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MAJOR ARTICLE

A Targeted Screening Program for Latent Tuberculosis Infection Among Hematopoietic Cell Transplant Recipients

Andrea Sosa-Moreno,[1] Masahiro Narita,[2,3] Christopher Spitters,[2,3] Michelle Swetky,[4] Sara Podczervinski,[5] Margaret L. Lind,[6,7] Leona Holmberg,[2,8] Catherine Liu,[2,7,8] Raleigh Edelstein,[7] and Steven A. Pergam[2,4,7,8]

[1]School of Public Health, University of Michigan, Ann Arbor, Michigan, USA, [2]Department of Medicine, University of Washington, Seattle, Washington, USA, [3]Public Health-Seattle & King County, Seattle, Washington, USA, [4]Infection Prevention, Seattle Cancer Care Alliance, Seattle, Washington, USA, [5]Washington State Department of Health, Shoreline, Washington, USA, [6]School of Public Health, University of Washington, Seattle, Washington, USA, [7]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA, [8]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

Background. US hematopoietic cell transplantation (HCT) recipients have a low prevalence of latent tuberculosis infection (LTBI), but if latently infected they are at risk for progression to active tuberculosis. At our center, all HCT recipients underwent LTBI testing pretransplant by tuberculin skin testing (TST) until 2013 when we implemented a targeted screening program. Our objective was to assess the utility of our screening program that incorporated a pretransplant LTBI questionnaire to target TST and QuantiFERON TB Gold (QFT) testing.

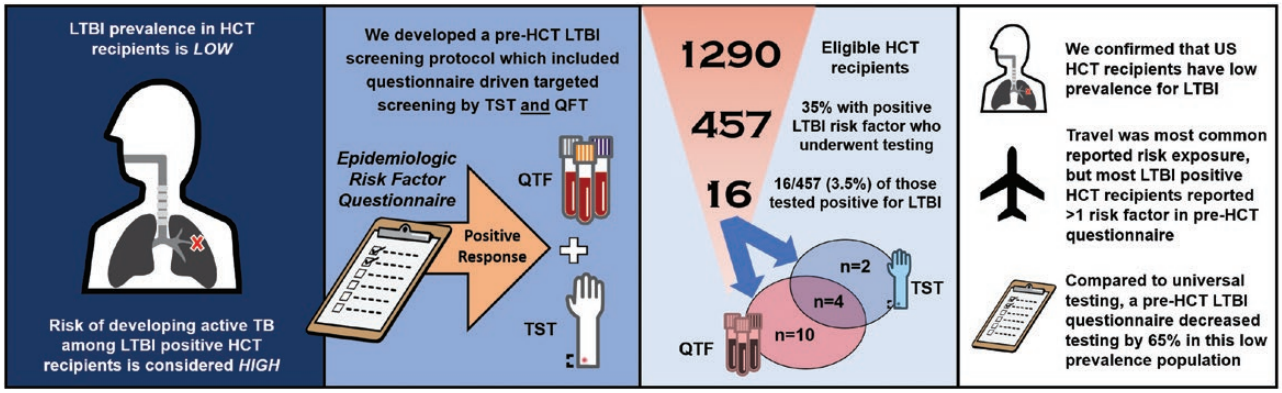
Methods. We performed a retrospective cohort study of HCT recipients undergoing first transplant from 2014 to 2016. Patients with positive, indeterminate, and a subset with negative QFT results underwent electronic medical record (EMR) review to assess TST results and risk factors for LTBI.

Results. Among 1290 eligible recipients, 457 (35%) had at least 1 risk factor for LTBI on the pretransplant questionnaire; nonwhites were more likely to undergo LTBI testing ($P < .0001$). Overall, 16 of 1290 (1.2%) had at least 1 positive LTBI test. Of those screened by QFT, 14 of 457 (3%) were positive and 52 (11%) were indeterminate. Among those undergoing EMR review, 123 of 267 (46%) had TST records; 4 of 123 (3%) positive by both TST and QFT, and 2 (2%) by TST alone. Two or more risk factors were reported among the majority of LTBI-positive patients (15 of 16 [94%]). All patients with at least 1 positive test for LTBI (n = 16) were evaluated, and 11 of 16 (69%) were recommended to receive treatment.

Conclusions. Incorporating a pretransplant LTBI questionnaire allowed for an approximate 65% reduction in LTBI testing when compared with universal testing among this low prevalence population.

Keywords. cancer; hematopoietic cell transplant; QuantiFERON; screening; tuberculosis.

Visual Abstract



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Correspondence: Steven A. Pergam, MD, MPH, 1100 Fairview Ave. N., E4-100, Seattle, WA 98109 (spergam@fhcrc.org).

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Tuberculosis (TB) is caused by the bacteria *Mycobacterium tuberculosis* and is spread through airborne droplets primarily from patients with active pulmonary disease [1]. It is estimated that approximately one quarter of the global population has latent TB infection (LTBI), 5%–10% of whom will go on to develop active disease in their lifetime [2].

Treatment of LTBI is the key strategy for TB control and elimination in the United States and other countries with low TB incidence. Risk factors for LTBI and progression from LTBI to active TB have been well characterized in epidemiologic studies.

Those in close contact with infectious TB patients, having lived in or prolonged travel to countries of high-prevalence of TB, healthcare professionals, or employees of other high-risk congregate settings (such as prisons and homeless shelters) are among a number of known risk factors for TB [3]. For those at high risk for LTBI, the tuberculin skin test (TST) or interferon gamma release assays, such as the QuantiFERON gold (QFT), are used to diagnose LTBI [4]. Targeted testing and treatment of LTBI is recommended among the high-risk groups, because it significantly decreases lifetime risk of progression to active TB [5].

Latent TB infection screening is recommended for populations at increased risk of progression to active TB, such as patients with human immunodeficiency virus (HIV) and those undergoing immunosuppressive therapy [3, 6]. The prevalence of LTBI among hematopoietic cell transplantation (HCT) recipients in the United States is low [7], but risk of progression from latent to active TB is higher when compared with the general population due to impaired cellular immunity [8–12]. Current national recommendations suggest pretransplant evaluation for LTBI in patients who have least 1 risk factor for LTBI [8, 13].

To improve TB screening within our center's HCT population, we incorporated an LTBI questionnaire, developed in consort with our local public health department, into the pretransplant evaluation process. This targeted screening took the place of our prior universal screening (TST only) practice and recommended that patients with positive pretransplant LTBI questionnaires undergo pretransplant testing with both TST and QFT. We conducted a retrospective study to determine the prevalence of LTBI among a cohort of HCT recipients, to compare methods for LTBI testing in these patients, and to assess the value of this pretransplant screening protocol. We estimated the prevalence of LTBI and compared testing methods (TST vs QFT) among these patients, and we assessed outcomes of patients with LTBI to better understand patterns of use and tolerability of LTBI treatment in the peri-HCT period.

METHODS

Study Design and Population

We conducted a single-center retrospective cohort study of patients who underwent HCT at our center in Seattle, Washington during a 3-year period between January 1, 2014 and December 31, 2016. Adult HCT recipients (≥18 years) who underwent any center-based HCT procedure were included in this study. For patients undergoing multiple transplants or tandem transplants, only the first HCT was included. The study was approved by the center's Institutional Review Board.

Questionnaire Development

In collaboration with Public Health & Seattle King County, a 9-item pretransplant questionnaire was developed, using the Missouri State Department of Health's screening tool as a template [14]. Feedback on the questionnaire's usability was solicited from transplant physicians, advanced practice providers, and nursing staff. In mid-2013, the questionnaire became standard practice pretransplant.

The pretransplant LTBI questionnaire (Appendix 1) specifically targets epidemiologic risk factors for TB: (1) prior TB diagnosis, (2) prior positive TB testing/screening, (3) bacillus Calmette-Guérin (BCG) vaccine, (4) exposure to a known TB case, (5) work or residence in congregate locations (including prisons, nursing homes, hospitals, mental institutions or homeless shelters), (6) migrant farm history, (7) born in high-risk TB country, and (8) travel to a high-risk TB country for a period ≥3 months. For the purpose of this study, we considered any travel to a high-risk TB country when reviewing provider rationale for testing. High-risk countries were defined as those with TB incidence rates of ≥20/100 000 population per World Health Organization (WHO) country profiles [15].

Latent Tuberculosis Status Assessment and Data Collection

As part of the adoption of the screening tool, guidelines recommend that patients with a positive response to any of the pretransplant questions undergo testing for LTBI by QFT and TST [3, 16]; during this period, the QuantiFERON-TB Gold in-tube assay was used. As per manufacturer's instructions, a positive QFT test had to meet all of the following criteria: (1) negative control stimulus must be ≤8.0 IU gamma interferon/mL, (2) TB antigen value minus negative control stimulus value must be ≥0.35 IU gamma interferon/mL, and (3) TB antigen value minus negative control stimulus value must be ≥25% of the negative control stimulus value. A negative QFT test had a negative response to TB antigens and successful controls, and an indeterminate QFT test reveals an unsuccessful positive control meaning that the results cannot be interpreted due to low mitogen response. If an indeterminate QFT test was repeated pretransplant, the latest QFT result was considered in the analysis.

Due to theoretical concerns that TST testing could trigger a boosting effect on QFT results [17–19], QFT testing occurred prior the placement of the TST. The TST was considered positive if skin induration is ≥10 mm, or ≥5 mm for patients on ≥1 month of 15 mg/kg prednisone-equivalents, or if known immunosuppressed pretransplant. Patients with positive TB testing (either TST or QFT) were seen by Infectious Diseases consultation service before transplantation to determine need for and timing of LTBI treatment; isoniazid (with pyridoxine) was the primary agent of choice for LTBI treatment.

All recipients with positive or indeterminate QFT results and a randomly selected subset of those with negative results (approximately 50% of the population) underwent additional medical chart review. To select a random sample of negative QFT results, we systematically sampled every 2nd subject from a list

of all negative patients. Clinical records were obtained from prospectively collected center databases and electronic medical record reviews. Chart review was used to confirm TST results, assess LTBI epidemiologic risk factors noted in clinicians' records, testing dates, and use of antibiotic prophylaxis for those with documented LTBI. The LTBI-positive cases were defined as those recipients with either a positive TST or QFT test pretransplant. Indeterminate cases were considered recipients with a negative TST (or unavailable TST test) and an indeterminate QFT. The LTBI-negative cases were defined as recipients with negative results by both tests, or negative results to QFT when the results of TST were unavailable or not done.

Antibacterial Prophylaxis Post-Hematopoietic Cell Transplantation. All HCT recipients are preferentially given 750 mg levofloxacin daily for bacterial prophylaxis during periods of posttransplant neutropenia. HCT recipients are given pre- and posttransplant prophylaxis for *Pneumocystis jirovecii* with trimethoprim-sulfamethoxazole (TMP-S), dapsone, or atovaquone; those not on TMP-S who have a known history of a splenectomy are also placed on daily oral penicillin-VK after count recovery.

Statistical Analysis

The prevalence of LTBI among our cohort was calculated as the number of LTBI-positive cases among all patients in the study cohort. HCT recipient demographics and disease-related variables were compared among those who were positive by the pretransplant questionnaire who underwent LTBI screening and those with a negative pretransplant questionnaire. Such variables included the following: age at transplantation, race/ethnicity (white, nonwhite), transplant type (allogeneic, autologous), underlying disease, and transplant year. Comparisons were also made between patients with positive testing for LTBI and those without LTBI and between patients with available and nonavailable TST results. All patients who underwent QFT testing were classified as either indeterminate and non-indeterminate (positive or negative results in QFT). Comparisons with those 2 groups in the proportion of posttransplant survival by the end of the final data analysis in June 2018 were calculated. To understand the impact of our positivity requirements, we mapped the distribution of the QFT test results (differences between antigen and negative control sample) by reported results and percentage of negative control. For all analyses, comparisons were done using Student's *t* test, Fisher's exact test, or Pearson's χ^2 test; confidence intervals (CIs) for LTBI prevalence were estimated using Poisson regression. All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Our cohort included 1290 eligible HCT recipients who were evaluated by the pretransplant LTBI questionnaire with clinical characteristics, diagnosis, and demographics summarized in Table 1. A total of 35% (457 of 1290) had positive responses to the pretransplant LTBI questionnaire and underwent QFT testing for LTBI (Figure 1). There were no significant age differences between HCT recipients with positive and negative LTBI pretransplant questionnaires, but females were more likely to have positive questionnaire compared with males (195 of 497 vs 262 of 793; $P = .027$), and nonwhite recipients were more likely to undergo LTBI testing due to a positive questionnaire than white HCT recipients (160 of 357 vs 297 of 933; $P < .0001$). Allogeneic transplant recipients were more likely to have positive responses to the LTBI pretransplant questionnaire and undergo screening when compared with autologous recipients (240 of 615 vs 217 of 675; $P = .011$). The majority of HCT recipients (431 of 457, 94%) were screened before transplant; none of those screened posttransplant were LTBI positive.

Latent Tuberculosis Prevalence

Overall, LTBI prevalence was 3.5% (16 of 457, 95% CI, 1.8%–5.2%) among those who had LTBI testing. All positive LTBI recipients were tested before transplant. Nonwhite recipients were more likely to screen positive for LTBI by QFT/TST than white HCT recipients (13 of 160 [8.1%] vs 3 of 297 [1%]; $P < .0001$). Autologous recipients had a significantly higher number of LTBI cases than allogenic recipients (12 of 217 vs 4 of 240; $P = .047$).

Testing Modality

Of all QFT results, 14 of 457 (3%) recipients were positive, 52 (11%) had indeterminate results, and 391 (86%) were negative. Among initial indeterminate results (n = 63), 13 (21%) had QFT test repeated pretransplant; 11 initially indeterminate patients were found to be negative. Overall, 267 recipients underwent medical chart review, and 123 (46%) of those had available TST records. Four (3%) were positive by both QFT and TST, but 2 (2%) were positive by TST alone (Figure 1);

Table 1. Characteristics of the Study Population, n = 1290

Variable	Subgroups	n (%)
Age (years) median [IQR]		57.3 [46.4–64.8]
Sex	Male	793 (61)
Race	White	933 (72)
Transplant Type	Allogeneic	615 (48)
	Related	414 (32)
	Unrelated	201 (16)
	Autologous	675 (52)
Underlying Disease	Acute leukemia	347 (28)
	MM	339 (28)
	MDS	112 (9)
	NHL	231 (19)
	Other	203 (16)
Transplant Year	2014	387 (30)
	2015	464 (36)
	2016	439 (34)

Abbreviations: IQR, interquartile range; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

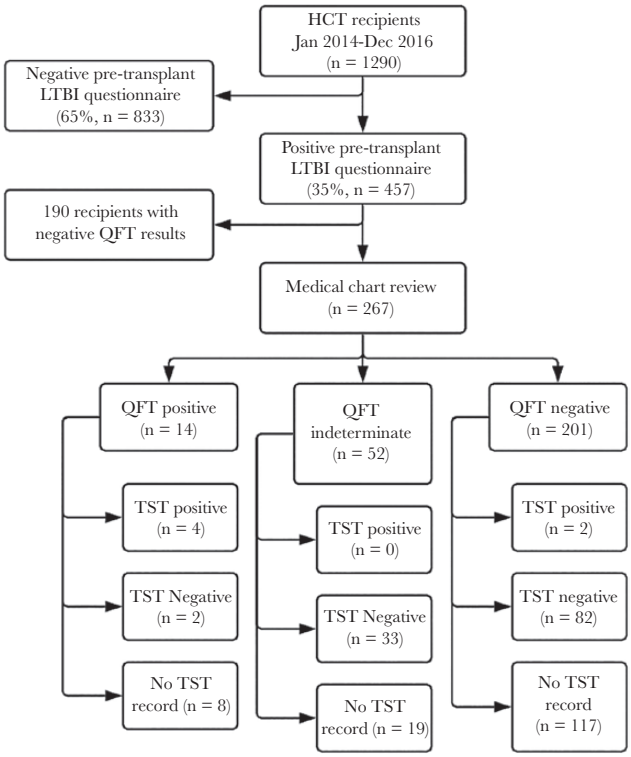

Figure 1. Flowchart of study schema. HCT, hematopoietic cell transplant; LTBI, latent tuberculosis infection; QFT, QuantiFERON-TB Gold test; TST, tuberculin skin test.

no patients with an indeterminate QFT had a positive TST. There was no demographic difference in age (P = .27), gender (P = .81), race (P = .70), or transplant type (P = .36) between recipients with available TST records and those without. However, there was a significant difference in the percentage of recipients without TST when compared with QFT result (8 of 14 [62% positive], 117 of 201 [58% negative], 19 of 52 [37% indeterminate]; P = .019). Among patients with positive or negative results, the most common QFT results ranged between −0.17 and 0.06 IU/mL, and the positivity cutoff (0.35 IU/mL) was in the right-hand tail of the distribution (Figure 2).

Latent Tuberculosis Risk factors

At least 1 epidemiologic risk factor was documented in 89% (238 of 267) of the reviewed patients who were screened due to a positive questionnaire for LTBI (Figure 3). The most frequent risk factor among those recipients was to have traveled to a high-risk TB country (n = 154) followed by being born in a high-risk TB country (n = 45). Moreover, 96 of 267 (36%) recipients reported travel as their only LTBI risk factor (Figure 3A).

Overall, 13 (81%) LTBI-positive patients were born in a high-risk TB country, 9 (56%) reported travel to those countries, 7 (44%) had a previous positive LTBI test, 4 (25%) reported BCG vaccination, 4 (25%) had contact with TB case/patient, and 3 (19%) had worked or resided in high-exposure areas. Only 1 case reported migrant farm history, and another recipient reported other medical reasons (Figure 3B). Two or more risk factors associated with LTBI were reported among 15 of 16 (94%) LTBI-positive patients. The percentage of subjects with multiple LTBI risk factors was higher among positive LTBI patients than among indeterminate (12 of 52, P < .001) and negative (46 of 199, P < .001) LTBI patients.

Latent Tuberculosis Management

All LTBI-positive patients (n = 16) received subspecialty consultation. On clinical review by the Infectious Diseases service, 5 (31%) were found to have been previously diagnosed with LTBI and had already received LTBI treatment. Of the remaining 11 (69%) LTBI-positive patients, all received treatment recommendations by the Infectious Diseases consultation service. Treatment with isoniazid at the center was documented in 8 of 11 (72%) of treatment eligible recipients, 6 of 11 (55%) of whom reported completion of prophylaxis; 2 of 11 (18%) were started on therapy but did not complete their treatment at the center. Adverse effects and short- or long-term suspension of treatment were documented in 4 of those treated with isoniazid, 3 due to liver dysfunction (elevated liver function tests) and the other due to somnolence; no patients were converted to alternate regimens. Three additional patients were recommended to receive prophylaxis after being discharged from the center. No active TB was documented within the cohort up to the end of this analysis in June 2018.

Outcomes Among Patients With QuantiFERON Tuberculosis Gold Testing

Among all recipients who underwent testing by QFT, 146 of 457 (32%) died by the final data analysis in June 2018. Of QFT tested recipients, more patients with indeterminate results died by the end of study follow-up (June 2018) than patients with either positive or negative results (26 of 52 vs 120 of 405, respectively; P = .005). Although not statistically significant, the percentage of patients who received allogeneic transplant was higher than the percentage receiving autologous transplant among indeterminate patients (38 of 52 vs 14 of 52, one-sample t test P = .2271).

DISCUSSION

Tuberculosis is a major concern for centers dealing with high-risk immunocompromised HCT recipients, but optimal methods for screening have not been clearly defined by available clinical guidelines [13, 20]. Although many centers advocate for routine screening, data demonstrate that LTBI incidence is low among those who received transplants in the United States [7]. In this study, we used a pretransplant LTBI questionnaire, with which patients with epidemiologic risk factors were selected for LTBI testing by TST and QFT. In our cohort of 1290 HCT transplant recipients, 457 (35%) who had epidemiologic risk factors for LTBI were referred for testing by QFT and TST, and among

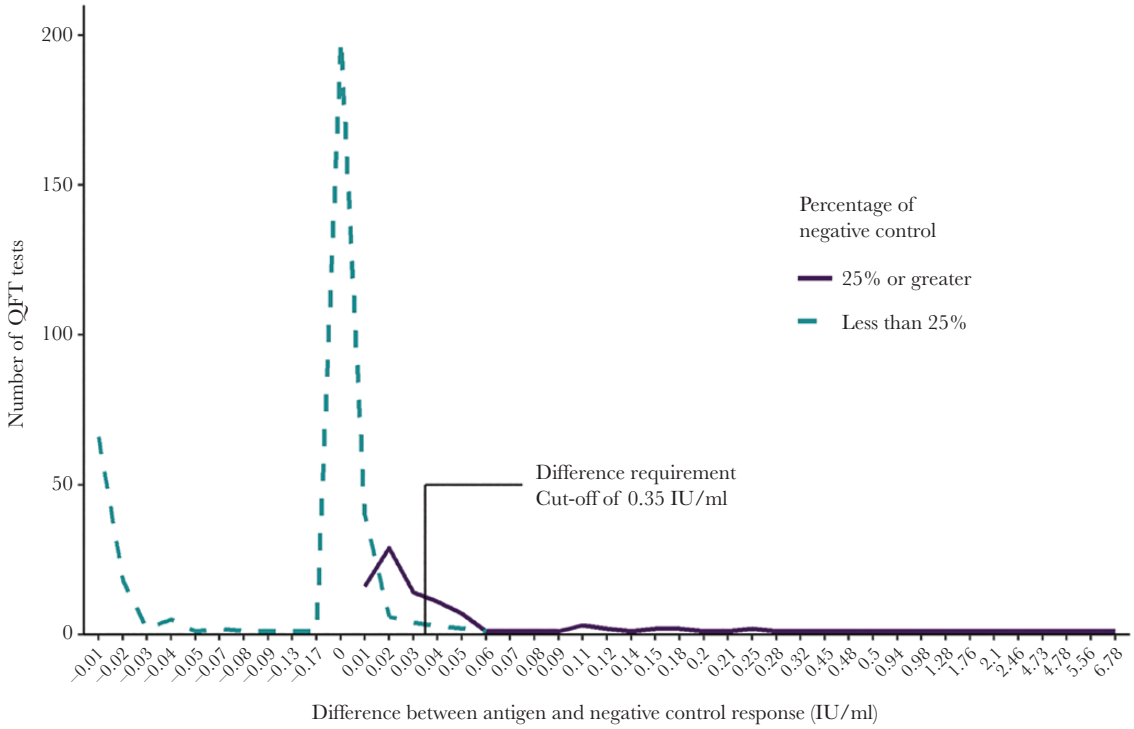

Figure 2. Distribution of difference between antigen and negative control QuantiFERON (QFT) test results by percentage of negative control. Positive definition for assay defined by QFT-TB Gold In-Tube manufacturer's instructions. Abbreviation: IU, international units.

those tested, 16 (3.5%) were positive. We found that QFT was more often positive, compared with TST, but that available QFT results significantly altered clinical decisions about TST placement despite internal guidelines recommending both tests. In addition, we found that travel was the most frequent reason for TB screening, but most patients with documented LTBI had ≥1 risk factor documented. Finally, pretransplant screening provided opportunities to consider LTBI treatment, and that when applied many patients were able to complete their course of therapy during the early posttransplant period.

In countries with low TB burden, reactivation and the development of active disease from LTBI are the main source of TB transmission [21]; therefore, screening for LTBI is essential to control the disease [6]. Identification of high-risk groups for TB-targeted testing has been recommended by the WHO [3], American Thoracic Society [22], and Centers for Disease Control

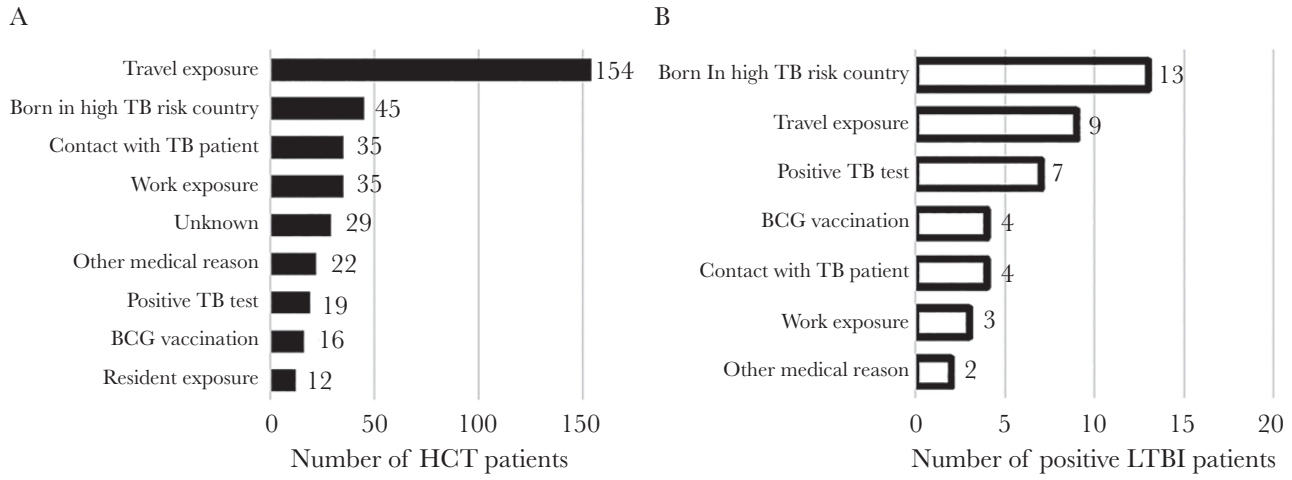

Figure 3. Epidemiologic risk factors associated with hematopoietic cell transplant (HCT) patients and positive latent tuberculosis infection (LTBI) patients. (A) Percentage of patients in total cohort of patients undergoing medical chart review (n = 267). (B) Percentage of patients with positive QuantiFERON-TB Gold In-tube or tuberculin skin test result. BCG, Bacillus Calmette-Guérin vaccine; TB, tuberculosis.

and Prevention (CDC) [14] to reduce false-positive tests among low-risk populations [23]. High-risk populations were those for which we screened using our pretransplant survey [22].

Guidelines for testing high-risk immunosuppressed populations generally fall into 2 categories: (1) routine testing of all patients or (2) targeted testing based on risk factors [20]. For instance, the CDC and National Institutes of Health recommend that all subjects with HIV should be tested for LTBI regardless of their risk of TB exposure [24]. Likewise, universal testing is recommended for patients who undergo antitumor necrosis factor alpha treatment [25, 26]. Regarding pre-HCT patients, guidelines vary as to whether LTBI screening should be considered routine [5, 8, 13]. At the same time, symptoms of active TB, cancer, non-TB infections, and other post-HCT complications can overlap (such as cough, fever, weight loss), making the diagnosis of active TB challenging, particularly because they may occur early post-HCT [11, 27]. A TB case can have broad impact at a large cancer center where delayed identification combined with large populations of immunosuppressed patients can lead to serious exposures [28, 29].

A reason that some centers focus on universal screening and not on epidemiologic risk factors for LTBI is to avoid missed cases. On one hand, it is important not to miss patients with documented LTBI who are undergoing immunosuppression, but routine universal screening among low-risk patients can lead to false-positive results. When the risk of progression to active TB disease is extremely high, clinicians may accept the risk of false-positive results and offer LTBI treatment. Even among high-prevalence populations, the lifetime risk of TB progression is said to be 5%–10% without any risk factors for TB progression, and thus the number needed to prevent 1 TB case is high.

Our pretransplant LTBI questionnaire targeted epidemiologic risk factors and allowed for more targeted testing. In comparison to prior policies of routine screening for all patients, we found that our questionnaire reduced the number of HCT recipients undergoing QFT and/or TST testing by approximately 65%. This reduction in screening low-risk patients likely helped to limit false-positive results, limiting excess cost and potentially adverse events of LTBI therapy. However, targeted screening may miss LTBI-positive cases without (or unrecognized) epidemiologic risk factors. One method to possibly identify more borderline cases would be to reduce the cutoff for positivity for the QTF assay [30]. Based on our data, even if we decreased our cutoff to 0.2 IU/mL, we would only see an increase in 5 cases or a single percentage point increase (from 3.5% to 4.5%). Such a modification could be considered in patients believed to be high-risk or could be supplemented by additional testing, such as chest radiography or alternate LTBI assays.

This policy assured that most recipients (94%) were screened before transplant, leading to an early LTBI diagnosis [22]. We observed a 3.5% LTBI prevalence among screened pre-HCT transplant recipients. Our results demonstrate similar prevalence of LTBI overall compared with a similar cohort among those universally screened by TST at another cancer center [7]. Lower LTBI prevalence, when considering our overall cohort, could suggest lower risk for LTBI within our center, an increase in false-positive LTBI results in those universally screened, or missed cases due to a lack of LTBI risk factors. Although there were no reports of active TB among our cohort of 1290 HCT recipients up to June 2018, we cannot disregard that active TB cases were missed in our review. Furthermore, with a high death rate among HCT recipients, subtle cases may have been missed because autopsies are no longer frequent in the modern era.

The QFT was done in all patients with a positive questionnaire screening response; however, only 46% of all reviewed recipients had available TST records. The TST testing is inexpensive but requires follow-up visits. The TST is prone to false positives or false negatives in this population [31] and may be falsely positive with non-TB mycobacterial infections or among those with prior BCG vaccination. The TST is known to have poor sensitivity in immunocompromised patients [4, 31]. The QFT, on the other hand, appears to have a higher sensitivity and specificity for TB than TST in immunocompromised patients [32, 33]. In this study, QFT identified more LTBI cases (n = 14) than TST (n = 6); only 2 were found by TST only. Comparisons of these modalities were not possible due to the lack of complete TST testing data among all patients undergoing QFT testing.

Patients with indeterminate QFT results reflect the immunosuppression status of patients [34–36] giving it a potential advantage over TST. We found that an indeterminate QFT was associated with worse posttransplant survival. Others have shown that HCT recipients and other cancer populations with poor mitogen responses post-HCT are associated with poor outcomes [37, 38]. Although intriguing, additional immunologic assessments, disease associations, and evaluation of other confounders need to be considered before considering the QFT mitogen response as a predictor for posttransplant outcomes.

Similar to prior studies, we found that most LTBI-positive patients were born in or had traveled to countries with high prevalence of TB [3, 6]. Most patients with documented LTBI had more than 1 risk factor for TB exposure. In-depth chart reviews of these cases found opportunities for improvements in the questionnaire components and application of this tool. Most patients tested had only short-term, low-risk travel exposures that did not meet testing guidelines (≥3 months travel time). Additional modifications to enhance this screening process incorporating these findings are currently being assessed.

There are several limitations to our study. Although only approximately half of the QFT-negative patients underwent medical review, the percentage of positive TST results among the selected negative QFT subjects that were reviewed was low

(<1%), so additional review of additional negative QFT patients would likely have altered our results. As with other studies of LTBI testing, the absence of a gold-standard for identification of LTBI prevented us from determining the performance characteristics of QFT and TST. Future studies using more next-generation assays used to detect LTBI such as T-SPOT.*TB* test and QuantiFERON-TB Gold Plus, or studies to augment diagnosis such as chest radiography, may provide help to improve accuracy of testing. Finally, the absence of TB cases in both the tested and untested groups, although empirically reassuring, does limit our ability to document the benefits of this screening approach on limiting progression to active TB among these patients.

CONCLUSIONS

The use of our pretransplant LTBI questionnaire, which assesses patients for epidemiologic risk factors for LTBI, can be used to target LTBI screening among this low-prevalence population. Quality improvement opportunities exist to improve screening using currently established tools, especially among HCT recipients and other immunosuppressed cancer patient populations.

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Author contributions. A. S.-M. designed the study, completed chart reviews, analyzed the data, created the figures, and drafted the manuscript. S. A. P. designed and supervised the study, developed study questionnaire, analyzed the data, created the figures, and drafted the manuscript. M. N., C. S., and S. P. developed the study questionnaire, discussed results, and revised the manuscript. R. E. accessed and curated data and revised the manuscript. M. L. L., M. S., L. H., and C. L., discussed results and revised the manuscript. All authors approved the final draft and manuscript submission.

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Potential conflicts of interest. S. A. P. receives research support from Global Life Technologies, Inc., and participates in research trials with Chimerix, Inc and Merck & Co. He also currently participates in a clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (U01-AI132004); vaccines for this trial are provided by Sanofi-Aventis. L. H. reports clinical trial support from Seattle Genetics, Takada/Millennium, Merck, Sanofi, Juno, Jansen, Bioline, and receives royalties from Up-To-Date and nonfinancial support from NCCN outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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