American Journal of Transplantation 2013; 13: 68–76
Wiley Periodicals Inc.

doi: 10.1111/ajt.12100

Special Article

Mycobacterium tuberculosis Infections in Solid Organ Transplantation

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Key words: Latent infection, *Mycobacterium tuberculosis*, PPD, prevention, tuberculous

Abbreviations: BCG, Bacillus calmette-guerin; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; MTB, *Mycobacterium tuberculosis*; SOT, solid organ transplant; TB, tuberculosis; TST, tuberculin skin test.

Introduction

The diagnosis and treatment of tuberculosis (TB) in organ transplant recipients presents several challenges. Impediments to rapid and accurate diagnosis may lead to treatment delay and include negative or indeterminate tuberculin skin tests (TST) or interferon-gamma release assays (IGRA), negative sputum smear results despite active disease and atypical clinical presentations (1–3). Therapeutic challenges arise from drug related toxicities, metabolic interactions between immunosuppressive and antituberculous drugs and side effects from antituberculous medications (4). Increasing drug resistance and inadequate immune responses to *Mycobacterium tuberculosis* (MTB) due to exogenous immunosuppression increase the complexity of treating TB in this population (5).

Recommendations for the diagnosis and treatment of latent TB infection and active TB disease in organ transplant recipients are made based on consensus guidelines formulated by experts in the field (6–11). Only a few controlled studies of treatment of latent or active TB in organ transplant candidates or recipients are available (3,12–14). Case series and epidemiologic surveys of organ transplant patients with TB are often used for guidance in this area (15–26).

Epidemiology

It should be noted that the rates of TB reported in the transplant literature often reflect cumulative rates in populations of patients followed over a number of years and cannot always be compared to or converted to annual incidence rates.

The frequency of active TB disease among solid organ transplant (SOT) patients is estimated to be 20–74 times that of the general population, but differs according to the organ transplanted (1). For active TB disease, the prevalence among SOT recipients in most developed countries is 1.2–6.4%, while the prevalence in SOT recipients in highly endemic areas has been reported to be up to 12% (1,27). Over two-thirds of reported cases of active TB disease in transplant recipients occur in the first posttransplant year, with the median time for presentation of disease reported as 6–11 months (2,28). Posttransplant TB has a crude mortality of 20–30% (2,29). One study from Spain reported an attributable mortality of 10% (11), but this may be higher in other countries due to the challenges associated with diagnosis in a highly immunosuppressed population.

In most cases, active TB disease is thought to arise by reactivation of old foci of infection, because primary infection has only been documented in a small number of cases posttransplant. TB may also be transmitted from the donor through transplantation. The US Organ Procurement and Transplant Network's Disease Transmission Advisory Committee (OPTN/DTAC) reviewed 22 recent donor reports of potential TB transmission. Acquisition of MTB from the donated organ was substantiated in at least 16 of 55 recipients of organs from these 22 donors. Donor-derived TB transmission has been reported in renal, hepatic and lung transplantation (2,30–33). Although donor-derived TB accounts for less than 5% of all active TB cases in transplant recipients, it may result in significant morbidity and mortality. TB can be acquired after transplant, with the rate of primary infection likely greater in developing countries, although this has not been carefully evaluated. Nosocomial acquisition of MTB has been documented during an outbreak on a renal transplant unit, though such events appear to be uncommon (34,35). Surprisingly, only 20–25% of all cases of active TB disease occurring after transplantation are in patients who had positive TST reactions before transplantation (1). This may in part be due to anergy in patients with end-stage organ failure and likely does not reflect posttransplant acquisition of infection. The precise frequency at which TST positive patients later develop active TB after transplantation has not been determined.

Few risk factors have been defined for the occurrence of active TB disease after transplantation (1,2,10,11). In

general, TB risk increases with TB incidence in one's country of origin, and social and medical risk factors such as homelessness, incarceration, cigarette smoking, diabetes mellitus, chronic kidney disease, malnutrition and known contact with TB. Reported risk factors for active TB after transplantation include prior residence outside the United States, history of untreated TB, the presence of findings on chest radiographs suggestive of healed TB and intensified immunosuppression for treatment of allograft rejection. It is clear that certain immunosuppressive drugs (e.g. T cell depleting antibodies) are associated with a greater risk of TB than others (1). Risks after kidney transplant appear to be increased in those with longer pretransplant hemodialysis treatment and in those with hepatitis C (36). Lung transplant recipients have a greater risk of active TB compared to other transplanted organs, with a 5.6-fold increased risk seen in a large Spanish cohort (11). The same study found recipient age to be an independent risk factor for post transplant TB, at least in Spain, where TB in the general population has decreased significantly in recent years. It may be that older persons are more likely to have latent TB; this may be true in other regions where TB control programs have been successful.

Clinical Manifestations and Diagnosis

The clinical manifestations of TB in transplant recipients can differ from those in normal hosts (1,2). Among SOT recipients, lung transplant patients are most likely to develop pulmonary manifestations of TB. However, about one-third to one-half of all cases of active TB disease after transplantation are disseminated or occur at extra-pulmonary sites, compared to only about 15% of cases in normal hosts (2). Classic symptoms of TB such as fever, night sweats and weight loss are usually seen, but may not always be present. One large series reported fever in 91% of transplant recipients with disseminated disease and in 64% of those with pulmonary disease (2). Atypical presentations may also be noted, such as pyomyositis, cutaneous ulcers or tenosynovitis.

A minority of transplant patients have classic cavitary changes on chest radiograph. Radiographic findings of pulmonary TB in SOT recipients may demonstrate a focal opacity, a miliary pattern, nodules, pleural effusions, diffuse interstitial opacities and cavities. The mortality of TB after transplantation is increased compared to immunocompetent hosts, especially in patients who have disseminated disease, those with prior rejection or after receipt of anti-T cell antibodies (1,2).

The diagnosis of active TB disease after transplantation requires a high index of suspicion and in practice is frequently delayed. A diagnostic invasive procedure, such as bronchoscopy with bronchoalveolar lavage or lung biopsy in pulmonary TB, or biopsy of skin lesions or abscess fluid in patients with skin and soft tissue involvement is often required (37). Specimens should be sent for smear and culture for acid-fast bacilli, along with histopathological evaluation. The use of rapid nucleic acid amplification techniques, such as Xpert MTB/RIF (Cepheid Inc, Sunnyvale, CA, USA), an automated molecular test for MTB and resistance to rifampin (RIF), can increase the sensitivity and decrease the time to diagnosis. However, such tests may be falsely negative when low levels of mycobacteria are present.

A diagnosis of latent TB infection may be made by documenting a positive TST or IGRA in a person without signs, symptoms, or chest radiographic evidence of active TB. IGRAs, including QuantiFERON-Gold (QFT, Cellestis) and T-SPOT TB (Oxford Immunotec Ltd, Abingdon, UK) have emerged as alternatives to the TST in the general population (38,39). The use of these tests in transplant candidates and donors is discussed later. It should be noted that neither the TST nor IGRA assays can distinguish latent TB infection from active disease. Both IGRA and TST should be interpreted with caution in patients receiving high levels of immunosuppressive drugs as they may yield falsely negative or indeterminate results (40,41). Therefore screening for LTBI should be done prior to administration of immunosuppressives. That said, the QFT and T-SPOT TB tests are highly specific, and a positive test should be interpreted as evidence of MTB infection. Compared to QFT, T-SPOT TB appears to have a slightly higher sensitivity for detecting MTB infection (42,43).

Prevention of Active TB Disease

Evaluation of transplantation candidates and donors

A careful history of previous exposure to MTB should be taken from all transplant candidates, including details about previous TST results and exposure to individuals with active TB in the household or workplace (III) (8,44). Further inquiry about possible institutional exposure and travel to areas highly endemic for TB is also helpful. Any history of active TB should be documented, as well as details regarding the length and type of treatment. It is also important to document previous treatment for latent TB and obtain relevant records. A chest radiograph should be examined for evidence of old healed TB. All transplant candidates, including those with a history of BCG vaccination, should undergo evaluation for latent TB infection (III). Conventional TST can be used in all situations, with a test being considered positive if there is $\geq$5 mm of induration at 48–72 h (III). If feasible, patients with negative reactions should have a second skin test performed 2 weeks later, as the TST can convert from being falsely negative to positive due to "boosting" in some individuals with remote MTB exposure. For individuals not highly immunosuppressed, the QFT and T-SPOT TB are alternatives to TST, and should be interpreted according to manufacturers' guidelines. IGRA testing may be preferred to TST in transplant candidates with a prior history of BCG vaccination, as IGRA results will not be impacted by prior receipt of BCG. Studies of the performance of the QFT in liver transplant candidates indicate their utility in patients with advanced liver disease, with indeterminate results more common in candidates with higher MELD scores (43,45,46). The T-SPOT TB test

may be more sensitive than TST in detecting LTBI in kidney transplant candidates (47). A Korean study of kidney transplant recipients revealed T-SPOT TB to be helpful in predicting risk for post transplant active TB in patients who were TST negative prior to transplant (10,48). In transplant candidates with epidemiologic evidence of high risk for latent or asymptomatic active TB, careful radiographic assessment with CXR and thoracic CT may be helpful if results of TST and IGRA are negative or indeterminate (3,49). Unfortunately, none of the available screening tests are infallible in diagnosing latent or active infection with MTB; therefore treatment decisions must be individualized based on the clinical likelihood of infection and a careful review of the available data. The management of discordant TST and IGRA test results also requires a thorough assessment of the candidate's individual TB risk (50). Since the sensitivities of TST and IGRA do not overlap fully, both modalities can be employed in screening, with appropriate timing to avoid the potential induction of false positive IGRA results (51). This should only be considered in transplant candidates with high pretest probability of LTBI in whom a single positive test result might change clinical management. Patients with a prior history of positive TST or IGRA testing may be screened for active TB and then treated as appropriate without retesting. A current negative screening test, especially in patients with organ failure awaiting transplantation, does not negate a prior positive test result. Individuals having a reliable prior history of treated latent TB infection or treated TB disease need not undergo TST, QFT or T-SPOT TB. However, these individuals should have a symptom review and chest X-ray, as well as additional testing if indicated, to screen for active TB.

Living donors should undergo an evaluation similar to that described for transplant recipient candidates (III). For living donors, the TST should be interpreted as positive or negative according to CDC guidelines for the general population (52). QFT and T-SPOT TB are alternatives and should be interpreted according to manufacturers' specifications. If a test reveals evidence of MTB infection, then active disease should be ruled out, starting with a symptom review and chest x-ray (III). For living donors with latent TB infection, treatment for latent TB infection should be considered prior to organ donation, especially for recent TST or IGRA converters. Organs from potential donors, whether living or deceased, with active TB disease should not be used. Also, a well-founded suspicion of active TB should contraindicate donation, and residual pulmonary lesions should contraindicate lung donation (10). It is not possible to accurately perform TST or IGRA on deceased donors, but a history should be obtained from the donor's family or relatives of previous active TB and any associated treatment. Ideally, it would also be desirable to know if the donor had exposure to active TB within the last 2 years.

Treatment of Latent TB

Public health authorities recommend treatment of latent TB in persons who are actively immunosuppressed (7). In highly endemic areas where TB transmission is common, some transplant experts recommend universal isoniazid prophylaxis for the first year posttransplant during the period of maximum immunosuppression (14). Treatment options for latent TB are listed in Table 1. The data supporting various treatment options for latent TB are extensive, with a paucity of information devoted to the management of transplant candidates (53–55).

The mainstay of latent TB treatment is isoniazid, but its use in transplant recipients was controversial in the past due to a high rate of hepatotoxicity reported in older studies (56–58). More recent data, however, show a low risk of hepatotoxicity due to isoniazid in renal transplant recipients without serious underlying liver disease (59), and in patients with compensated liver disease awaiting liver transplantation (60,61). A 4-month course of rifampin monotherapy can be used for the treatment of latent TB (62), but is limited by drug–drug interactions that preclude continuation of treatment posttransplant, thus it is preferable to complete the course of rifampin prior to transplantation. A previously recommended regimen of pyrazinamide and rifampin daily for 2 months has been associated with a high rate of hepatotoxicity and is no longer recommended. A promising new regimen for treatment of LTBI is a 12-week course of isoniazid and rifapentine (63). It is recommended weekly as directly observed therapy in otherwise healthy individuals $\geq$12 years of age who have a risk factor for developing active TB (64). However, it has not been studied in patients with organ failure, such as those awaiting transplantation. Use of this regimen after transplantation is limited by severe drug interactions between rifamycins and immunosuppressive agents.

The rationale for latent TB treatment in this setting is supported by the fact that active TB disease is difficult to diagnose in transplant recipients, the cause of appreciable morbidity and mortality and a potential public health risk. LTBI treatment significantly reduces the incidence of TB reactivation in transplant recipients (65). It must be stressed that a thorough clinical evaluation to rule out active TB must be performed prior to initiating treatment for LTBI. Neither TST nor IGRA testing can distinguish active from latent infection. With this in mind, the following recommendations are made regarding candidates for treatment and timing the following recommendations are made:

(1) Isoniazid preventive treatment for 9 months—given daily, or twice weekly by directly observed therapy (DOT)—should be considered for all transplant patients who have a positive TST or IGRA (II-1), unless they have received a prior adequate course of treatment for LTBI or active TB. Pyridoxine (vitamin B6) 25–50 mg daily should be administered concomitantly with isoniazid to all transplant candidates and recipients, since they are at increased risk of neurotoxicity (III). Because 9 months of treatment confers additional protection over 6 months, a 6-month course of isoniazid is not routinely

Table 1: Treatment of latent TB

Medication	Adult dose	Pediatric dose	Duration	Notes
Isoniazid (INH) (daily)	5 mg/kg (max 300 mg/day)	10–15 mg (max 300 mg/day)	9 months preferred over 6 months due to additional protection	Pyridoxine 25–50 mg/day with INH to decrease risk of neurotoxicity. Some recommend INH dose adjustment with renal insufficiency, but generally do not change dose with hemodialysis.
Isoniazid (twice weekly by directly observed therapy)	15 mg/kg (max 900 mg/dose)	20–25 mg/kg (max 900 mg/dose)	Same	Same
Rifampin	10 mg/kg (maximum of 600 mg	10–20 mg/kg (maximum of 600 mg) for children.	4 months	Best to complete prior to transplant due to immunosuppressive drug interaction.
Isoniazid (INH) with Rifapentine (RFP) (63,64)	INH: 15 mg/kg q week (max 900 mg/dose) RFP: <50 kg 750 mg/week; >50 kg 900 mg/week	Recommended for ≥12 years of age. INH: same as adult RFP: 25–32 kg: 600 mg/week, 32–50 kg: 750 mg/week	Once weekly for 12 weeks, only studied as directly observed therapy, with at least monthly clinical assessment	Pyridoxine 25–50 mg/day should be given with INH. Best to complete prior to transplant due to drug interactions. Not studied in patients with organ failure or transplant recipients.

recommended in transplant patients (II-1). Regimens that employ rifampin for 4 months are not preferred due to limited data on efficacy (II-3), but may be used prior to transplantation; after transplantation they are to be avoided due to drug interactions with immunosuppressive agents (III) (52). If standard treatment is not tolerated, alternative regimens such as ethambutol plus either levofloxacin or moxifloxacin have been used and could be considered for high-risk individuals (III) (10). If no alternative treatment is possible, then careful clinical follow-up with prompt diagnostic attention to protracted fever or pulmonary symptoms is likely the best course (III).

(2) Most of the patients who develop active TB disease after transplantation have a negative TST before transplantation. For this reason, most authorities in low TB prevalence areas recommend the use of isoniazid preventive therapy in TST negative (or IGRA negative/indeterminate) patients who: (i) have radiographic evidence of previous TB and no history of adequate treatment, (ii) have received an organ from a donor who is TST positive, had recent exposure to active TB or had radiographic evidence of untreated TB or (iii) have had close and prolonged contact with a case of active TB, a circumstance in which the risk of de novo infection may be 50% or higher (III).

(3) If either the recipient or donor has recently converted their TST or IGRA from negative to positive, then prompt recipient evaluation and treatment for LTBI is indicated if there is no evidence of active TB disease (III).

(4) Underlying liver disease limits use of isoniazid preventive therapy in transplant recipients. Latent TB therapy should still be strongly considered in patients with liver disease if they are known to be recent TST converters (III), since the risk of progression to active TB disease is high in this setting. The interaction between isoniazid and calcineurin inhibitors is not clinically significant enough to preclude the use of isoniazid. If candidates cannot tolerate treatment prior to transplantation, then treatment should be initiated as soon as possible following transplantation.

(5) The timing of isoniazid administration requires balancing risks and benefits for individual patients. Factors that require consideration include the current medical condition, transplant urgency, risk of progression to active TB and anticipated timing of transplantation (if not yet performed). Individuals with recent TB exposure and/or recent TST conversion should receive evaluation and LTBI treatment as soon as medically practicable, due to heightened risk for progression to active TB. Renal transplant candidates awaiting deceased donor transplantation should be treated before transplantation, as they may face long waiting times and renal failure is itself a risk factor for active TB disease. Treatment should be considered before lung transplantation in TST or IGRA positive individuals, because active TB may be difficult to diagnose in the presence of chronic lung disease (III). In some transplant candidates it may be preferable to delay the administration of isoniazid until after transplantation, at which time the risk for active TB is higher and the patient may be more stable medically. The administration of isoniazid to liver transplant recipients is somewhat controversial. In this population, it may be prudent to delay the initiation of isoniazid until liver function is relatively stable

(III). In liver transplant recipients who are taking isoniazid, rise in serum transaminase levels should not be automatically ascribed to isoniazid. A specific diagnosis should be sought, with liver biopsy, if necessary.

(6) Transplant recipients receiving isoniazid should routinely be monitored for hepatotoxicity. A suggested approach is to monitor at 2-week intervals for 6 weeks and then monthly. A single blood test (ALT) should suffice. Low-grade elevations of hepatic transaminases to 1.5–3 times normal are relatively common during the first months of isoniazid use and may not require immediate discontinuation, but should prompt more frequent laboratory monitoring (III). LTBI treatment should be discontinued with a threefold increase in hepatic transaminases and signs and symptoms of hepatotoxicity, or fivefold elevation without symptoms (52).

(7) Organ transplantation may be performed in patients who are receiving treatment for LTBI, especially if the potential benefit of early transplantation outweighs the risk of reactivation TB (III). After transplantation, latent TB treatment should be resumed as soon as medically possible and continued until completion of originally planned course.

(8) If treatment of LTBI has been delayed until after transplantation, then the selected regimen should be initiated as soon as medically possible after the recipient is stabilized (III).

Treatment of Active TB

Because of the challenges of treating active TB disease after transplant, every effort must be made to diagnose and treat active TB pretransplant. A major challenge when screening transplant candidates is distinguishing latent TB from clinically asymptomatic active TB. Should asymptomatic candidates not receive a diagnosis of active TB until after transplant, successful treatment is still possible with early aggressive management (66). Drugs commonly used to treat active TB disease are listed in Table 2. Also noted are their standard adult and pediatric doses, the degree of dose adjustment required for renal dysfunction, and common side effects (6,7). Drug interactions are addressed in Chapter 32.

The standard treatment recommendation for active TB disease in the general population is to administer a four-drug regimen of isoniazid, rifampin, pyrazinamide and ethambutol for the first 2 months ("intensive phase") followed by isoniazid and rifampin alone for an additional 4 months ("continuation phase") (I). Ethambutol can be discontinued if the MTB isolate is susceptible to isoniazid, rifampin and pyrazinamide. Fluoroquinolones including moxifloxacin and levofloxacin have potent activity against MTB, and while not recommended for use as "first-line" therapy, they can be useful components of multidrug regimens in individuals who have hepatotoxicity on standard TB therapy or who have poor liver function.

With respect to dosing interval, daily TB therapy is recommended. Twice- or thrice-weekly administration of TB therapy is not recommended due to the increased risk of relapse associated with intermittent dosing (II-2) (67) and the potential for wide fluctuations in immunosuppressive drug levels due to drug–drug interactions with rifamycins. With respect to treatment duration, published data in renal transplant recipients indicate that 6 months of treatment should be adequate; however, some experts disagree (10,17). A longer duration of therapy is recommended for the treatment of bone and joint disease (6–9 months) (I), central nervous system disease (9–12 months) (II-2), and should be considered in individuals with severe disseminated disease (6–9 months) (II-1). In addition, 9 months of treatment is recommended for individuals with cavitary pulmonary TB in whom sputum at completion of 2 months of treatment is still culture-positive for MTB (I). Longer treatment duration should always be considered if the response to treatment is slow. Longer treatment courses are mandated if second line drugs are used to replace first line drugs, or if there is resistance to rifampin ± other drugs (III). For drug susceptible TB, when treatment is extended beyond 6 months, the intensive phase remains two months in duration and the duration of the continuation phase is extended.

DOT programs have been shown to improve adherence and outcome in TB patients and are recommended for transplant recipients (II-2). If a transplant recipient receives antituberculous medication in a public health clinic, close communication with the health clinic is necessary to ensure that clinic personnel are aware of transplant specific issues. Consultation with a TB expert is recommended for any patient with active TB, and is imperative for patients whose TB is complicated by drug resistance or drug intolerance, as well as those who require nonstandard treatment for whatever reason.

The major difficulty in administering antituberculous therapy to transplant patients is drug–drug interactions involving rifampin. Nevertheless, a rifamycin-containing regimen is strongly preferred due to the potent MTB sterilizing activity of this drug class. Rifampin is a strong inducer of the microsomal enzymes that metabolize cyclosporine, tacrolimus, sirolimus, and everolimus. To some extent rifampin may also interfere with corticosteroid metabolism. It may be difficult to maintain adequate levels of immunosuppressive drugs while using rifampin, and rejection episodes occurring in conjunction with rifampin use have been widely reported. Successful use of rifampin has been reported in transplant recipients, but doses of cyclosporine, tacrolimus and sirolimus will have to be increased at least two- to fivefold (II-3). An option is to replace rifampin with rifabutin (another rifamycin) (I). Rifabutin has

Table 2: Medications for treatment of active tuberculosis

Drug	Daily dose (Adults)	Daily dose (Pediatrics)[1]	Dose alteration for renal dysfunction[2]	Common adverse events
First line drugs				
Isoniazid	5 mg/kg PO or IV (maximum 300 mg)	10–15 mg/kg (maximum 300 mg)	Minimal	Hepatotoxicity Neurotoxicity (peripheral neuropathy, optic neuritis, seizures) Cytopenias Drug interactions
Rifampin	10 mg/kg PO or IV (maximum 600 mg)	10–20 mg/kg (maximum 600 mg)	None	Hepatotoxicity Cytopenias Red-orange body fluids Interstitial nephritis Severe rash Major drug interactions
Pyrazinamide	40–55 kg: 1000 mg 56–75 kg 1500 76–90 kg 2000 mg (Use lean body weight)	Over 2 years old, <40 kg: 15–30 mg/kg/day	Mild	Hepatotoxicity Cytopenias Hyperuricemia Interstitial nephritis
Ethambutol	15–25 mg/kg PO (maximum 1.6 g)	15–20 mg/kg PO (maximum 1.0 g)	Mild	Hepatotoxicity Neurotoxicity (optic neuritis, visual loss) Cytopenias
Streptomycin	15 mg/kg (max 1 g) IM or IV[3] given 2–5 times/week	20–30 mg/kg IM or IV (max 1 g)	Major	Nephrotoxicity Ototoxicity (auditory and vestibular) Neuromuscular blockade Cytopenias
Second line drugs				
Kanamycin	15 mg/kg (maximum 1.0 g) IM or IV[3]	15–30 mg/kg (maximum 1.0 g) IM or IV[3]	Major	Nephrotoxicity Ototoxicity (auditory and vestibular) Neuromuscular blockade
Amikacin	15 mg/kg (maximum 1.0 g) IM or IV[3]	15–30 mg/kg (maximum 1.0 gm) IM or IV[3]	Major	Nephrotoxicity Ototoxicity (auditory and vestibular) Neuromuscular blockade
Rifabutin	5 mg/kg PO (maximum 300 mg)	Appropriate dosing for children is unknown	None	Cytopenias Red-orange colored body fluids
Levofloxacin	750 mg/day PO or IV	N/A	Moderate	*C difficile*-associated diarrhea QT prolongation Tendonitis
Ethionamide	15–20 mg/kg (maximum 1.0 g; usual daily dose 500–750 mg)	15–20 mg/kg (maximum 1.0 g)	Mild	Hepatitis Neurotoxicity (peripheral neuropathy and optic neuritis) Hypothyroidism
Cycloserine	10–15 mg/kg (maximum 1.0 g/d in two doses; usual dose 500–750 mg/d in two doses)	15–20 mg/kg (maximum 1.0 g/d in two doses)	Moderate	Neurotoxicity (seizures, psychosis) Congestive heart failure Transaminitis
Capreomycin	15 mg/kg (maximum 1.0 g) IM or IV[3]	15–30 mg/kg (maximum 1.0 g) IM or IV[3]	Major	Nephrotoxicity Ototoxicity (auditory and vestibular) Neuromuscular blockade

Dosing was adapted from Ref. (6).

[1]Children weighing more than 40 kg should be dosed as adults.

[2]The degree of drug dose alteration for renal dysfunction reflects the creatinine clearance at which dose reduction is first necessary: Thus it is minimal when dose reduction is first necessary for CrCl $\leq$ 10 cc/min, mild for CrCl $\leq$ 30 cc/min, moderate for CrCl $\leq$50 cc/min and major for CrCl $\leq$ 70 cc/min.

[3]Smaller doses (10 mg/kg) are generally used in adults over the age of 50. Streptomycin is usually not given more than five times a week and frequency may be reduced to 2–3 times a week as patients clear their infection.

activity against MTB that is similar to rifampin, but rifabutin is a much less potent inducer of cytochrome P3A4, and therefore immunosuppressant levels may be easier to maintain (68). There is relatively little published clinical experience using rifabutin after transplantation, since active TB is relatively uncommon in transplant recipients in the United States and rifabutin is generally not available in parts of the world in which TB is more common. However, in HIV-infected individuals, the effectiveness of rifabutin-containing regimens appears no different than that of rifampin-containing regimens. Rifabutin dose is 5 mg/kg (maximum 300 mg) given once daily. With either rifampin or rifabutin, immunosuppressant levels should be monitored closely when the rifamycin is started (as higher doses of the immunosuppressant will be required) and when it is stopped (as the dose may then need to be reduced). Management of posttransplant TB with nonrifamycin regimens has been successful in countries where rifabutin is not available (69,70). When prescribing medications for treatment of latent or active TB a careful review of all drug-drug interactions is recommended. Refer to Chapter 32 in the guidelines for further information.

The hepatotoxicity of isoniazid, rifampin and pyrazinamide used in combination is greater than isoniazid alone and noted to be particularly severe in liver recipients (57). Liver function tests should be closely monitored. Isoniazid use may be associated with peripheral neuropathy and other neurotoxicity. Ethambutol use can impair visual acuity; early detection with periodic ophthalmologic monitoring for toxicity is recommended.

Future Directions and Research

Transplant physicians can derive valuable information about the management of TB after transplantation from ongoing research in nontransplant populations. Since immunosuppression may eliminate TST and IGRA responses, development of diagnostic tests for LTBI that do not rely on an intact T cell response would greatly improve diagnosis and clinical management, especially in the case of donor derived infections. Another important advance would be the development and/or clinical validation of antituberculous drugs that are free of significant organ toxicities and drug–drug interactions. New treatment regimens are on the horizon, including potent drugs that may have the potential to shorten and simplify anti-TB therapy (4). Evaluation of these in transplant candidates and recipients may provide useful treatment alternatives for this population in the future.

Acknowledgment

This manuscript was modified from a previous guideline written by Aruna Subramanian and Susan Dorman published in *American Journal of Transplantation* 2009;9 (Suppl 4): S57–S62 and endorsed by the American Society of Transplantation/Canadian Society of Transplantation.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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