88 (94.7)	15 (100)	0.63
Other	1 (9)	5 (5.3)	0 (0)	
Liver diagnosis [n (%)]				
Hepatitis C	4 (36.4)	35 (37.6)	1 (6.7)	0.82
Alcohol	2 (18.2)	20 (21.5)	1 (6.7)	0.74
Primary sclerosing cholangitis	0 (0)	5 (1.1)	3 (20.0)	0.43
Hepatitis B	1 (9.1)	3 (3.2)	1 (6.7)	0.34
Cryptogenic	3 (27.3)	10 (10.8)	5 (33.3)	0.16
Other	1 (9.1)	20 (21.5)	4 (26.7)	0.33
Hepatocellular cancer [n (%)]	1 (9.1)	18 (19.4)	2 (13.3)	0.36
Lab MELD score at listing	12.1 ± 4.6	15.9 ± 6.8	20.7 ± 10.8	0.078
Wait-list outcomes during follow-up [n (%)]				
Underwent transplantation	4 (36)	42 (45)	11 (73)	0.58
Died before LT	1 (9)	10 (11)	0 (0)	0.87
Still waiting	6 (55)	41 (44)	4 (27)	0.51
Mean follow-up before LT (months)	5.04 ± 6.18	4.16 ± 2.18	3.84 ± 5.4	0.54

NOTE: Data are reported as numbers and percentages or means and standard deviations.
*QFT-positive versus QFT-negative.

(78.2%) had a negative result (Table 2). Although the proportion with positive QFT test results was higher than that seen with PPD testing, this trend was not significant (9.2% versus 6.0%, $P = 0.204$). The mean age of the 11 QFT-positive patients was 54.0 ± 11.1 years; 7 (63.6%) were male; and there were 4 Caucasians (36.4%), 2 Asian Americans (18.2%), 3 African Americans (27.3%), and 1 Hispanic patient (9.1%). The primary liver diagnoses included hepatitis C (36.4%), cryptogenic cirrhosis (27.3%), alcohol (18.2%), and hepatitis B (9.1%), and only 1 patient (9.1%) had hepatocellular carcinoma. The mean MELD score at listing was 12.1 ± 4.6. During a mean follow-up of 10 months, 4 (36%) of the QFT-positive patients proceeded to LT, whereas 1 (9%) died before LT. The mean ages, percentages of males, etiologies of liver disease, MELD scores at listing, and proportions undergoing transplantation were similar in the QFT-positive and QFT-negative groups. However, QFT-positive subjects were significantly more likely to be non-Caucasian versus the QFT-negative patients (64% versus 16%, $P = 0.006$).

Between March 2008 and October 2009, 25 of the 119 patients who underwent QFT testing also underwent PPD testing. The test results were concordant for the presence of latent TB (QFT-positive/PPD-positive) in 2 patients and for the absence of latent TB (QFT-negative/PPD-negative) in 22 patients. In addition, there were discordant test results for 1 patient who was QFT-positive and PPD-negative.

Clinical risk factors for TB infection were identified during a retrospective chart review in only 2 (18%) of the 11 QFT-positive patients. In addition, only 3 (27%) had radiographic evidence of latent TB, and 1 of the QFT-positive patients had been previously treated for active TB. While awaiting LT, 1 QFT-positive patient with a negative PPD test developed active isoniazid-resistant MTB in a culture from a pleural biopsy sample. This 49-year-old African American female with cryptogenic cirrhosis presented with a worsening right pleural effusion when her MELD score was 11. She had never undergone testing for latent TB and had not received any immunosuppression in the year to presentation. She likely acquired latent TB in South Africa, where she had traveled frequently as part of her occupation. The patient was treated with ethambutol, rifabutin, and moxifloxacin for 6 months, and her pleural effusion was resolved; she is currently awaiting LT.

QFT-Indeterminate Patients

The ages, gender distributions, etiologies of liver disease, and ethnicities were similar for the 15 patients

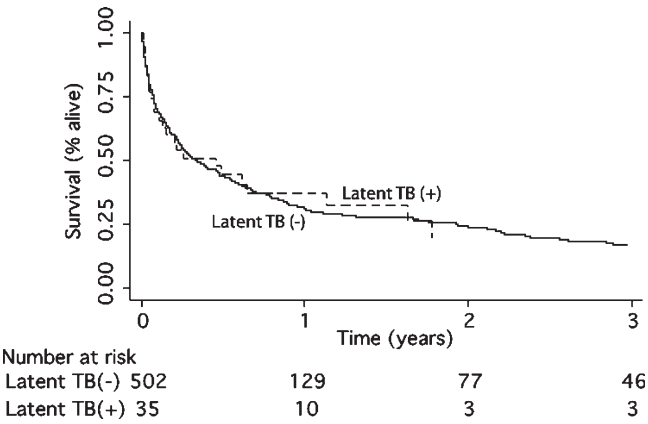

Figure 1. Transplant-free survival in LT candidates with or without latent TB infection. The actuarial transplant-free survival rates were similar in the 35 patients with latent TB infection and the 502 patients without latent TB infection (hazard ratio = 0.96, 95% CI = 0.64-1.44, $P = 0.84$).

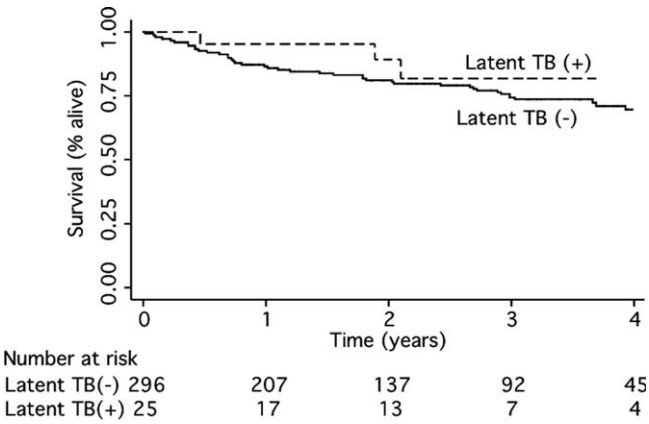

Figure 2. Posttransplant survival in LT recipients with or without latent TB infection. The posttransplant survival rate of 25 patients with latent TB infection was similar to the rate observed for 296 patients without latent TB infection (hazard ratio = 0.75, 95% CI = 0.27-2.07, $P = 0.58$).

with indeterminate QFT test results and the QFT-negative group (Table 2). However, the QFT-indeterminate patients had a significantly higher MELD score at listing in comparison with both the QFT-positive patients (20.7 ± 10.8 versus 12.1 ± 4.6, $P = 0.021$) and the QFT-negative patients (20.7 ± 10.8 versus 15.9 ± 6.8, $P = 0.023$). Interestingly, for 6 (40%) of the QFT-indeterminate patients, the test was performed while they were hospitalized for a complication of cirrhosis. A careful review showed that none of the QFT-indeterminate patients had clinical risk factors for latent TB infection or radiological evidence of latent TB on chest imaging, and none had been previously treated with isoniazid. In addition, follow-up testing in 9 of these patients showed negative PPD test results. Repeat QFT testing was performed for 5 patients and showed negative QFT results in 2 and persistent indeterminate test results in 3. During follow-up, 11 (73%) of the QFT-indeterminate patients underwent transplantation with no evidence of TB reactivation during a mean posttransplant follow-up period of 8 months.

Patient Survival and Latent TB Status

There was no significant difference in the transplant-free survival rates of the 35 subjects with latent TB and the 502 subjects without latent TB [hazard ratio = 0.96, 95% confidence interval (CI) = 0.64-1.44, $P = 0.84$; Fig. 1]. The mean 3-year transplant-free survival rate was 19.7% in both groups. During follow-up, 321 (59.6%) of the 539 patients reviewed in this study underwent LT, and this included 25 with latent TB and 296 without latent TB. The posttransplant patient survival rate of the 25 latent TB–positive patients was similar to the survival rate of the 296 LT recipients without latent TB (hazard ratio = 0.75, 95% CI = 0.27-2.07, $P = 0.58$; Fig. 2), with mean 3-year post-transplant patient survival rates of 78.7% and 74.6%, respectively.

Management of Latent TB After LT

To date, 15 (60%) of the 25 latent TB positive patients have received isoniazid chemoprophylaxis along with pyridoxine after transplantation. The mean time to the initiation of isoniazid was 0.67 months after transplantation (range = 0-5 months). Seven of the 15 treated patients (46%) completed at least 6 months of isoniazid therapy, whereas treatment was prematurely discontinued in 8 subjects after a mean of 2.2 months. Reasons for early discontinuation of isoniazid included concomitant thrombocytopenia in 3 patients, poor compliance in 2, nausea and vomiting in 1, mild rejection in 1, hepatotoxicity in 1, and high tacrolimus troughs in 1. None of these 8 patients have been retreated with isoniazid or alternative prophylactic regimens. Notably, none of the 25 LT recipients with latent TB demonstrated evidence of TB reactivation during a mean follow-up of 34 months.

DISCUSSION

Immunosuppression greatly enhances the risk of TB reactivation in patients with latent TB.[15] Previous studies have demonstrated a 0.3% to 15% incidence of TB reactivation in solid organ transplant recipients, which is 8- to 100-fold higher than that observed in the general population.[16] In one study, the median time between transplantation and the development of TB reactivation was 31 months.[17] In another series, LT recipients had an 18-fold increase in the risk of TB reactivation and a 4-fold increase in the case fatality rate in comparison with the general population.[18] In addition, the management of active TB infection in LT recipients is complicated by the potential development of drug hepatotoxicity from the recommended agents, which can be difficult to distinguish from rejection and other causes of allograft dysfunction as well as potential drug interactions.[19] Therefore, the accurate diagnosis and management of organ transplant

TABLE 3. Previous Studies of Latent TB Testing in LT Candidates

	Study					
Feature	Benito et al.[3] (2002)	Schluger et al.[42] (1996)	Chaparro et al.[43] (1999)	Manuel et al.[7] (2007)	Lindemann et al.[11] (2009)	Current series (2010)
Country	Spain	United States	United States	Canada	Germany	United States
Test years	1988-1998	1988-1995	1988-1998	2006-2007	2004-2007	2004-2009
Tested patients (n)	373	918	273	153	48	539
Male (%)	60.9	NR		79.7	56	59.9
Age (years)	50	45 ± 14		54.6 ± 8.2	54 (22-69)	52.5 ± 8.7
Caucasian/African American/Asian/Other (%)	NR	NR		81/3/13/3	NR	81/8/2/9
PPD-positive [n (%)]	89 (24)	14 (1.5)	46 (16.8)	37 (24.2)	6 (12)	25 (5.9)
QFT-positive [n (%)]	ND	ND	ND	34 (22.2)	4 (8.3)	11 (9.2)
Liver disease (%)	NR	NR				
Hepatitis C				48	25	38
Alcohol				21	17	20
Primary sclerosing cholangitis				4	8	9
Hepatitis B				10	12	3
Cryptogenic				0	15	13
Other				17	23	17
MELD score	NR	NR		13.6 ± 4.4	16 (7-43)	16.3 ± 6.8

NOTE: Data are reported as numbers and percentages, means and standard deviations, or medians and ranges. Fifteen had active TB after LT, and 8 were only PPD-positive.

candidates with latent TB are critical for optimizing patient outcomes.

With an estimated prevalence of 0.5% to 3%, the United States is considered a low-risk population for individuals with latent TB infection.[10,20] However, our data indicate that at least 6% to 9% of consecutive adult LT candidates have evidence of latent TB infection (Tables 1 and 2). Our data are consistent with other reports from Western countries that demonstrate a higher rate of latent TB infection among LT candidates versus the general population (Table 3). The reason for the higher rate of latent TB infection may be the inclusion of many patients with alcoholic liver disease, which is a commonly cited risk factor for exposure to MTB in the United States.[5,20] We also noted a significantly higher rate of hepatitis C infection in the PPD-positive subgroup, which may be due to the frequent presence of concomitant alcohol abuse in LT candidates with hepatitis C virus.[21] In addition, ethnic minorities were significantly more common among those with PPD-positive and QFT-positive test results, and this is consistent with other studies of the epidemiology of latent TB in the United States.[20]

Our data demonstrate a trend toward an increased rate of detecting latent TB infection with the QFT assay versus PPD testing. However, simultaneous testing with both methods was performed only in 25 subjects in this series. Therefore, further assessment of a larger independent LT patient population is required to determine if one test has higher sensitivity and specificity in LT candidates. Advantages of the QFT assay include its objective and standardized reporting features as well as the need for only a single blood draw with no follow-up patient visit (a follow-up visit is required for skin testing). However, the QFT assay is not widely available and is more expensive than PPD testing.[5] Furthermore, its utility and validity in patients with severe underlying illness have not been established.[22,23] Nonetheless, QFT testing is believed to be more specific and less likely to lead to false-positive tests due to the exposure of patients to atypical mycobacteria or BCG vaccination.[24] The improved specificity of the QFT assay arises from its inclusion of unique MTB proteins. However, our data also demonstrate a relatively high rate of indeterminate QFT test results versus that reported in the general population (ie, 12.6% versus <1%). An indeterminate QFT result is characterized by the absence of a host immune response to both the control antigen (phytohemagglutinin) and the MTB antigens. When indeterminate test results are reported, a repeat test is suggested to ensure that the result was not due to improper specimen handling or storage. In the current series, only 5 of the 15 subjects with indeterminate results had repeat testing completed. The relatively high rate of indeterminate test results for our LT candidates presumably is related to the generalized anergy that severely ill patients with advanced liver failure frequently manifest.[7,25,26] In support of this, the laboratory MELD scores of the indeterminate group were significantly higher versus the other subgroups (Table 2). In addition, 40% of the patients with

TABLE 4. Studies of Isoniazid Chemoprophylaxis Before and After LT

	Study				
Feature	Singh et al.[35] (2002)	Jahng et al.[34] (2007)	Schluger et al.[42] (1996)	Benito et al.[3] (2002)	Current series (2010)
Country	United States	United States	United States	Spain	United States
Test years	1992-2001	2003-2006	1988-1995	1988-1998	2004-2009
Tested patients (n)			908	373	539
Patients positive for latent TB (n)	18	14	8	89	25
Phase of isoniazid therapy	Before LT	Before LT	After LT	After LT	After LT (<6 months)
Patients given isoniazid (n)	18	5	8	23	15
Dose of isoniazid (mg/day)	300	300	300	300	300
Intended duration of isoniazid (months)	12	9	≥6	12	6
Patients discontinuing isoniazid [n (%)]	0 (0)	2 (22)	0 (0)	6 (26)	8 (53)
Reasons for discontinuation	Not applicable	Hepatitis B virus reactivation (1) Alcohol abuse (1)		Hepatotoxicity (4)	Thrombocytopenia (3) Hepatotoxicity (1) Compliance (2) Nausea/vomiting (1) Rejection (1) Tacrolimus toxicity (1)

indeterminate QFT test results were hospitalized when they were tested, and studies have shown that severely ill hospitalized patients frequently do not respond adequately to control antigens.[7,27] We surmise that the subjects with indeterminate QFT test results in our study were probably true negatives without latent TB infection because none of the follow-up PPD tests were positive, none had clinical risk factors for MTB infection, and none developed TB reactivation after transplantation. However, because there is no gold standard test for latent TB, the interpretation of indeterminate QFT tests remains uncertain. The association of indeterminate QFT test results with high MELD scores observed in our series also highlights the importance of assessing latent TB infection early on in patients with cirrhosis who may ultimately require LT.

The transplant-free survival rate in the 35 LT candidates with latent TB infection was similar to that observed in the 502 patients without latent TB infection (Fig. 1). This is reassuring and indicates that patients with latent TB are not more likely to develop fatal complications with LT. However, preoperative chest imaging of all LT candidates with latent TB infection is recommended to exclude active TB infection. Notably, 1 latent TB patient developed TB reactivation on the waiting list. Interestingly, this patient did not have evidence of apical scarring on a chest X-ray but rather had a typical right-sided pleural effusion seen in many patients with cirrhosis. Fortunately, a diagnosis of active TB infection was made via pleural biopsy prompted by a positive QFT test, and she was successfully treated with triple-drug therapy and is currently awaiting LT. This individual case demonstrates the incremental value of QFT testing in detecting TB infection in patients with advanced cirrhosis who have negative PPD results.

The posttransplant survival rate of the 25 latent TB patients was similar to that observed in the 296 LT recipients without latent TB infection (Fig. 2). The generally favorable posttransplant outcomes that we observed were similar to those in other series of LT candidates with latent TB infection in the literature (Table 4). In addition, none of our 25 subjects with latent TB developed evidence of TB reactivation during a mean follow-up of 33 months. Although our clinical protocol was to treat all of these patients with isoniazid within the first year of transplantation, to date, only 15 patients have been treated with isoniazid. The administration of isoniazid early after transplantation was difficult because of adverse events possibly related to isoniazid, although the etiologies of high tacrolimus levels and thrombocytopenia early after LT are usually multifactorial and are not commonly attributed to isoniazid use alone. In particular, problems in distinguishing acute rejection from drug hepatotoxicity make it difficult to use isoniazid within the first 6 months after transplantation. Our high rate of drug discontinuation is greater than that reported by Benito et al.[3] from Spain, who gave 23 patients isoniazid after transplantation. However, isoniazid still had to be discontinued in 26% of the Spanish patients,

mostly because of hepatotoxicity (Table 4). Overall, our data and those of others indicate that subjects with latent TB should not be denied access to transplantation because of concerns about greater posttransplant morbidity and/or mortality.

Guidelines of the American Society of Transplantation recommend that all organ transplant candidates undergo an evaluation for latent TB infection regardless of their BCG status.[2] However, transplant centers vary in their approach to the detection and treatment of latent TB in LT candidates.[28] In our study, the frequency of clinical risk factors for latent TB was generally low in those who were PPD-positive (24%) and QFT-positive (18%). Our retrospective data, obtained through chart abstraction, likely underestimate the true frequency of clinical risk factors because we were not able to prospectively interview patients for potential TB exposures or travel or habitation in foreign countries with a high rate of endemic TB. Some centers treat patients with latent TB in the pretransplant period, others treat patients after transplantation, and others simply observe the patient over time. Some transplant centers neither test for nor treat latent TB because of the perceived lack of efficacy and potential toxicity of isoniazid in LT candidates.[29,30] However, the treatment of latent TB in LT patients with either isoniazid or rifampin is recommended because there is a higher incidence of active TB in transplant patients versus the general population, reactivation of latent TB is the most common route of active infection, and the mortality rate in LT recipients with TB reactivation is as high as 30%.[31-33] At the same time, the safety of chemoprophylaxis has been questioned in LT recipients because of the potential hepatotoxicity of both isoniazid and rifampin and potential drug interactions with calcineurin inhibitors.[34] The frequency and severity of isoniazid hepatotoxicity in patients with decompensated liver disease or after LT have not been well studied.[34,35] However, asymptomatic serum alanine aminotransferase elevations are seen in up to 25% of immunocompetent patients receiving isoniazid monotherapy, but this may spontaneously resolve with continued treatment.[36,37] Moreover, clinically overt and potentially severe isoniazid hepatotoxicity also occurs in 0.1% to 3% of adults.[38,39] In fact, isoniazid hepatotoxicity is the most commonly implicated agent leading to drug-induced acute liver failure in the United States and the most common reason that adults require emergency LT for idiosyncratic drug hepatotoxicity.[40,41] In a recent systematic review, isoniazid treatment was associated with a significant reduction in MTB reactivation in LT patients versus no treatment (0.0% versus 8.2%, $P = 0.02$), and isoniazid hepatotoxicity occurred in only 6% of treated patients, with no reported deaths.[18] Therefore, although the administration of isoniazid before and after transplantation is difficult, the preponderance of evidence supports its use in selected patients with latent TB at high risk for reactivation.

In conclusion, our study results demonstrate that QFT testing leads to a similar rate of detection of latent TB infection in LT candidates versus historical controls undergoing PPD testing. In the 25 subjects who underwent both tests, the 2 tests performed similarly. Our retrospective cohort data are consistent with other reports and support the utility of considering this platform for the screening of LT candidates.[6,7] However, our data also demonstrate a relatively high rate of indeterminate QFT test results (ie, 12.6%), and this will necessitate the development of a follow-up algorithm in centers that adapt interferon-γ release assays as their preferred screening tests. Components of this algorithm will likely include repeat QFT testing to exclude laboratory error, PPD testing, a review of the patient's chest imaging and medical history, and consultation with local infectious disease experts.[42] The similar pretransplant and posttransplant outcomes that we observed in patients with latent TB infection and patients without latent TB infection, combined with the results of other published reports, indicate that latent TB infection should not exclude individual patients from consideration for LT.[2] Our study findings also demonstrate the difficulty in administering isoniazid to LT recipients in the early posttransplant period and suggest that deferring isoniazid chemoprophylaxis until at least 6 months of follow-up may be reasonable, but additional confirmatory studies are needed.

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