Challenging Issues in Tuberculosis in Solid Organ Transplantation

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Solid organ transplant (SOT) recipients are at risk for opportunistic infections including tuberculosis. Although guidelines on the management of latent tuberculosis and active tuberculosis are available, there remain a number of clinical areas with limited guidance. We discuss challenges in the diagnosis, management, and treatment of latent and active tuberculosis in SOT candidates and recipients who reside in low-tuberculosis-prevalence areas. We discuss the diagnosis of latent tuberculosis in SOT candidates/recipients using tuberculin skin tests and interferon-γ release assays and risk stratification of SOT candidates/recipients that would identify individuals at high risk for latent tuberculosis despite negative test results. Through a careful review of posttransplant tuberculosis cases, we identify a history of treated tuberculosis in SOT recipients as a risk factor for development of posttransplant active tuberculosis. Finally, we include comparisons of recommendations by several large transplant organizations and identify areas for future research.

Keywords. tuberculosis; solid organ transplant.

Solid organ transplant (SOT) recipients are at increased risk for opportunistic infections due to lifelong immunosuppression. The risk for active tuberculosis in SOT recipients is estimated to be 20–74 times higher than in the general population [1]. Guidelines on the management of latent tuberculosis and active tuberculosis in SOT candidates and recipients are available [2–4]. In this article, we discuss the challenges encountered in the prevention of tuberculosis in SOT recipients using illustrative cases. In discussing these challenges, we review recommendations from published guidelines, highlight areas with limited or differing recommendations, and offer our perspective based on clinical experience. The discussion is limited to low-prevalence settings, as the management of latent tuberculosis and active tuberculosis in the SOT population may differ by tuberculosis prevalence.

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BACKGROUND

The frequency of active tuberculosis in SOT recipients in low-prevalence regions (<20 tuberculosis cases per 100 000 population) varies from 0.26% to 6.5% [5–7]. We reviewed published reports from the United States of tuberculosis in SOT recipients and identified 160 cases (Supplementary Data). This underrepresents the true burden of tuberculosis in the SOT population, as 45 cases of tuberculosis in individuals with a history of SOT were reported to the US Centers for Disease Control and Prevention (CDC) in 2010 alone (personal communication, Thomas Navin, CDC). In addition to an increased risk for tuberculosis, tuberculosis-associated mortality is higher in SOT recipients (6%–22%) [6–9], compared to other tuberculosis patients (<5% in the United States) [10]. Features of tuberculosis in SOT recipients and comparisons to tuberculosis in non-SOT recipients are presented in Table 1.

IDENTIFICATION OF SOT PATIENTS AT RISK FOR TUBERCULOSIS INFECTION

Case 1

A 64-year-old man underwent lung transplant for idiopathic pulmonary fibrosis. He was born in the

Table 1. Characteristics of Tuberculosis in Solid Organ Transplant Recipients

Characteristic	SOT Recipients	Non-SOT Individuals
Organ involvement	• Extrapulmonary and disseminated tuberculosis more common (45%–67% of cases) [5, 6, 8] • May occur in uncommon sites of tuberculosis involvement including kidneys, gastrointestinal tract, joints, and skin	• Any extrapulmonary tuberculosis in 32% of US tuberculosis cases in 2011 [11]
Risk factors	• In addition to standard tuberculosis risk factors: T-cell–depleting antibodies, higher intensity immunosuppression, liver disease, renal insufficiency and hemodialysis, diabetes mellitus, and increased recipient age [3, 7, 8, 12, 13] • Lung transplant recipients at higher risk for tuberculosis in most studies [5, 7]	• History of tuberculosis, latent tuberculosis, or tuberculosis exposures; fibrotic changes on chest radiograph, silicosis, HIV infection, country of origin, and social risk factors such as homelessness, incarceration, and injection drug use [14]
Symptoms	• Symptoms may be nonspecific including fever, weight loss, night sweats • Fever seen in most patients and tuberculosis should be considered in SOT recipients with fever of unknown origin [6]	• In pulmonary tuberculosis cough is present in 75% [15] • Constitutional symptoms include fever (50%–60%), weight loss, night sweats
Imaging	• Chest imaging findings include focal infiltrates (40%), miliary pattern (22%), pleural effusions (13%), and nodules (5%) • Cavities unusual (4%) [6]	• Upper lobe infiltrates and cavities characteristic for pulmonary tuberculosis • Atypical appearances (lower lobe disease, lymphadenopathy) more common in children and HIV-infected adults
Time to diagnosis	• Often delayed due to extrapulmonary involvement, atypical presentations and imaging, and coinfections [6–8, 16] • Lack of obvious tuberculosis risk factors may increase time to diagnosis: liver transplant recipients born outside the US were diagnosed with tuberculosis sooner than US born [17]	• Delays in tuberculosis diagnosis occur in extrapulmonary tuberculosis, sputum-smear-negative disease, and individuals with poor healthcare access [11]
Mortality	• Overall mortality approximately 30%; higher mortality due to immunosuppression and comorbidities [6, 17] • Increased mortality associated with delayed diagnosis, disseminated disease, prior organ rejection, and receipt of anti–T-cell antibodies [6, 17]	• US tuberculosis-related mortality <5% • Increased mortality associated with age, comorbidities, delays in treatment, increased disease burden [18]

Abbreviations: HIV, human immunodeficiency virus; SOT, solid organ transplant.

Philippines and had lived in the United States for 30 years. Pretransplant evaluation while the patient was on prednisone and azathioprine revealed a negative tuberculin skin test (TST). Three months posttransplant, he developed a febrile illness and respiratory failure. Bronchoalveolar lavage (BAL) fluid grew *Mycobacterium tuberculosis*. Despite initiation of a 4-drug regimen, he died 4 months after transplant due to respiratory failure.

Discussion

As was likely in case 1, active tuberculosis in SOT recipients in low-prevalence regions is usually the result of reactivation of preexisting latent infection in recipients [19]. Thus, it is important to identify and treat patients with latent tuberculosis to decrease the risk of reactivation tuberculosis posttransplant, especially given the substantial morbidity and mortality associated with active tuberculosis in SOT recipients.

Screening for Latent Tuberculosis in SOT Patients

The optimal screening and testing strategies for latent tuberculosis in pre- and post-SOT recipients are not based on controlled trials, but guidelines address this important issue (Table 2). Current guidelines are consistent in recommending that all candidates be routinely screened for latent tuberculosis, and that this be done prior to transplant when feasible. Similarly, there are generally consistent recommendations that epidemiologic risk factors and chest radiography be performed as part of the assessment for latent tuberculosis.

Recommendations for specific methods of testing for latent tuberculosis vary slightly among the guidelines, but all include a TST and/or interferon-γ release assay (IGRA). The TST is the best-studied test for latent tuberculosis diagnosis in SOT recipients. A positive TST, especially in patients who do not receive treatment, is associated with an increased risk for active tuberculosis: 22%–50% of SOT recipients with a positive TST who do not

Table 2. Major Guideline Recommendations on LTBI Screening and Treatment in the SOT Population

Guideline	[4]	[2]	[24]	[3]
Applicable population(s)	All SOT	All SOT	Kidney transplant only	All SOT
Who to routinely screen for latent tuberculosis				
Candidates	All candidates	All candidates (alternative: candidates with at least 1 additional risk factor)	All candidates	All candidates
Timing of screening	Pretransplant	Pretransplant	Pretransplant	Pretransplant
Recommended routine risk assessment				
Epidemiologic risk/ history	Yes	Yes	Yes	Yes
CXR	Routine	Routine	Routine	Selective (if TST positive or symptomatic)
Routine diagnostic testing for latent tuberculosis in candidates pretransplant				
TST and interpretive threshold	Yes	Yes	Yes (IGRA preferred)	Yes
Threshold for positive	≥5 mm	≥10 mm for BCG vaccinated ≥5 w/o prior BCG	Not mentioned	≥5 mm
Booster testing	Yes	Yes	Not mentioned	Yes
IGRA	Yes	Yes	Yes (with or without TST)	Not specifically mentioned
Sequential/booster testing	Yes, for high risk	Not mentioned	Not mentioned	Not mentioned
Treatment				
Selection of SOT candidates for latent tuberculosis treatment				
TST or IGRA positive	Treat for LTBI	Treat for LTBI	Treat for LTBI	Treat for LTBI
Other criteria	(i) Have radiographic evidence of previous tuberculosis and no history of adequate treatment; (ii) have received an organ from a donor who is TST positive, had recent exposure to active tuberculosis, or had radiographic evidence of untreated tuberculosis; or (iii) have had close and prolonged contact with a person with active tuberculosis	(i) Fibrotic or calcified lesions on chest imaging; (ii) a strong history of exposure or documentation of a previous positive TST or IGRA; (iii) individuals originating from a country with a very high incidence (eg, >100 per 100 000 population)	(i) Consider in all black African and Asian patients born outside the UK; (ii) CXR consistent with old tuberculosis, untreated; (iii) recent contact	(i) Patients with CXR findings consistent with untreated tuberculosis; (ii) a history of contact with a patient with active tuberculosis
Latent tuberculosis treatment regimens				
INH × 6–12 months	INH + viatmin B6 daily, or twice weekly by DOT for 9 mo	INH for 9–12 mo	INH + viatmin B6 daily for 6 mo	INH + viatmin B6 daily for 9 mo
Rifampin × 4–6 mo	Rifampin for 4 mo (not preferred; best to complete prior to transplant)	4 mo of rifampin or a combination of 3 mo of INH plus rifampin or rifapentine.	Rifampin for 4–6 mo	Rifampin for 4 mo
DOT INH + rifapentine × 12 wks	INH + rifapentine once weekly for 12 wks (best to complete prior to transplant)	INH plus rifapentine for 12 wks	Not mentioned	Not mentioned

Table 2 continued.

Guideline	[4]	[2]	[24]	[3]
Rifampin and INH for 3–4 mo	Not mentioned	INH plus rifampin for 3 mo	INH + rifampin + viatmin B6 for 3 mo	INH + rifampin for 4 mo
Rifabutin/ fluoroquinolones	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Listing for transplantation				
Prior to completion of therapy	Yes	Yes	Not mentioned	Yes (all liver candidates)
Minimum duration prior to listing	Not specified	Not specified	Not specified	Not specified

Abbreviations: BCG, Bacillus Calmette–Guérin; CXR, chest radiography; DOT, directly observed therapy; IGRA, interferon-γ release assay; INH, isoniazid; LTBI, latent tuberculosis infection; SOT, solid organ transplant; TST, tuberculin skin test.

receive LTBI treatment subsequently develop active tuberculosis [6, 7, 17, 20]. Repeating the TST if negative ("boosting") is recommended by US and Spanish guidelines (Table 2) [3, 4].

IGRAs are ex vivo tests that measure T-cell release of interferon-γ after stimulation with *M. tuberculosis*–specific antigens. Although there is a large body of data on the use of commercially available IGRAs (QuantiFERON-TB Gold In-Tube, Cellestis, and T-SPOT.*TB*, Oxford Immunotec), there are limited data about their utility in SOT candidates/recipients. Like TSTs, IGRAs are less sensitive in immunocompromised individuals [21]. A systematic review of latent tuberculosis diagnosis in individuals with end-stage kidney disease found that QuantiFERON assays, compared to TSTs, had a greater association with tuberculosis risk factors, suggesting improved accuracy [22]. Interestingly, the performance of IGRAs may differ by transplant type: 41% of pre–liver transplant patients had indeterminate QuantiFERON results compared to 12% of non–liver transplant patients [23]. Most guidelines on tuberculosis in SOT recipients do not support the preferential use of a latent tuberculosis test [2–4, 24] (Table 2).

Studies demonstrate that when TSTs and IGRAs are applied simultaneously, there may be discordance in test results, particularly among immunosuppressed individuals [25, 26]. Testing with both TST and IGRA may minimize false-negative tests (any positive result indicating latent tuberculosis) and is suggested when there is a high pretest probability for latent tuberculosis or concern over false-negative test results [2, 4, 23, 27]. Akin to boosting seen with repeat TSTs, negative IGRA results may become positive when performed at least 3 days after a TST [28]. The American Society of Transplantation recommends against a dual testing strategy that utilizes boosting, cautioning that it may induce a "false-positive" result [4]. However, the effects of purified protein derivative injection on an IGRA would be expected to boost anamnestic T-cell responses that are due to *M. tuberculosis* infection [14, 21], representing a true and possibly remote exposure; the use of a dual test with boosting approach has been suggested prior to anti–tumor necrosis factor-α initiation [27, 28].

Selection of Patients for Treatment of Latent Tuberculosis

Published guidelines agree on treating latent tuberculosis in SOT candidates or recipients with a positive TST or IGRA (Table 2). However, most SOT recipients who develop tuberculosis would have had negative TST and/or IGRA on pretransplant testing [4]. Considering the lack of sensitivity of latent tuberculosis screening tests in this population, recommendations addressing the identification of SOT recipients who would benefit from treatment of latent tuberculosis in the absence of a positive screening test are limited (Table 2). There is agreement that significant tuberculosis exposures or findings suggestive of prior tuberculosis infection on chest radiography

should be considered as an indication for treatment of latent tuberculosis [2–4]. Pretransplant chest computed tomography (CT) may be useful for the detection of tuberculosis-compatible abnormalities not seen on chest radiography, although interpretation may be difficult in lung transplant candidates due to abnormalities related to their lung disease [4, 29]. At least 2 guidelines recommend the treatment of all SOT recipients from regions with a high prevalence of tuberculosis [2, 24, 30]. Research into patient characteristics that support empiric latent tuberculosis treatment is needed.

Case 1 demonstrates the limitations in diagnosing latent tuberculosis using available tests in SOT candidates. Although the guidelines are clear on the need for testing and treatment of SOT candidates/recipients with latent tuberculosis, there remain several outstanding questions including the use of IGRAs in SOT candidates/recipients, the role and timing of dual testing with TSTs and IGRAs, and the identification of patients who would benefit from further investigations or treatment regardless of TST/IGRA results. In our transplant center, we routinely screen SOT candidates during transplant evaluation using a combination of epidemiologic risk assessment, chest radiography, and IGRA. We recommend treatment for latent tuberculosis in candidates with either a positive IGRA or strong epidemiologic risk factors for tuberculosis, even if the IGRA is negative, on a case-by-case basis.

TREATMENT OF LATENT TUBERCULOSIS IN SOT PATIENTS

Case 2

A 51-year-old US-born man underwent liver transplant 6 years prior for end-stage liver disease secondary to hepatitis C virus infection. His medications included cyclosporine and azathioprine. He was exposed to a household member who had smear-positive pulmonary tuberculosis. After being evaluated for active tuberculosis, he was started on isoniazid (alanine aminotransferase [ALT] level, 22 U/L). Several weeks into treatment, he experienced nausea and abdominal pain; repeat ALT was 220. After his transaminases normalized, he was placed on rifabutin and completed a 4-month course without incident.

Discussion

A number of studies have demonstrated a benefit to latent tuberculosis treatment with isoniazid in the SOT population [17, 31]. Despite this, SOT candidates diagnosed with latent tuberculosis are not universally offered treatment: one-half of TST-positive SOT recipients in the Spanish Network of Infection in Transplantation (RESITRA) cohort did not receive isoniazid treatment [7].

Latent tuberculosis treatment may be administered pre- or posttransplant with the timing determined by treatment risks and benefits (Table 3). Isoniazid, the best studied latent tuberculosis treatment in the SOT population, is relatively well tolerated even among pre–liver transplant patients [6, 14, 19, 20, 23, 32]. However, the hepatotoxic effects of isoniazid may be increased post–liver transplant (occurring in 6%–40%) [6, 17], leading to high rates of discontinuation [33, 34].

Alternative latent tuberculosis treatments are often needed, particularly for liver transplant recipients or when hepatic dysfunction is present. Rifampin for 4 months carries a lower risk for liver injury than isoniazid, but is a potent inducer of the cytochrome P450 superfamily, accelerates the metabolism of immunosuppressive agents, and may lead to rejection and allograft loss [19, 35]. A recently approved regimen, isoniazid/

Table 3. Factors Affecting Timing of Latent Tuberculosis Treatment Among Solid Organ Transplant Candidates and Recipients

	Timing	
Factor	Pretransplant	Posttransplant
Advantages	• Possibly higher efficacy in absence of concurrent immunosuppression • Fewer drug–drug interactions • Lower medication/pill burden with corresponding better anticipated adherence • Generally well tolerated, even in liver transplant candidates	• Targets treatment to period of greatest risk for tuberculosis reactivation
Disadvantages	• Potentially insufficient calendar time to complete therapy due to unpredictable timing of transplant • Difficulties in differentiating drug toxicity from signs/symptoms of underlying organ disease • Drug-induced liver injury could be fatal with preexisting advanced liver disease in liver transplant candidates	• Possibly lower efficacy in setting of concurrent immunosuppression • Additional pill burden to an already complex medication regimen • Potentially severe drug interactions with immunosuppressants • Higher reported rate of drug-induced liver injury and discontinuation in liver graft recipients • Any elevation in liver function tests creates need for extensive evaluation including invasive procedures (eg, liver biopsy to rule out rejection)

rifapentine once weekly for 12 weeks, significantly shortens treatment duration but does not avoid isoniazid adverse effects or rifamycin-related effects on drug metabolism [36]. Fluoroquinolones confer a much lower risk of hepatic injury, although their efficacy in latent tuberculosis treatment is not well studied [4]. Rifabutin, a rifamycin, is used for active tuberculosis treatment, particularly in human immunodeficiency virus (HIV)–infected patients receiving protease inhibitors, as it is a less potent cytochrome inducer than rifampin [37, 38]. Rifabutin may be safely used following rifampin-related adverse effects [39]. Although advocated as part of regimens to treat active tuberculosis in SOT recipients, guidelines do not discuss rifabutin as an alternative in latent tuberculosis treatment (Table 2) [4]. Similar to our experience in case 2, a recent case report describes latent tuberculosis treatment using rifabutin in a kidney/liver transplant recipient [15].

We identify 3 aspects of latent tuberculosis treatment in SOT patients that merit further study: (1) the role of 12-dose isoniazid/rifapentine in SOT candidates/recipients, (2) the use of rifabutin as an alternative to rifampin for the treatment of latent tuberculosis, and (3) the use of fluoroquinolones as alternatives to isoniazid and rifamycins when necessary. Additionally, although guidelines are in agreement that patients may be listed for transplant prior to completion of therapy for latent tuberculosis, none provide a specific recommendation regarding the minimum duration of treatment prior to listing. At our transplant center, we initiate treatment for latent tuberculosis as soon as feasible during the transplant evaluation process, with a goal of completing therapy prior to transplant. In our experience, a directly observed weekly regimen of isoniazid/rifapentine/B6 is generally well tolerated, even in candidates with severe liver disease (Limaye AP, unpublished data). We do not delay transplant in those who are unable to complete latent tuberculosis treatment prior to transplant, but do attempt to provide a minimum of 1 month of treatment prior to listing. In candidates who do not complete the entire treatment course prior to transplant, we complete the remainder of the course posttransplant.

DONOR TRANSMISSION

Case 3

A 49-year-old US-born woman who had previously received a single lung transplant for idiopathic pulmonary fibrosis underwent double-lung retransplant due to bronchiolitis obliterans. On postoperative day 1, bronchoscopy was performed to ensure anastomotic integrity. BAL specimens, smear-negative for acid-fast bacilli (AFB), grew *M. tuberculosis* on culture. Chest CT revealed small nodules in the left upper lobe; repeat bronchial washings on postoperative day 10 confirmed tuberculosis. The patient successfully completed tuberculosis therapy. The organ donor was a 21-year-old Guatemalan immigrant whose pretransplant chest radiograph showed a faint upper lobe opacity and scattered calcifications in the midlung zones (case reproduced from [40]).

Discussion

Case 3 represents donor-derived transmission of tuberculosis, which accounts for <5% of US tuberculosis cases after SOT [6, 41]. Donor transmission has occurred through all organ types and within days to as late as 38 months after transplant [35]. The diagnosis of tuberculosis in SOT recipients should prompt investigation of possible donor-derived infection [42]. Since 2005, the Organ Procurement and Transplantation Network has required that all suspected or confirmed donor-derived disease transmissions be reported [41]. Consensus guidelines on the screening of living and deceased donors for tuberculosis, including recently published recommendations by the American Society of Transplantation, are summarized in Table 4 [43]. In general, there is either less agreement or fewer specific recommendations among the guidelines for several important issues related to donor-derived tuberculosis.

Suspected or confirmed active tuberculosis in a potential donor precludes organ donation. The presence of residual pulmonary lesions suspicious for tuberculosis also contraindicates lung donation [4]. Organ donors may be categorized as low, moderate or high risk for active tuberculosis or latent tuberculosis based on tuberculosis risk factors, especially prior countries of residence [43]. However, adequate donor screening for active tuberculosis may be difficult or impossible in deceased donors [43]. Guidance on donor-derived tuberculosis infection recommends that deceased donor candidates with moderate to high tuberculosis risk and imaging suggestive of tuberculosis have samples collected for AFB smears [43]. This approach may miss deceased donors with active disease who have subtle radiographic findings (as in case 3), or who have smear-negative tuberculosis. We suggest that consideration be given to chest CTs in high-risk deceased donors (eg, from tuberculosis-endemic countries) with normal or difficult-to-interpret chest radiographs to evaluate for evidence of prior, healed tuberculosis or active disease, especially when lung transplant is being considered. In addition, we suggest that any time AFB smears are obtained for suspicion of active tuberculosis, that nucleic acid amplification testing be included due to its superior sensitivity and specificity for the diagnosis of pulmonary tuberculosis compared to sputum smear and the rapid availability of results [44].

Although donor-transmitted tuberculosis is typically due to the transplantation of organs from a donor with unrecognized active tuberculosis, donor transmission may also be due to reactivation of latent infection in the graft [45]. Living donors should have a TST or IGRA performed, and if positive, receive latent tuberculosis treatment prior to transplantation [46]. The diagnosis of latent tuberculosis is more difficult when the donor is deceased

Table 4. Major guideline recommendations on LTBI screening and treatment in transplant donors

Donor-Derived Tuberculosis Guidelines	[43]	[2]	[24]	[3]
Applicable population(s)	All SOT	All SOT	Kidney transplant only	All SOT
Which donors to routinely screen for latent tuberculosis	All donors	Not mentioned	Not mentioned	Living donors only
Routine diagnostic testing for latent tuberculosis				
Living donors				
TST	Yes (cutoff using CDC guidelines)	Not mentioned	Not mentioned	Yes
IGRA	Yes (alternative to TST)	Feasible, but the best choice is unclear	Not mentioned	Not mentioned
Contraindicated donors	(i) Active tuberculosis; (ii) well-founded suspicion of active tuberculosis	(i) Active tuberculosis	Not mentioned	(i) Active tuberculosis as well as a well-founded suspicion of active tuberculosis; (ii) residual pulmonary lesions in the donor for lung transplant
Routine diagnostic testing for latent tuberculosis				
Deceased donors	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Treatment				
Living donors	Latent tuberculosis treatment in the recipient if a donor is TST positive, had recent exposure to active tuberculosis, or had radiographic evidence of untreated prior tuberculosis. Latent tuberculosis treatment should be considered prior to organ donation, especially for TST or IGRA converters	For living donors, the benefit of prophylactic chemotherapy to reduce the risk of tuberculosis transmission is uncertain	Not mentioned	Treatment of latent tuberculosis must be administered to recipients of an organ whose donor has a history of or data that suggest untreated tuberculosis
Treatment				
Deceased donors	Latent tuberculosis treatment in the recipient if a donor has a history of TST positive (but untreated), had recent exposure to active tuberculosis or had radiographic evidence of untreated tuberculosis	If latent tuberculosis is thought to be present in a deceased donor, the recipient of the lung transplant should be treated for latent tuberculosis	Not mentioned	Latent tuberculosis treatment must be administered to recipients of an organ whose donor has a history of or data that suggest untreated tuberculosis

Abbreviations: CDC, Centers for Disease Control and Prevention; IGRA, interferon-γ release assay; LTBI, latent tuberculosis infection; SOT, solid organ transplant; TST, tuberculin skin test.

(Table 4). For example, the time required for an interpretable TST is an important logistical hurdle in deceased donors. IGRAs would seem to be attractive options for assessing latent tuberculosis status in deceased donors. However, IGRA performance in deceased donors has not been studied and cell-mediated immunity may be depressed following head injury [43].

For deceased donors with untreated latent tuberculosis, chemoprophylaxis is recommended for the organ recipients, especially in the case of lung transplants [2, 43]. Recent guidelines recommend clinical monitoring in SOT recipients when the deceased donors had tuberculosis risk factors but were not tested for latent tuberculosis [43]. Studies of donor risk factors that warrant empiric chemo- prophylaxis in the recipient are needed. In our practice, for deceased donors with latent tuberculosis risk factors (particularly immigration from a tuberculosis-endemic country), we initiate active surveillance in recipients (symptom assessment, chest radiography during the first 6 months) and, on a case-by-case basis, provide chemoprophylaxis, particularly to lung recipients.

TUBERCULOSIS IN INDIVIDUALS WITH A HISTORY OF TREATED TUBERCULOSIS

Case 4

A 63-year-old US-born woman underwent liver transplant for cryptogenic cirrhosis. She reported a history of treated tuberculosis at age 7. She had no other tuberculosis risk factors. Six

Table 5. Studies in Low-Incidence Tuberculosis Countries Reporting History of Active Tuberculosis in Solid Organ Transplant Recipients

Study, First Author	Country	Type of Transplant	Total Transplants	Total No. of SOT Recipients With History of Active Tuberculosis	Total Cases of Active Tuberculosis Posttransplant	Cases of Active Tuberculosis Posttransplant With Prior Tuberculosis History
Riska 1987 [52]	Finland	Kidney	1280	42	29	2
Grauhan 1995 [51]	Germany	Liver	462	4	5	1
Meyers 2000 [53]	US	Liver	924	NR	9	1
Canet 2011 [8]	France	Kidney	16 146	NR	49	9
Theodoropoulos 2012 [23]	US	Liver	694	NR	8	1

Abbreviations: NR, not reported; SOT, solid organ transplant.

months after transplant she presented with a febrile illness and neurologic deficits. Noncontrast magnetic resonance imaging of the brain showed multiple intracerebral masses. Cerebrospinal fluid (white blood cell count 6 cells/mm^3, protein 63 mg/dL, glucose 46 mg/dL) was negative for tuberculosis DNA by polymerase chain reaction (PCR). Brain biopsy was AFB-smear positive and eventually grew pan-susceptbile *M. tuberculosis*. In addition, a chest CT demonstrated biapical nodular opacities and *M. tuberculosis* was isolated from AFB smear-negative respiratory specimens. The patient completed an adequate course of tuberculosis therapy and is doing well 3 years posttransplant.

Discussion

We believe that case 4 represents recurrence of previously treated tuberculosis. Among all US tuberculosis patients, the rate of recurrent tuberculosis after completion of 6 months of treatment with standard 4-drug therapy is 3.5% at 2 years, which likely results from endogenous relapse rather than exogenous reinfection [47]. Relapse is the result of persistent tubercle bacilli after treatment despite apparent cure [48]. Risk factors for tuberculosis relapse in non-SOT recipients include non-rifamycin-containing treatment regimens, intermittent therapy, residual cavitation, greater lung involvement by disease, delayed sputum culture conversion, HIV infection, and *M. tuberculosis* strain [49–51]. These studies suggest that eradication of viable mycobacteria is impacted by the treatment regimen, initial bacillary burden, and host and pathogen factors.

Several case series of SOT recipients from countries with low tuberculosis incidence include individuals with a history of treated tuberculosis who developed tuberculosis recurrence following SOT. As shown in Table 5, the proportion of patients with post-SOT tuberculosis with a history of tuberculosis prior to transplant ranged from 2% to 20%.

What is the risk of tuberculosis in SOT recipients with a history of pretransplant tuberculosis that was adequately or partially treated? Is it possible to identify SOT recipients with a pretransplant history of tuberculosis who are at higher risk for tuberculosis relapse?

Although there is guidance when the donor has a history of treated tuberculosis, including recipient chemoprophylaxis when the transplanted organ was involved, no similar recommendations

Table 6. Areas for Future Research

- How can we improve on screening strategies for latent tuberculosis diagnosis?
- What is the role for a dual strategy that uses both TST and IGRA and what is the appropriate timing of the 2 tests?
- How can we risk-stratify SOT recipients to identify individuals who would benefit from chemoprophylaxis despite negative results on screening tests (TST/IGRA)?
- How can we implement safer drug regimens for chemoprophylaxis with respect to toxicities and interactions with immunosuppressive regimens? In particular, is rifabutin being underutilized in the posttransplant setting? Is the new 12-dose regimen safe in the SOT population? What role might fluoroquinolones play in the treatment of latent tuberculosis for liver transplant candidates/recipients?
- In deceased donors, can we stratify risk to identify individuals in whom additional testing would be beneficial to evaluate for active tuberculosis?
- In deceased donors, can we diagnose latent tuberculosis using IGRAs? In the absence of screening test results, are there risk factors that can assist us in determining likelihood of latent tuberculosis in deceased donors?
- Should recipients of organs other than lungs receive tuberculosis chemoprophylaxis if the deceased donor is known to have or suspected of having latent tuberculosis?
- What is the risk for tuberculosis recurrence in SOT recipients with a history of treated active tuberculosis?
  Are there aspects of an individual's tuberculosis treatment history, immunosuppressive regimen, or other factors that can predict individuals at higher risk for tuberculosis recurrence despite treatment?

Abbreviations: IGRA, interferon-γ release assay; SOT, solid organ transplant; TST, tuberculin skin test.

are available when the recipient is the one with a history of treated tuberculosis [43]. Are there factors that may assist in stratifying risk? For example, could the receipt of T-cell antibodies, remoteness of treatment for tuberculosis, tuberculosis treatment regimen, or extensive radiographic findings identify a high-risk group who would benefit from chemoprophylaxis? In practice, it may be difficult to obtain an accurate tuberculosis treatment history from patients, particularly if the treatment occurred at a remote date or in a different country. If surveillance is chosen, for what period of time following SOT should close monitoring be maintained? In our transplant center, we carefully assess all candidates with a history of prior tuberculosis and attempt to document receipt of adequate therapy; however, in many instances this is not feasible. At the present time, we do not routinely provide secondary prophylaxis after transplant, but perform active surveillance, including symptom assessment, periodic chest radiography, and a low threshold to initiate diagnostic testing specifically for tuberculosis.

CONCLUSIONS

We have used a case-based format to discuss challenges that we have encountered related to tuberculosis in SOT recipients. In Table 6, we highlight areas with limited guidance that would benefit from further research. We anticipate that tuberculosis in the SOT population will remain an important clinical challenge even in low-incidence regions given global patterns of migration.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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