# Prevention and Management of Tuberculosis in Solid Organ Transplant Recipients

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**KEYWORDS**

• Solid organ transplantation • Tuberculosis • Latent tuberculosis infection
• Opportunistic infections • Donor derived infections

**KEY POINTS**

- Solid organ transplant recipients are at increased risk for tuberculosis reactivation owing to immunosuppression. Some candidates have risk factors for tuberculosis reactivation even pretransplantation.
- Screening for latent tuberculosis infection involves a detailed history, a tuberculin skin test or tuberculosis interferon-gamma release assay, and a chest radiograph.
- Isoniazid for 9 months is the preferred therapy for patients with rifamycin drug interactions. Rifamycins may be preferred for patients at risk of hepatotoxicity from isoniazid.
- Tuberculosis occurs months or years after transplantation. Patients can present with typical features of tuberculosis or with unusual or nonspecific manifestations.
- Tuberculosis treatment in solid organ transplant recipients may be complicated by drug interactions and adverse drug reactions and requires close monitoring.

## INTRODUCTION

### *History and Importance*

Because immune suppression to prevent allograft rejection is a cornerstone of solid organ transplantation (SOT), infections occur with relative frequency and often with increased severity. Given the ubiquity of tuberculosis (TB), it is not surprising that this infection has been reported in patients undergoing SOT since the 1960s and 1970s.[1,2]

SOT candidates and recipients contend with unique challenges in TB diagnosis and treatment. They are at high risk for TB reactivation after transplantation, and many enter transplantation with conditions such as end-stage renal disease, diabetes mellitus, or iatrogenic immunosuppression predisposing them to TB reactivation. The

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Infect Dis Clin N Am 32 (2018) 703–718
https://doi.org/10.1016/j.idc.2018.05.002
id.theclinics.com

signs or symptoms of their underlying end-stage organ failure may overlap with the protean manifestations of TB, including weight loss, cough, and malaise. Given their comorbid conditions and medications, they may be at increased risk of adverse drug reactions (ADRs) from antituberculous therapy (ATT), including neuropathy, hepatotoxicity, and gout, and may contend with multiple drug interactions. Finally, posttransplant TB has been associated with allograft loss and increased mortality.[3,4]

### *Pathogenesis*

The pathways through which SOT recipients may develop active TB are several, and can differ from those relevant to non-SOT recipients. SOT candidates may present with latent TB infection (LTBI; **Fig. 1**A) or active TB (**Fig. 1**D). After SOT, those with LTBI may or may not reactivate; those with active TB would be expected to have disease progression. Although difficult to prove, most SOT recipients who develop active TB presumably do so as a reactivation in the context of prior LTBI, especially in countries with low rates of TB endemicity where there is less likelihood of exposure after SOT. Previously uninfected SOT recipients may develop de novo infection through exposure to someone with infectious (typically pulmonary or laryngeal) TB (**Fig. 1**C), but, uniquely, may also contract TB as a donor-derived infection (**Fig. 1**B). TB bacilli may exist in transplanted organs in a spectrum of metabolic activity from quiescent infection in an otherwise healthy donor to florid infection that may have gone unrecognized.[5] Some of these donor-derived infections may be controlled by the recipient's immune system, but many of these recipients will likely develop clinically apparent TB disease.

The most obvious mechanism by which SOT recipients are at increased risk for TB reactivation involves intensive iatrogenic suppression of the immune system. In nearly all cases, SOT recipients are treated with combinations of corticosteroids, antimetabolites, calcineurin inhibitors (CNIs), and mammalian target of rapamycin inhibitors. Initial induction immunosuppression and treatment for rejection often involve administration of antibodies resulting in T-lymphocyte depletion or signaling impairment, including alemtuzumab, antithymocyte globulin, and basiliximab. Additionally, corticosteroids, CNIs, and mechanistic target of rapamycin inhibitors predispose to posttransplant diabetes mellitus, a known risk factor for TB reactivation. Patients can also develop other risk factors for TB reactivation posttransplant, such as end-stage renal disease owing to CNIs or significant weight loss.

### *Epidemiology*

SOT has long been recognized as a strong risk factor for TB reactivation and testing and treating for LTBI has been recommended in these patients in guidelines dating back several decades.[6,7] Several recent studies have established that SOT recipients have a substantially increased risk of TB, with an incidence of at least 4 times that of the general population, and in some studies nearly 30 times that of the general population.[8–11] TB incidence is increased at least 2-fold, even when SOT recipients are matched closely with patients with end-organ disease who did do not ultimately undergo transplantation.[12] Some of these studies included patients who were screened and treated for LTBI, suggesting the incidence comparisons discussed may underestimate the natural history of the disease. Although high-quality data on the incidence of TB among SOT recipients in the United States are not available, the TB incidence among diverse SOT recipients in Spain, a country with a similar although slightly higher TB incidence, was found to be markedly elevated at more than 400 cases per 100,000 person-years.[8,13] Data are insufficient to address whether recipients of some organs are at greater risk than others, with the exception of lung transplantation, which confers a particularly high risk of TB.[8]

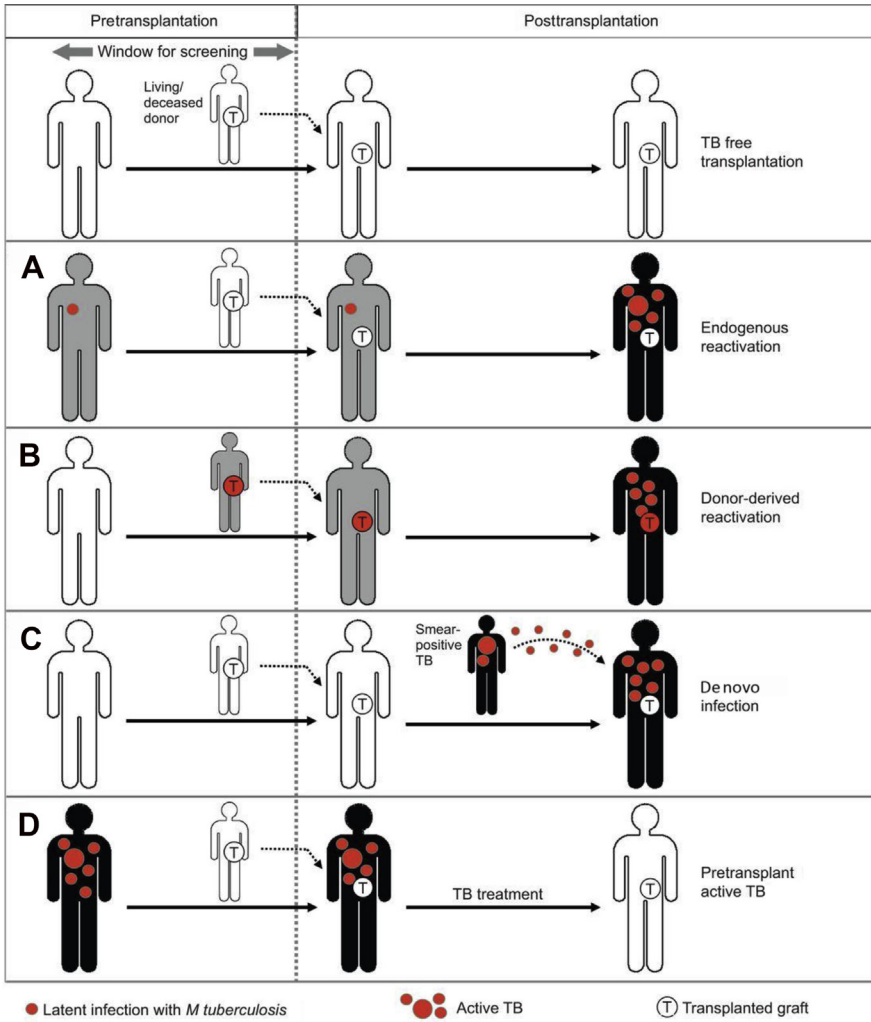


**Fig. 1.** The 4 different scenarios for infection with *Mycobacterium tuberculosis* in the transplant setting. (*A*) Endogenous reactivation owing to latent infection with *M tuberculosis* (LTBI) in the candidate recipient. (*B*) Donor-derived reactivation owing to LTBI in a living or deceased donor. (*C*) De novo exposure and infection posttransplantation. (*D*) When a patient with active TB urgently requires a transplant (ie, urgent liver transplantation). White, gray, and black figures represent uninfected individuals, individuals with LTBI, and individuals with active TB, respectively. (*Reproduced from* Bumbacea D, Arend SM, Eyuboglu F, et al. The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement. Eur Respir J 2012;40(4):992; with permission from the ©ERS 2018.)

## PREVENTION OF TUBERCULOSIS

### *Pretransplant Evaluation for Latent Tuberculosis Infection and Chemoprophylaxis to Prevent Reactivation of Latent Tuberculosis in the Recipient or from the Donor*

LTBI has been defined as evidence of immunologic sensitization to TB based on a test for LTBI in those without active disease. Immunologic assays have traditionally involved tuberculin skin tests (TSTs), most commonly using purified protein derivative. More recently,

*Mycobacterium tuberculosis* (MTB) interferon-gamma release assays (IGRAs) have been used, based on either enzyme-linked immunosorbent assay or enzyme-linked immunospot techniques. This definition of LTBI is problematic because an acquired immune response to TB may result in a positive test for LTBI even though TB bacilli have been eliminated; alternatively, viable TB bacilli may be present despite a false-negative test.[5] Furthermore, the distinction between latent and active infection is somewhat arbitrary, and depends in part on how aggressively evidence is sought for replicating bacilli.[5] Tests for LTBI have been approved for clinical use based on their ability to predict active disease and their correlation with epidemiologic risk factors for TB infection.

These immunologic tests for LTBI—namely, TST, enzyme-linked immunosorbent assay, and enzyme-linked immunospot—correlate only fairly to moderately with each other, highlighting flaws in their validity.[14–21] MTB IGRAs occasionally yield indeterminate results, most commonly in patients with impaired cellular immunity whose lymphocytes fail to sufficiently respond to the mitogen in the positive control tube.[14–21] Although indeterminate test results of IGRAS confound their interpretation, the lack of positive controls in TSTs as typically performed could theoretically provide false reassurance that LTBI is not present in those with immunologic impairment. When comparing the results of a test for LTBI with clinical, epidemiologic, and radiographic evidence of TB exposure, IGRAs may be more sensitive than TSTs with at least similar specificity, and likely greater specificity among those who were vaccinated with the Bacillus Calmette-Guérin vaccine.[22,23] Both the TST and MTB IGRA have been demonstrated to predict the risk of TB after transplantation.[9,24] Therefore, although the MTB IGRA is likely the preferred initial test, those who test negative but have an increased likelihood of having LTBI based on epidemiologic, clinical, or radiographic features should potentially be tested with a TST as well.[23] Those with known LTBI from a previous testing do not need to undergo repeat testing, but should be evaluated to determine whether they have received adequate therapy and whether they may have been reinfected since treatment (**Fig. 2** illustrates these authors' approach to LTBI evaluation in SOT candidates).

In fact, rather than relying solely on TSTs or IGRAs, the most accurate approach to diagnosing LTBI likely involves evaluating a patient's prior TB contact and chest imaging features suggestive of prior TB infection, in addition to querying immunologic evidence of prior TB infection. For example, a study of liver and kidney transplant recipients in China demonstrated that SOT recipients with any of multiple risk factors—positive TST or IGRA, chest radiographs suggestive of prior TB, or recent TB contact—were at increased risk for development of posttransplant TB.[25] Another study of South Korean liver transplant recipients found that those with linear scars or calcified nodules on pretransplant chest radiographs, which likely represent prior TB infection in this epidemiologic setting, were more likely to develop posttransplant TB.[26] In this same study, pretransplant computed tomography (CT) scans of the chest were able to identify evidence of healed or prior TB—such as irregular lines, calcified and noncalcified nodules, and fibrosis—that predicted development of posttransplant TB even in those with normal chest radiographs.[26] Another study confirmed the predictive value of chest CT scans in patients before undergoing lung transplantation to identify those with LTBI at risk for reactivation.[13] Therefore, SOT candidates without recent chest radiographs in the prior 3 to 6 months should generally have them performed, even if they have negative test for LTBI.[25,26] Similarly, a CT scan should be considered among those patients with negative test for LTBI but with high-risk clinical or epidemiologic features for LTBI.[13,25,26]

As is the case for all patients, all those with a positive test for LTBI should undergo a chest radiograph and a careful history and examination to rule out active TB before considering treatment for LTBI (and before pursing transplantation and attendant

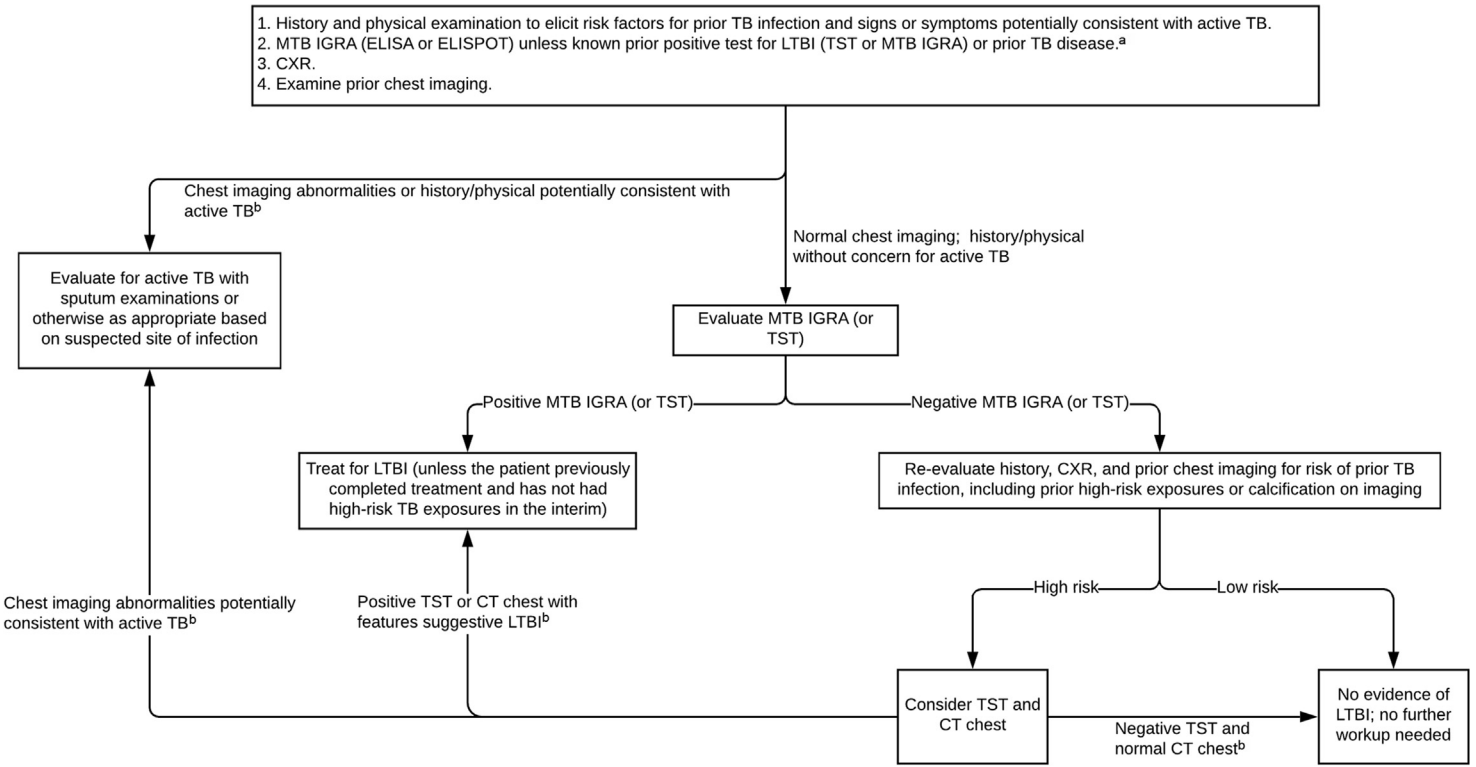


**Fig. 2.** Algorithm for evaluation of tuberculosis (TB) and latent TB infection (LTBI) among solid organ transplant candidates. CT, computed tomography; CXR, chest radiograph; ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunospot; IGRA, interferon-gamma release assay; MTB, *Mycobacterium tuberculosis*; TST, tuberculin skin test. [a] Those with prior TB who successfully completed treatment should generally not undergo further testing or treatment for LTBI, except in cases of known high-risk exposures occurring after TB treatment completed. [b] Chest radiographs, CT scans, and other studies showing only fully calcified pulmonary nodules, calcified hilar lymph nodes, or apical pleural scarring do not suggest active disease and these patients generally do not need to be evaluated for active TB based on these features alone.

immunosuppression). Diligence in ruling out active TB is key both to avoid promoting drug-resistant TB by treating active disease with monotherapy, and to defer intensive immunosuppression in the face of an active and uncontrolled pulmonary infection, apart from public health concerns. In those with a chest radiograph showing features potentially consistent with pulmonary after primary or reactivation TB—especially upper lobe infiltrates or cavities—at least 3 induced or expectorated sputum samples, collected 8 hours apart with 1 collected in the early morning should be obtained for MTB polymerase chain reaction testing, acid-fast bacilli smear, and acid-fast bacilli culture. In these cases, a CT scan of the chest can reveal the pattern and extent of disease for diagnostic and prognostic purposes, although it should be noted that pulmonary (and thoracic extrapulmonary) TB can have protean radiographic manifestations, including lobar consolidations, pleural effusions, lymphadenopathy, and osseous involvement. Because chest radiographs can occasionally be normal in those with active pulmonary TB, particularly in patients with immune impairment before transplantation, those with signs or symptoms suggestive of pulmonary TB, such as fever, cough, dyspnea, or chest pain, should undergo further evaluation with serial sputum examinations as detailed and a CT scan.[27] Perhaps with the exception of solitary micronodules stable over several months or features (such as fully calcified nodules or lymph nodes or apical pleural scarring), incidentally discovered pulmonary parenchymal abnormalities on prior scans should similarly prompt collection of sputum to rule out active disease and other workup as appropriate. Finally, those with positive test for LTBI and signs or symptoms that could be consistent with extrapulmonary TB should undergo appropriate workup based on the nature of these localizing features.

The treatment of LTBI, once active disease is ruled out, typically consists of several months of treatment with 1 or more drugs active against MTB. LTBI treatment is intended to decrease the risk of development of active TB by sterilizing bacilli before they become metabolically active and cause clinically apparent disease. Ideal regimens for LTBI treatment, apart from clinical efficacy, would be safe, well-tolerated, of short duration, and without significant drug interactions. In the uncommon situation that the SOT candidate is a known contact of someone with a drug-resistant isolate of TB, antimicrobial susceptibility testing results of the contact will determine in part the best LTBI treatment regimen.[7]

These authors' approach to LTBI treatment is largely similar to patients who are not SOT candidates. **Table 1** provides treatment options for LTBI.[28–34] Nine months of isoniazid (INH [9H]) has been traditionally the treatment of choice for LTBI, and its use in SOT candidates and recipients is supported by more clinical experience and

**Table 1**
**Regimens used for treatment of LTBI**

| First-line regimens: | Alternative regimens with disadvantages relative to first-line regimens: | Regimens not typically recommended owing to concerns about safety or efficacy and/or limited data: |
|---|---|---|
| • 9H (INH ×9 months)[28] | • 6H (INH ×6 months)[28] | • 2RZ (RIF/PZA ×2 months)[28] |
| • 4R (RIF ×4 months)[28] | • RFB ×4 mo[28] | • FQ ± EMB, ETO, or PZA ×6-12 mo[31–33] |
| • 3HP (weekly INH/RPT ×12 doses via DOT)[28] | • 3HR (INH/RIF ×3 months)[29,30] | • PZA ± EMB or ETO ×12 mo[33,34] |
| | • 4HR (INH/RIF ×4 months)[30] | • ETO/CS ×12 mo[34] |

*Abbreviations:* CS, cycloserine; DOT, directly observed therapy; EMB, ethambutol; ETO, ethionamide; FQ, fluoroquinolone; INH, isoniazid; LTBI, latent tuberculosis infection; PZA, pyrazinamide; RFB, rifabutin; RIF, rifampin; RPT, rifapentine.

evidence than other regimens.[35] A particular advantage of this regimen is that it can be started pretransplant and usually continued after transplantation, owing to the lack of significant drug interactions. If transplantation is needed urgently, this regimen is particularly attractive. Still, in the wider population of LTBI patients, clinicians and public health programs are increasingly choosing 4 months of rifampin (RIF [4R]) as a preferred regimen given emerging evidence of better adherence, increased tolerability, and fewer ADRs, particularly hepatotoxicity, compared with 9H.[36–39] Three months of weekly INH and rifapentine (3HP) is an alternative regimen with a shorter duration, potentially allowing completion of LTBI therapy before transplantation, although it is disadvantaged by relatively high rates of ADRs.[40] Another disadvantage of the 3HP regimen is the typical requirement that it be administered via directly observed therapy, although newer data support self-administration.[41] The decision of which of these 3 regimens to use should be based on drug interactions, risk of ADRs, and patient and provider preference. In general, rifamycins should be avoided for LTBI treatment after transplantation given the significant drug interactions with CNIs such as tacrolimus and cyclosporine used for immunosuppression. RIF and rifapentine are potent inducers of cytochrome P450 enzymes,[42] and because the pharmacokinetic effects of chronically administered rifamycins can persist for weeks or longer after the drug is discontinued, 4R should generally not be started unless SOT will be unlikely to occur in the next 6 months.

Liver transplant candidates with LTBI constitute a unique group whom clinicians have sometimes avoided treating given concern for drug-induced liver injury. **Fig. 3** provides these authors' approach to LTBI treatment in liver transplant candidates or others with liver disease or who are at increased risk of hepatotoxicity. Treatment for LTBI should be deferred for those with decompensated cirrhosis or acute hepatitis. The risks and benefits of treatment should be considered carefully for other patients with significant liver disease, including those with a baseline alanine transaminase value of more than 3 times the upper limit of normal or bilirubin greater than 2 mg/dL.[43] Sometimes, liver disease stabilizes sufficiently before transplantation to allow LTBI treatment. Often, however, treatment can be deferred until after liver transplantation occurs, when liver function stabilizes. Patients without such severe hepatic dysfunction that treatment is entirely precluded could likely receive 4R. A randomized clinical trial comparing 9H and 4R in a population with high rates of viral hepatitis and baseline transaminase abnormalities showed that none of the RIF-treated patients developed biochemical hepatitis requiring treatment

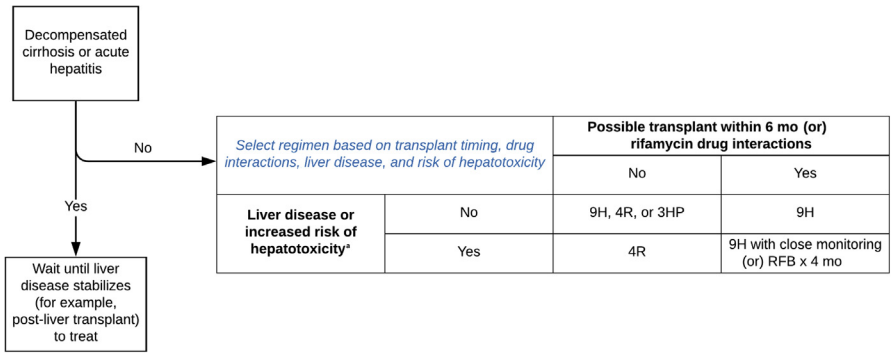


**Fig. 3.** Algorithm for treatment of latent tuberculosis infection (LTBI) in liver transplant candidates and other organ transplant candidates with liver disease or at increased risk of hepatotoxicity. 3HP, 3 months of weekly isoniazid and rifapentine via directly-observed therapy; 4R, rifampin ×4 months; 9H, isoniazid ×9 months; RFB, rifabutin. [a] See text for risk stratification.

discontinuation, compared with more than 5% of the INH-treated patients.[37] However, patients with compensated cirrhosis who are not eligible for 4R or 3HP can still often tolerate treatment with 9H with close monitoring. Several case series report the successful treatment with 9H of patients with cirrhosis before undergoing liver transplantation without significant ADRs but with the occasional need to interrupt therapy owing to transaminase elevations.[44–46] Another option for patients who are unable to take RIF owing to drug interactions or potential SOT transplantation in the near future is rifabutin.[7,47] Rifabutin is highly active against MTB and similarly less hepatotoxic than INH, but with significantly less (although still significant) cytochrome P450 induction.[47] Its use as a substitute for RIF as treatment for TB and LTBI has been established over many years among patients with human immunodeficiency virus infection taking protease inhibitors.[7]

Issues related to patient monitoring and treatment interruption are generally handled similarly to other patients with LTBI. Patients should be seen by the treating health care provider monthly to assess for signs or symptoms of hepatitis or other ADRs, medication adherence, and in rare cases evidence of development of active TB.[7] Patients should be instructed to immediately stop medications and contact the provider should they develop signs or symptoms potentially concerning for hepatitis or other significant ADRs.[7] Laboratory testing should at a minimum include liver tests (including transaminases and bilirubin) at baseline before treatment, and every 2 to 4 weeks thereafter.[43] Those with significant liver disease should likely have baseline and periodic monitoring of prothrombin time and International Normalized Ratio as well.[43] Those being treated with rifamycin-containing regimens should likely be monitored with a complete blood count with a white blood cell differential given that cytopenias are occasionally reported with long-term rifamycin use.[7] Patients who undergo SOT midtreatment should generally have medications withheld in the immediate peritransplant period until they are tolerating oral medications and clinically stable. Liver transplant recipients should generally wait a few weeks after SOT until liver function stabilizes. Fortunately, interruptions are permitted without requiring therapy to be started anew. For example, patients treated on 9H must complete 9 months of INH (or 270 doses) within 12 months, 120 doses of RIF in 4R treatment must be completed within 6 months, and 11 or 12 doses of 3HP must be completed within 16 weeks.[7,48]

Fluoroquinolones have been appealing candidates for LTBI treatment regimens owing to their in vitro activity against MTB, efficacy as a part of multidrug therapy for active TB, and perceived tolerability and favorable ADR profile. Levofloxacin, particularly, has been suggested as a possible treatment option for LTBI in those with cirrhosis, given the relatively low rates of hepatotoxicity and potentially greater efficacy and safety relative to other minimally hepatotoxic ATT drugs (such as ethambutol [EMB], cycloserine, and aminoglycosides). Unfortunately, an open-label randomized clinical trial comparing levofloxacin with INH for treatment of LTBI among liver transplant candidates was stopped early when nearly 20% of patients in the levofloxacin arm developed tenosynovitis.[31] This experience has been countered by others who report good tolerability of fluoroquinolones for LTBI treatment in this population.[49] Perhaps most important, fluoroquinolones, particularly as monotherapy, have never been demonstrated by reasonable quality evidence to be effective in reducing rates of TB reactivation. Fluoroquinolone-based regimens have been used for LTBI treatment among those exposed to patients with INH-resistant or RIF-resistant TB strains, and a metaanalysis estimated this approach has an efficacy of slightly more than 60%.[33] Although this approach may be reasonable in patients with no other choice, it should not be used for SOT recipients who have treatment alternatives.

### *Prevention of Donor-Derived Infections*

Donor-derived TB has been infrequently described; however, it may have devastating consequences for recipients of multiple organs from the same donor.[50–55] Moreover, such cases may erode confidence in the safety of SOT with programmatic and public health consequences. In other cases, donor-derived TB infection may be mistakenly diagnosed as reactivation TB. Compared with data addressing diagnosis and treatment of LTBI among SOT candidates, interventions to prevent donor-derived infections have sparse data to guide recommendations. Our recommendations herein conform with those proffered by a consensus conference report.[56] Two obvious challenges exist in this arena. First, TST or MTB IGRAs are in vivo and ex vivo tests, respectively, and there are theoretic concerns about their performance in deceased (including brain dead) donors; these assays have not been meaningfully tested on deceased donors. Second, although heart and particularly lung transplants are likely associated with a greater risk of donor-derived TB infection, the risk of abdominal organs less well-known, although documented instances of donor-derived infection through both thoracic and abdominal SOT are well-described.[50–55] Countries of intermediate TB endemicity often do not treat for LTBI when donors are latently infected and this approach does not seem to be associated with high rates of donor-derived TB.[57,58] Still, given the pathophysiology of TB involving early hematogenous and lymphatic spread, we favor treating the recipient for known LTBI, regardless of the organ involved.

Prevention of deceased donor-derived infections involves questioning family members of the potential donor for a known history of LTBI, TB exposure, or risks associated with TB exposure. Rarely, a deceased donor may have a known diagnosis of LTBI, which should not preclude donation unless this individual was a known recent contact of someone with multidrug-resistant TB. Rather, in these cases the recipient should be treated for LTBI after transplantation in case metabolically inactive bacilli present are present in the donated organ or accompanying lymphoid tissue. In other cases, deceased donor LTBI may be suspected based on a history of known exposure or high-risk interactions, potentially accompanied by otherwise unexplained calcified granulomas visualized on imaging, in which case treatment of the recipient for LTBI could be considered on a case-by-case basis. Although donors with known active TB are excluded, lungs of a donor with undiagnosed active pulmonary TB may occasionally be transplanted when routine acid-fast bacilli cultures grow TB weeks later, in which case the recipient should be treated for active disease as described elsewhere in this article.

We favor testing living donors for LTBI according to an algorithm similar to that applied to SOT recipients and treating either the donor or recipient. This approach is particularly important for heart and even more so lung transplants, although we endorse its use for abdominal organ transplants as discussed. Presumably, treating the donor before SOT or the recipient after SOT would be similarly effective; however, because the donor may benefit from treatment and because the recipient may be more at risk from ADRs associated with LTBI therapy, treating the donor rather than recipient may be optimal.

## DIAGNOSIS AND TREATMENT OF ACTIVE TUBERCULOSIS

### *Tuberculosis Diagnosis in Solid Organ Transplant Candidates and Recipients*

As in other patients with active TB, SOT recipients with TB disease frequently present with cough, fever, and other constitutional signs and symptoms.[10,59–64] Still, these typical manifestations of TB are not universal, and recipients may have blunted inflammatory responses owing to immunosuppression. Additionally, when SOT recipients present with cough, parenchymal consolidations, or other clinical findings, the differential diagnosis may be more expansive than in other patients, complicating the diagnosis.

Notably, SOT patients commonly present with disseminated and extrapulmonary disease, perhaps at rates higher than in the general population.[3,4,8,10,11,25,59–61,63–69] Radiographic presentations of pulmonary TB are highly varied in SOT patients. Patients may present with normal chest radiographs, or with interstitial opacities or lobar consolidations; cavitary disease is less common, although as in immunocompetent patients with pulmonary TB, lesions commonly affect the upper lobes.[59,64]

TB after SOT is generally a late phenomenon, with large studies reporting median times to TB diagnosis of 5 to 26 months after transplantation (and most studies reporting medians of 8–14 months).[3,10,11,25,60,61,63–67,69,70] Cases of TB diagnosed within 1 month of SOT have been described, but diagnosis this early raises the possibility that at least some of these patients may have had TB that was already active but undiagnosed before transplantation. Notably, the late onset of TB in SOT recipients contrasts sharply with the generally rapid tempo of TB reactivation in the context of tumor necrosis factor-alpha inhibitor use, with a median time to TB reactivation of 12 weeks reported with use of infliximab.[71]

Uniquely, SOT recipients who develop donor-derived TB often present with disease manifestations particular to the type of allograft received. Recipients of infected kidneys, for example, may develop increased creatinine; SOT recipients may also develop wound dehiscence, abscesses, or other surgical site infections owing to TB.[51,54,72] Disseminated infection may be more likely in the case of donor-derived infections as well.[51,54,72]

### *Tuberculosis Treatment in Solid Organ Transplant Candidates and Recipients*

With some exceptions and caveats related to unique circumstances of SOT candidates and recipients, treatment of drug-susceptible TB should generally adhere to recently published guidelines for the general population.[73] Particular features of SOT recipients include immunosuppression with a relatively high risk for progressive or disseminated disease, suggesting early empiric treatment for TB when this diagnosis is seriously considered pending confirmation with microbiologic or other testing.[73] Daily rather than intermittent dosing of ATT and use of directly observed therapy are preferred given their established benefits and to minimize irregular drug interactions with immunosuppressive medications.[73] Additionally, pyridoxine should be universally administered to SOT candidates and recipients, given the multiple comorbidities intrinsic to this population that may increase risk of INH-associated neuropathy.[73] Those being treated for active TB should be evaluated at least monthly in person by the treating provider; more frequent follow-up may be needed.[73] These patients should be monitored at least monthly with complete blood counts, liver tests (including bilirubin and transaminases), and potentially creatinine.[73]

Drug interactions pose a significant challenge to ATT in SOT recipients and candidates. Similar to LTBI, as discussed, rifabutin can be used in place of RIF given less potent induction of hepatic enzymes with less disruption of CNI dosing.[73,74] Even with use of rifabutin, therapeutic levels of CNIs can sometimes be difficult to achieve.[47] All rifamycins also significantly reduce serum levels of mold-active azoles, which undergo significant hepatic metabolism.[42] When concomitant mold-active antifungal therapy is required, isavuconazole may be a more difficult choice given lack of widely available therapeutic drug monitoring (TDM); itraconazole and posaconazole suspension should likely be avoided given the difficulties achieving therapeutic levels. Posaconazole delayed release tablets and voriconazole could be considered when needed with appropriate TDM, although both agents substantially increase rifabutin levels; these bidirectional interactions are particularly challenging.[42] Still, because rifamycins are the most active drugs against TB and form the backbone of ATT, rifamycin-sparing regimens should be used only in the rarest of circumstances because they may be less

effective and require a minimum of 12 months of therapy (or 18 months if no injectable agent is used in the first 2 months).[34,75]

Furthermore, renal insufficiency is relatively common among SOT recipients. Among first-line drugs, EMB and pyrazinamide (in addition to rifabutin) undergo varying degrees of renal clearance.[73] TDM of these drugs should be considered for patients with renal insufficiency.[73] Some experts avoid EMB altogether in those with profound renal insufficiency, including those on renal replacement therapy, given unpredictable pharmacokinetics, replacing it with levofloxacin or moxifloxacin. TDM of ATT medications should also be considered in patients who have impaired absorption owing to gastroparesis, malabsorption, or diarrhea.[73]

Patients on ATT with significant liver disease on multiple potentially hepatotoxic agents, including INH and pyrazinamide, should undergo close monitoring, with blood tests every 1 to 4 weeks.[73] For patients with decompensated cirrhosis or acute hepatitis, options for ATT include starting a standard TB regimen with close monitoring, eliminating pyrazinamide (and potentially replacing it with levofloxacin before antimicrobial susceptibility testing results have returned) and extending therapy for pulmonary disease from 6 to 9 months, or treating the patient with exclusively nonhepatotoxic drugs (typically a combination of an aminoglycoside or capreomycin, EMB, cycloserine, and levofloxacin), at least until the patient's liver disease stabilizes.[34,73]

Uncontrolled infection is typically considered a contraindication to SOT.[76] Sparse data exist to support decision making regarding timing of SOT in organ transplant candidates with active TB. Those with kidney failure evaluated for renal transplantation and those with non–life-threatening liver disease should likely defer SOT until they complete TB treatment. Case series have demonstrated the feasibility of liver transplantation in patients with active TB and acute liver failure owing to drug-induced liver injury from ATT.[77] For these and other patients, including those with life-threatening heart or lung failure, decisions about timing should be individualized.

## SUMMARY

TB and LTBI are relatively common conditions with frequent diagnostic and management challenges. The unique circumstances of SOT candidates and recipients complicate evaluation and treatment of these diseases further. Particular challenges surround diagnosis and management of LTBI, diagnostic delays and confusion in patients with end organ disease, and avoidance and management of ADRs and drug interactions.

## CONTROVERSIES AND AREAS FOR FUTURE STUDY

Despite innumerable publications on issues related to TB and LTBI in SOT candidates and recipients, very few high-quality interventional studies have been performed to answer outstanding questions. High priority should be given to randomized clinical trials evaluating the optimal approach to TB and LTBI diagnosis and treatment, specifically optimal testing algorithms for LTBI and the safety and efficacy of fluoroquinolone-containing regimens and newer ATT medications still in development.

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