Tuberculosis and Transplantation

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ABSTRACT Mycobacterium tuberculosis is a major opportunistic pathogen in transplant recipients. Compared to that in the general population, the frequency of tuberculosis (TB) is 10 to 40 times higher in hematopoietic stem cell transplant (HSCT) recipients and 20 to 74 times higher in solid-organ transplant (SOT) recipients. Transplant recipients with TB are also more likely to develop disseminated disease, have longer time to definitive diagnosis, require more invasive diagnostic procedures, and experience greater anti-TB treatment-related toxicity than the general population. Specific risk factors for TB in SOT recipients include previous exposure to M. tuberculosis (positive tuberculin skin tests and/or residual TB lesions in pretransplant chest X ray) and the intensity of immunosuppression (use of antilymphocyte antibodies, type of basal immunosuppression, and intensification of immunosuppressive therapy for allograft rejection). Risk factors in HSCT recipients are allogeneic transplantation from an unrelated donor; chronic graft-versus-host disease treated with corticosteroids; unrelated or mismatched allograft; pretransplant conditioning using total body irradiation, busulfan, or cyclophosphamide; and type and stage of primary hematological disorder. Transplant recipients with evidence of prior exposure to M. tuberculosis should receive treatment appropriate for latent TB infection. Optimal management of active TB disease is particularly challenging due to significant drug interactions between the anti-TB agents and the immunosuppressive therapy. In this chapter, we address the epidemiology, clinical presentation, diagnostic considerations, and management strategies for TB in SOT and HSCT recipients.

TUBERCULOSIS AND ORGAN TRANSPLANTATION

Epidemiology and Risk Factors
Mycobacterium tuberculosis is an important opportunistic pathogen in solid-organ transplant (SOT) recipients (1–4), with high morbidity and mortality rates. The frequency of tuberculosis (TB) in SOT recipients ranges from 1.2 to 15% (1–3), which is 20 to 74 times higher than that of the general population. Unfortunately, the exact incidence of tuberculosis in SOT recipients is not well known. Table 1 shows the prevalence and incidence rates of TB in SOT recipients in the most numerous series in the literature (1–8) and compares them with information available from the Spanish Network of Infection in Transplantation (RESITRA) (7).

Though SOT recipients should be considered a high-risk group for TB, the risks of developing TB vary among the different types of transplants. As an example, the incidence of TB is particularly high in lung transplant recipients (9, 10). Lung transplant recipients have 5.6 times higher risk of developing TB than other SOT recipients and a 73.3 times higher risk of TB than non-immunosuppressed patients (2). In the RESITRA series, the overall TB incidence in SOT recipients was 2.5 times higher than in the general population, 4 times higher than in allogeneic hematopoietic stem cell transplant (HSCT) recipients (11), and 6 times higher than in candidates for a transplant (7). A recent study that compared the clinical features of SOT recipients diagnosed with TB with those from the general population reported that SOT patients were significantly more likely to develop disseminated TB and anti-TB-related toxicity and that the time to a definitive diagnosis was longer in the
SOT population and generally required invasive procedures (12).

Most cases of TB in SOT recipients are caused by reactivation of latent infection upon initiation of immunosuppressive therapy. However, few risk factors have been clearly defined for these patients (13, 14), since most series are retrospective or small and lack control transplant recipients without TB (13, 15–17). Furthermore, most of the available information refers to kidney recipients, and this cannot necessarily be extrapolated to other transplant recipients.

Previously described risk factors (Table 2) include history of prior exposure to Mycobacterium tuberculosis (positive tuberculin skin tests [TST] and/or residual TB lesions in pretransplant chest X ray). Recipient’s age, dialysis, diabetes mellitus, chronic liver disease, hepatitis C virus infection, previous transplantation, and the intensity of immunosuppression (use of antilymphocyte antibodies, baseline immunosuppression, and intensification of immunosuppressive treatment as a result of rejection) are known risk factors for developing TB after transplantation (3, 7, 13, 14, 18, 19). The intensification of immunosuppression therapy appears to be particularly important (20). Indeed, 65% of the patients in some series were considered to be overimmunosuppressed, as they required treatment for rejection (1). Everolimus was an independent risk factor for TB in lung transplantation according to one report (21). It has been suggested that the use of antilymphocyte antibodies (in particular OKT3) increases the risk of dissemination (22), as shown in murine models (23). However, the crude mortality does not appear to increase when these immunosuppressants are used (1). Monoclonal antibodies (daclizumab or basiliximab) do not appear to increase the risk of TB in SOT recipients (7). It seems reasonable to assume that other factors associated with increased risk of TB in the general population are also relevant in transplant recipients, such as smoking, malnutrition, or human immunodeficiency virus (HIV) infection.

### TABLE 1 Prevalence and incidence of TB in SOT

<table>
<thead>
<tr>
<th>Frequency measure</th>
<th>Overall</th>
<th>Pulmonary</th>
<th>Cardiac</th>
<th>Kidney</th>
<th>Hepatic</th>
<th>Kidney-Pancreas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Literature*</td>
<td>1.2–6.4%</td>
<td>2–6.5%</td>
<td>1–1.5%</td>
<td>0.5–15%</td>
<td>0.7–2.3%</td>
<td></td>
</tr>
<tr>
<td>RESITRA</td>
<td>15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence (cases/10^6 transplants/yr [range])</td>
<td>512 (317–783)</td>
<td>2,072 (565–5,306)</td>
<td>255 (6.5–1,421)</td>
<td>358 (144–728)</td>
<td>541 (269–1,065)</td>
<td>1,204 (30.5–6,710)</td>
</tr>
</tbody>
</table>

*Data from references 1 to 4, 7, 8, and 17.
*Data from RESITRA (7).
*In developed countries.
*In areas where TB is highly endemic.

### TABLE 2 Risk factors for TB

- History of previous exposure to Mycobacterium tuberculosis
- Positive purified protein derivative result (degree of evidence III)
- Radiological evidence of untreated previous TB (degree of evidence III)
- Pretransplant clinical conditions
  - Recipient’s age
  - Chronic renal insufficiency or hemodialysis (kidney transplant) (degree of evidence II)
  - Diabetes mellitus (degree of evidence II)
  - Hepatitis C virus (kidney transplant) (degree of evidence III)
  - Chronic liver disease (degree of evidence III)
  - Other coexisting infections: severe mycoses, cytomegalovirus, Pneumocystis jirovecii or Nocardia pneumonia (degree of evidence III)
- Immunosuppressive therapy
  - OKT3 or anti-T-lymphocyte antibodies (degree of evidence III)
  - Intensification of immunosuppression associated with graft rejection (degree of evidence III)
  - Mycophenolate mofetil and tacrolimus vs azathioprine-cyclosporine-prednisone (degree of evidence III)
  - Everolimus in lung transplantation

**CLINICAL PRESENTATION: CHRONOLOGY AND CLINICAL SYMPTOMS**

The time of the onset of symptoms of TB after transplantation varies. Although a bimodal distribution has been observed (1, 20, 24), most SOT recipients develop TB in the first year after transplant, with a median time of onset of 9 months (7). However, up to one-third of the patients may develop TB later in the posttransplant period. We have observed that renal transplant patients have later onset of symptoms than other SOT recipients (7). This may be due in part to the lower intensity of immunosuppression received by these patients than for lung or heart transplant recipients, for example.
Although it has been suggested that patients developing early (during the first year of transplantation) TB were more severely immunosuppressed than patients with late TB (25), we and other authors (1, 20) did not confirm this finding. Nevertheless, patients with prior clinical or radiological evidence of TB develop the disease earlier. These data suggest that patients with a history of TB have a higher risk of reactivation during the first months after transplantation, independently of the type of immunosuppression received.

Pulmonary TB is the most frequent type of disease in an SOT setting. Nevertheless, the number of patients who develop extrapulmonary or disseminated forms of TB is higher than in the general population (26), with incidence rates as high as 38 to 64% (26, 27). Extrapulmonary or disseminated forms are more frequent in the first 6 months after transplantation, coinciding with the peak of maximum iatrogenic immunosuppression.

The most common symptoms are fever, cough, dyspnea, musculoskeletal pain, night sweats, and weight loss, along with lymphadenopathy. Unlike in the general population, TB in SOT recipients can be asymptomatic, and the diagnosis is established by routine surveillance cultures; not infrequently, the diagnosis is made at necropsy. Additionally, up to one-third of the patients may have a normal chest radiograph (28).

Pulmonary TB usually manifests with cough, fever, tachypnea, hemoptysis, and radiological images of parenchymal involvement in upper lobes, diffuse involvement, or miliary dissemination. Cavitation is rare, as also shown in highly immunosuppressed HIV patients. The most common presentation of gastrointestinal TB is fever, gastrointestinal bleeding, and abdominal pain (29). The ileocecal area is most frequently affected. Patients with urological TB develop urinary symptoms, back pain, and fever accompanied by sterile pyuria.

The most common presenting symptom of disseminated TB is fever. Initial symptoms may resemble life-threatening sepsis or adverse drug reactions. Involvement of less typical sites, such as osteoarticular and cutaneous sites, is often a manifestation of dissemination. No association has been documented between age, type of organ transplanted, type of immunosuppressive therapy, rejection, or history of exposure to mycobacteria and the development of disseminated TB.

**DIAGNOSTIC CONSIDERATIONS**

Establishing the diagnosis can be challenging, and it is not uncommon for the diagnosis of TB in SOT recipients to be delayed for weeks, due to lack of clinical suspicion. Diagnosis is particularly difficult because the patients are often asymptomatic or minimally symptomatic and only about one-quarter of the patients have clinical or radiological findings typical of TB. In addition, a large proportion of SOT recipients have a negative TST due to anergy secondary to pharmacological immunosuppression.

The presence of fever, night sweats, weight loss, lymphadenopathy, or radiographic abnormalities should raise suspicion of TB, especially in patients with a history of contact with M. tuberculosis who have not received treatment for latent TB infection. TB is particularly worrisome in lung transplant recipients; TST and pretransplant thoracic imaging have little value, as TB can be secondary to the reactivation of a latent infection of the graft (7).

Once TB is suspected, it is necessary to perform microbiologic tests to confirm the diagnosis, including collection of sputum samples and/or urine for acid-fast bacillus smears and culture. Isolation by culture is the most sensitive method for diagnosis, identification of species, and drug susceptibility testing. Nucleic acid amplification testing of respiratory and or extrapulmonary specimens may also be required to confirm the diagnosis. If the diagnosis cannot be established with the usual techniques and clinical suspicion remains high, invasive diagnostic procedures such as bronchoscopy, mediastinoscopy, or laparoscopy with biopsy should be considered.

The diagnostic yield of TST is low after transplantation. Regardless, TST remains the initial step in posttransplant evaluation of suspected TB. Unfortunately, in spite of being widely recommended, TST was carried out for only 40.6% of the patients (7) and prophylaxis was employed in less than half of those with positive TST in the RESITRA cohort.

A positive TST should be regarded as an induration over or equal to 5 mm in diameter 48 to 72 h after the administration of 2 IU of strain RT-23, equivalent to 5 IU of purified protein derivative tuberculosis. Two T-cell interferon gamma release assays (IGRAs) are now available for detection of latent TB infection: the QuantiFERON-Gold In-Tube test (Cellestis) and T-SPOT.TB (Oxford Immunotec Ltd.) (30, 31). Both tests employ a mitogen-induced positive control to differentiate between anergic and true negative patients, and results can be qualitative or quantitative. QuantiFERON had higher positivity than TST for determining the risk of latent TB infection and development of TB in kidney transplant recipients (32, 33). Although QuantiFERON is technically easier to perform, T-SPOT had greater sensitivity and specificity with immunosuppressed patients (31).
TST or IGRAs do not differentiate between TB infection and disease, but they can be helpful in newly positive recipients with suspicion of TB disease. Both modalities can be used for SOT recipients, with appropriate timing between them in order to avoid induction of a false-positive IGRA result (34).

**EVALUATION OF CANDIDATES AND DONORS**

**Evaluation of SOT Candidates**

SOT candidates must be screened for clinical evidence of TB infection or active disease and for previous TB treatments (type of drugs prescribed and length of treatment). It is important to assess if the patient has been exposed to individuals with active TB disease in the household, in the workplace, or via travel to areas where TB is endemic as well as to assess the results of previous TST or IGRA.

All candidates should undergo TST, even if they have been vaccinated against *Mycobacterium bovis* BCG (degree of evidence AII). This test should be repeated 2 weeks later (booster effect) whenever the TST is considered negative and IGRA results are unavailable. The concurrent use of TST and IGRA can increase the sensitivity of the diagnosis of TB. Patients previously treated for latent TB infection or for active TB disease do not need to undergo TST or IGRA (30). Therefore, the TST must be interpreted in context of whether the transplant candidate has received treatment for latent *M. tuberculosis* infection. The TST result should also be interpreted independently of the BCG vaccination status (35). Discordant TST and IGRA results also require an exhaustive assessment of the candidate’s TB risk (30).

Chest radiography should also be performed to evaluate for lesions of old healed TB. Active TB should always be ruled out in patients with positive TST or IGRA results, and it contraindicates transplantation. A patient with active pulmonary TB could possibly be considered a candidate for nonpulmonary SOT, as long as the patient is already receiving treatment and stains for the detection of acid-fast bacilli in sputum are negative when the transplant is to be performed.

Before initiation of treatment of latent *M. tuberculosis* infection, active TB (culture and PCR for mycobacteria in sputum and urine samples) should be carefully excluded. For patients with radiological findings consistent with TB who are unable to expectorate, sputum should be induced with hypertonic saline or a fiber optic bronchoscopy should be performed (36).

**Management of Candidates with a Positive TST or IGRA Result**

Patients with a positive TST or IGRA result warrant exclusion of TB (AII). If clinical or radiological data suggest TB, sputum smears and culture must be performed, and if this is not feasible, bronchoscopy and culture of the bronchoalveolar aspirate/lavage fluid should be performed. Clinically guided additional examinations may be necessary, such as abdominal ultrasound to detect enlarged abdominal lymph nodes or biopsy and lymph node culture. For asymptomatic patients whose chest radiograph reveals residual lesions, sputum should be cultured and, in specific cases, bronchoscopy and culture of aspirate or lavage fluid should be performed. Once active TB has been ruled out, treatment for latent TB infection can be initiated while the patient is on the waiting list (see below) and, if necessary, continued after the transplant to complete the appropriate duration of treatment.

**Evaluation of SOT Donors**

TB transmission from donors to recipients has been described for kidney, lung, and liver transplantation (37–39). Living donors should undergo evaluation similar to that of SOT candidates (30, 31, 40), and treatment for latent TB, when recommended, should be considered prior to transplantation. It is imperative to rule out active TB, starting with a meticulous clinical review of the donor and a chest X-ray (AII) (30). The value of the radiological data as an indication of a history of TB is greater in areas such as Europe, where regional mycoses that could cause similar lesions, such as histoplasmosis, coccidioidomycosis, or blastomycosis, are not prevalent. Techniques that amplify the nucleic acids of *M. tuberculosis* are highly sensitive and specific in respiratory samples and may prove useful in the evaluation of donors (30, 31). Unfortunately, in the case of nonliving donors, clinical data concerning history of TB are usually not available. Therefore, biopsies and cultures of lymph nodes should be performed at the time of transplantation to rule out active TB disease. Moreover, a previous history of TB—especially in the previous 2 years—should be obtained from the donor’s family (31). Individuals for whom active TB is a strong consideration should not be considered potential donors (AII). Residual pulmonary lesions compatible with TB also contraindicate lung donation. Recipients of an organ whose donor has clinical data that suggest untreated TB should receive treatment for latent TB infection (3, 30, 31, 41).
TREATMENT OF LATENT M. TUBERCULOSIS INFECTION IN SOT CANDIDATES AND RECIPIENTS

Indications for Treatment of Latent M. tuberculosis Infection

TB is a significant cause of morbidity and mortality in SOT recipients and an important public health issue globally. Therefore, treatment for latent M. tuberculosis infection should be employed for transplant candidates awaiting transplantation or SOT recipients who have one or more of the following conditions: (i) a TST (initial or after a booster effect) with an induration of ≥5 mm and/or a positive IGRA, (ii) clinical data or chest radiograph findings compatible with untreated TB (apical scarring lesions, calcified solitary nodules or lymph nodes, and pleural thickening), or (iii) a history of contact with a patient with active TB (AII) (30, 31). Active TB disease must be ruled out before initiating treatment. Treatment of latent M. tuberculosis infection should begin before transplantation, although this approach can be challenging in the case of liver transplant candidates. If the treatment was not completed before transplantation, then it should be resumed as soon as the recipient is medically stabilized and continued as planned (30, 31).

Recommendations for the Treatment of Latent M. tuberculosis Infection

According to the American Society of Transplantation (30) and the European Society of Clinical Microbiology and Infectious Diseases (31), isoniazid (INH; 300 mg/daily), supplemented with pyridoxine (vitamin B₆) for 9 months, is the drug of choice for treatment of latent M. tuberculosis infection (3, 35, 42–44). Prophylaxis with INH has proven to prevent TB in randomized studies involving kidney recipients (43, 45, 46) (AII).

The length and dose of INH therapy are similar irrespective of whether it is administered before or after transplantation (30, 31). Patients who have completed therapy before transplantation do not need to repeat it after the procedure (30, 31).

All patients receiving INH should be routinely monitored for hepatotoxicity. Tolerance to INH is generally good (46–48) and the interaction with calcineurin inhibitors is very limited (49, 50), although some increase of the corticosteroid levels has been reported. In a cohort of kidney transplant patients receiving INH prophylaxis, 11% had evidence of hepatic dysfunction attributable solely to INH and 2.5% developed major hepatic dysfunction, with two deaths related to liver failure (51). These results have prompted some investigators to suggest that INH chemoprophylaxis be limited to high-risk patients, i.e., patients born in areas of endemicity and those with chronic advanced underlying illness, rejection treatment and/or adjunctive immunosuppression, abnormal chest X ray, or recent TST or IGRA conversion.

All patients should have baseline hepatic measurements of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin (30, 31). A possible follow-up approach is to monitor at 2-week intervals in the first 6 weeks and monthly thereafter (30). Patients should be informed about the side effects associated with treatment of latent TB and advised to discontinue it and promptly seek medical evaluation if they occur. Low-grade elevations of AST and ALT are relatively common. Treatment of latent M. tuberculosis infection should be discontinued if these values increase 3-fold in patients with symptoms or signs of hepatotoxicity or if the increase is 5-fold in patients without accompanying symptoms (30, 31, 52). These patients should be closely monitored, and treatment of latent M. tuberculosis infection should be completed with drugs other than INH, especially in high-risk patients, such as recipients or donors with recent conversion of TST or IGRA or lung transplant recipients, for whom the risk factors should be individualized (31). If the standard treatment is not an option, alternative regimens with moxifloxacin or levofloxacin with or without ethambutol have been previously used, although data are still limited (30, 31). A liver biopsy is also recommended when there is a doubtful diagnosis or when laboratory values do not return to normal after treatment is stopped (31).

Other prophylactic regimens include INH (maximum of 900 mg) twice weekly for 9 months by directly observed therapy (DOT), rifampin (maximum of 600 mg daily) for 4 months (with or without INH), and weekly rifapentine with INH for 3 months by DOT (30) (Table 3). Combined regimens allow a shorter duration of treatment and a higher possibility of therapy completion before transplantation and appear to have fewer side effects. The combined regimen of rifampin with pyrazinamide for 2 months was associated with severe liver toxicity and is no longer recommended (30, 31). It is advisable to use treatment regimens that include rifampin or rifapentine prior to transplantation given significant drug interactions between the rifamycins and the immunosuppressive drugs.

When active TB cannot be ruled out in an SOT recipient, it is recommended to start treatment with 3 drugs (INH, ethambutol, and pyrazinamide) (35). A
fourth drug, e.g., a fluoroquinolone, should be added if the disease is severe or until susceptibilities are known. Treatment can be completed with only INH if, after 8 weeks, cultures are negative for *M. tuberculosis* and the chest radiograph is considered normal (35).

Patients who have previously received adequate treatment for latent *M. tuberculosis* infection or active TB disease need not be treated again after transplantation.

**Treatment of Latent TB in Liver Transplant Recipients**

It is prudent to delay the administration of INH until after transplantation in liver transplant candidates (30, 31). Recent published data suggested that levofloxacin or moxifloxacin prior to transplantation could be an alternative to INH, although adverse effects were described (36).

Latent *M. tuberculosis* infection treatment in liver transplant recipients remains controversial, and the decision should be individualized. Some authors consider that the risk of hepatotoxicity outweighs any potential benefits, since the frequency of TB reactivation is not particularly high (36, 54). Nevertheless, a recent review documented significant reduction in TB reactivation and minimal INH-related toxicity in liver transplant recipients (35, 56). The Group for the Study of Infection in Transplant Recipients (GESITRA) consensus statement (35) recommends delaying the administration of treatment until after transplantation, starting as soon as the graft function is stable. It seems advisable to treat all liver recipients with high-risk factors for developing TB disease such as recent TST or IGRA conversion, a history of inappropriately treated TB, direct contact with an untreated person with active TB, residual TB lesions on the chest radiograph, and additional immunosuppression factors (e.g., treatment of graft rejection episodes in patients with a positive TST who have not received treatment for latent TB infection). An increase in AST or ALT in liver transplant recipients should not be instinctively attributed to INH, and a specific diagnosis should be sought (30).

**TREATMENT OF TB IN SOT RECIPIENTS**

Treatment of TB in transplant patients is complicated due to high risk of toxicity, particularly in liver recipients. The recommendations for the treatment of TB in transplant recipients are similar to those in the general population (30, 31, 35). Nevertheless, the interaction between rifamycins (rifampin, rifabutin, or rifapentine) and the calcineurin inhibitor immunosuppressive agents (cyclosporine and tacrolimus), rapamycin, and corticosteroids warrants careful monitoring of the levels of these drugs. Moreover, the optimal duration of treatment is controversial and the recommendations are extrapolated largely from case series, studies in the general population, and consensus guidelines based on expert opinion (7, 30, 31, 35, 57, 58).

The decision to use specific regimens in SOT recipients is driven by the rate of resistance in each country and based on the epidemiology in individual cases. Mycobacterial susceptibility testing is critical for designing the treatment of TB in SOT recipients, especially in the settings of multidrug-resistant and extensively drug-resistant TB. Although rifampin has been widely used in SOT recipients (mainly kidney recipients), it is controversial whether rifampin should be used at all in this host population or in a specific group of SOT patients (6, 31, 59). It is prudent to avoid rifamycins in patients with localized, nonsevere forms of TB and without suspicion or evidence of resistance to INH (35). The GESITRA consensus statement (35) recommends rifamycins only for patients with severe or disseminated forms of TB or with suspicion or evidence of resistance to INH (Table 4).

Rifampin causes a profound reduction in the serum levels of tacrolimus, cyclosporine, rapamycin (sirolimus), everolimus, and corticosteroids and poses a high risk of graft rejection (60, 61). Therefore, the dose of calcineurin inhibitors should be increased 3- to 5-fold, and levels should be closely monitored (31). Even with careful monitoring, concurrent use of rifampin and cyclosporine incurs substantial risk of graft rejection, graft loss, and overall TB-related mortality (1–3). Rifabutin could be

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**TABLE 3 Suggested regimens for the treatment of latent TB in SOT**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH (5 mg/kg daily)</td>
<td>9 mo</td>
<td>Combine with pyridoxine, 25–50 mg/day, to decrease the risk of INH-induced neurotoxicity</td>
</tr>
<tr>
<td>INH (15 mg/kg twice weekly, DOT)</td>
<td>9 mo</td>
<td>Combine with pyridoxine, 25–50 mg/day, to decrease the risk of INH-induced neurotoxicity</td>
</tr>
<tr>
<td>Rifampin (10 mg/kg)</td>
<td>4 mo</td>
<td>Used preferably before transplantation due to interaction with immunosuppressive drugs</td>
</tr>
<tr>
<td>INH (15 mg/kg) plus RFP (&lt;50 kg, Once weekly)</td>
<td>9 mo</td>
<td>Used preferably before transplantation due to RFP interaction with immunosuppressive drugs</td>
</tr>
<tr>
<td>750 mg: &gt;50 kg, 900 mg (DOT)</td>
<td>3 mo</td>
<td>Used preferably before transplantation due to RFP interaction with immunosuppressive drugs</td>
</tr>
</tbody>
</table>

*INH, isoniazid; RFP, rifapentine; SOT, solid-organ transplantation.*
TABLE 4 Treatment of TB in SOT recipients according to the GESITRA of the Spanish Society of Infectious Diseases and Clinical Microbiology (35)

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Initial treatment</th>
<th>Maintenance treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with localized, nonsevere forms of TB without suspicion or evidence of resistance to INH</td>
<td>INH, ethambutol, and pyrazinamide (or levofloxacin) Avoid the use of rifamycins; if rifamycins are used, the levels of immunosuppressors should be closely monitored and the doses of cyclosporine or tacrolimus increased (AII) If treatment is started early, it is not necessary to reduce immunosuppression (CIII)</td>
<td>INH and ethambutol (or pyrazinamide) are recommended for 12–18 mo (CIII) Incorporation of a third drug, such as pyrazinamide or levofloxacin,* could reduce this period to 12 mo (CIII)</td>
</tr>
<tr>
<td>Severe, mainly disseminated, forms of TB or suspicion or evidence of resistance to INH*</td>
<td>Consider adding rifampin or rifabutin to INH, ethambutol, and pyrazinamide (or levofloxacin) (BIII)*</td>
<td>Complete treatment with INH and rifampin or rifabutin until completion of at least 9 mo of treatment</td>
</tr>
<tr>
<td>In cases of multiresistance or when there is limitation for the use of the above-mentioned drugs</td>
<td>If INH and rifamycins cannot be used, induction treatment should include 4–6 drugs, including injectable antimicrobials—such as streptomycin,6 amikacin, kanamycin, capreomycin, linezolid, or other second-line drugs (CIII)*</td>
<td>Absence of INH and rifamycin in initial treatment makes it difficult to calculate duration of treatment and types of drugs to be used; therapy should be individualized</td>
</tr>
</tbody>
</table>

*Prolonged use of fluorquinolones can be associated with arthralgias, and the combination of pyrazinamide and levofloxacin is poorly tolerated due to gastrointestinal side effects.

1The use of rifampin or rifabutin would require increased doses of cyclosporine or tacrolimus and closer monitoring of the levels of these drugs (AII). Resistance to rifampin is associated with cross-resistance to rifabutin and rifapentine; therefore, these are not suitable alternatives (DII).

If INH cannot be used, initial and maintenance treatment that includes four drugs for at least 18 months should be employed (CIII).

In cases of resistance to streptomycin, there is no cross-resistance with other parenteral drugs (amikacin, kanamycin, or capreomycin); however, cross-resistance between amikacin and kanamycin is universal. The combination of injectable drugs is not recommended, given their intolerance and side effects (DII).

There is no experience with the use of intermittent regimens, which regardless are not recommended in the management of multiresistant TB, except for the use of injectable drugs once a period of at least 2 to 3 months of daily administration has been completed (DII).

In liver recipients, the development of liver toxicity is a particular concern during the treatment of TB (31). In recipients of other organs, INH is generally well tolerated, although hepatotoxicity has been reported for kidney recipients. As noted above, rifampin must be used with extreme caution when treating TB in transplant recipients. When combined with INH, there is substantial increase in hepatotoxicity, especially in liver recipients. Initial treatment with INH, rifampin, and pyrazinamide in liver recipients has been associated with histologically confirmed hepatotoxicity in 88% of cases (69). A particularly high risk of hepatotoxicity has also been reported with the combination of rifampin and pyrazinamide for the treatment of latent M. tuberculosis infection (69). The length of TB treatment in SOT recipients remains a controversial issue and is discussed separately in this chapter.

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Special Considerations for HIV-Infected Transplant Recipients

More than 200 liver transplantations have been performed in HIV-infected patients, and the risk of TB does not seem to be significantly greater after transplantation than it is before transplantation (70). The main challenges after transplantation are the drug interactions and the recurrence of hepatitis C virus infection, which may increase the risk of TB and attendant toxicity (14, 71).

The standard regimen used for treatment of TB in HIV-infected transplant recipients seems to be as effective as in other HIV-infected patients (72). Rifamycins may lead to greater hepatotoxicity in HIV-infected patients than in non-HIV-infected patients and jeopardize antiretroviral therapy because of their interaction with protease inhibitors and nonnucleoside reverse transcriptase inhibitors. All three groups of drugs can inhibit or induce the isoenzyme family of cytochrome P450, thus leading to interactions that are difficult to manage. A combination of INH, pyrazinamide, ethambutol, and a quinolone is recommended for these patients. The use of aminoglycosides is limited by the risk of nephrotoxicity induced by calcineurin inhibitors.

Risk of IRS

It is noteworthy that, as in the case of HIV-infected patients, SOT recipients with TB can develop an immune reconstitution syndrome (IRS) related to changes of the immunosuppressive therapy and/or to interactions between the immunosuppressant agents and the anti-TB drugs, especially rifamycins (73–75). IRS in SOT recipients could be interpreted as failure of therapy or a relapse, often leading to unnecessary changes in therapy and inappropriate management decisions (76). The most common symptoms of TB-associated IRS are fever, lymphadenopathy, and worsening respiratory symptoms (77). A recent study that included 64 consecutive SOT recipients with TB monitored for 13 months reported IRS for 14% of these patients (75). Liver transplant recipients, patients with prior cytomegalovirus infection, and recipients of a rifampin-based anti-TB regimen were more likely to develop an IRS during the follow-up (75).

Duration of TB Treatment in SOT Recipients

The duration of treatment and type of drugs to be used after the first 2 months are controversial, especially if rifampin is not used or must be discontinued due to side effects. Some authors recommend a daily 6-month treatment for TB in SOT recipients (30). The length of treatment should be extended in patients with osteoarticular disease (6 to 9 months), central nervous system (CNS) disease (9 to 12 months), severe disseminated disease (6 to 9 months), and cavitary pulmonary TB and culture-positive sputum after 2 months of treatment (9 months) and in recipients of second-line drug regimens or rifamycin-free regimens, as rifamycins have potent bactericidal activity against M. tuberculosis (30). In these cases, the induction phase would be 2 months, but the continuation or maintenance phase should be longer.

Treatment for less than 9 months has been associated with greater mortality (1). The only factor that was significantly associated with recurrence of TB was the duration of treatment; no recurrence was observed in patients who received more than 12 months of therapy, irrespective of whether the treatment regimen included rifampin (78). For this reason, the European Society of Clinical Microbiology and Infectious Diseases (31) recommends a minimum of 9 months of treatment that includes a rifamycin-containing regimen and 12 to 18 months of treatment for rifamycin-sparing regimens (31). This Society also suggests 12 to 18 months of treatment for recipients with extrapulmonary TB and for recipients with cavitary pulmonary TB that remain culture positive after 2 months (31).

Extrapolating from data for the general population, relapses in optimally managed anti-TB regimens that do not include rifampin are usually associated with a rifamycin-susceptible strain. However, in rifamycin-sparing regimens, especially in unsupervised settings, drug resistance is more common (58).

In the general population, INH, pyrazinamide, and streptomycin have proven to be effective when administered for 9 months (58), although it is difficult to use streptomycin over long periods because of the risk of ototoxicity and renal toxicity. There are no studies on the use of ethambutol instead of streptomycin in these circumstances. Nevertheless, in the general population, and therefore in transplant recipients, oral regimens should be maintained for 12 to 18 months (CIII) and the benefit of injectable agents should be evaluated during the first 2 to 3 months in extensive or cavitary forms.

Outcome and Risk Factors Influencing Mortality

TB has implications relevant for outcomes in transplant patients. The overall mortality rate in solid-organ recipients with TB is as high as 29% (45). Disseminated TB (for example, the number of organs involved), prior rejection, and immunosuppressive therapy with antilymphocyte antibodies were associated with poor prognosis in these patients (3). The mortality rates attributable...
directly to TB can be up to 15%. TB-related mortality in these patients is significantly higher than in the general population and in transplant patients without TB (79, 80). However, a recent study including 64 transplant recipients with TB, when divided into 2 consecutive cohorts (cases occurring from 2003 to 2007 and cases from 2008 to 2011), showed a decrease of the mortality rate (21% to 10%, respectively), with ~90% of the patients now surviving TB (81).

The drug interactions associated with anti-TB therapy in SOT recipients are unique and play a considerable role in the poor outcome of TB in this population. We have previously shown that up to 25% of the patients lost their grafts due to rejection, and in the majority of cases, rejection was due to the interference of rifampin with cyclosporine. Other authors have reported similar findings (60, 61, 82). Rejection following interactions of rifampin with cyclosporine or tacrolimus was among the most significant risk factors for both crude and TB-related mortality.

TB AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

Epidemiology and Risk Factors

Although TB develops ∼10 times less commonly in HSCT recipients than in SOT recipients, the frequency of TB is 10 to 40 times higher in HSCT recipients than in the general population (12, 83–85). The incidence of TB in autologous HSCT recipients ranges from 0.05% to 0.26%, which is comparable to that in the general population. Allogeneic HSCT recipients, however, have a higher incidence, ranging from 0.1% to 5.5% (11, 86, 87). Approximately 95% of the cases of TB in HSCT recipients have been reported from developing countries, where HSCT is infrequently performed, in contrast to developed countries, where most HSCTs are performed (83). A vast majority of TB cases in HSCT recipients have been documented from areas where TB is endemic, such as Asia and certain parts of Europe. The incidence of TB varies from 1.6% in Spain and Turkey and 2.3% in India to 8.5% in Hong Kong and Taiwan and is as high as 16% in Pakistan (11, 84, 88–93). In a study comprising recipients of T-cell-depleted allografts in the United States, TB was documented for 0.69% of the patients; all were foreign born and originally came from areas where TB is endemic (92).

An estimated one-fourth of the cases in HSCT recipients are due to reactivation of latent *M. tuberculosis* infection (94). The median time to onset of TB is 257 days post-HSCT, although the disease has been documented as early as 2 weeks and as late as 1,410 days after HSCT (85, 90, 95, 96). The predisposition of HSCT recipients to TB is attributable largely to impairment of cell-mediated immunity due to (i) pretransplant conditioning therapy, (ii) immunosuppression in the posttransplant period, and (iii) graft-versus-host disease (GvHD) (83, 96, 97). Recipients of T-cell-depleted allografts have more profound and prolonged deficiency of cell-mediated immunity (98, 99). Major risk factors for TB are allogeneic transplantation from an unrelated donor, total-body irradiation, and chronic GvHD, with relative risks of 23.9, 4.9, and 3.6, respectively (95, 100). Patients with acute or chronic GvHD treated with corticosteroids were particularly at risk (88, 96, 101, 102). Other risk factors include unrelated or mismatched allograft; pretransplant conditioning regimens using total-body irradiation, busulfan, or cyclophosphamide; and type and stage of primary hematological disorders (83, 86, 88, 92, 100, 103–109) (Table 5).

Clinical Presentation

TB following HSCT typically has an indolent clinical course. Pulmonary TB is the most common manifestation (83, 96, 100, 110, 111). Clinical presentation of pulmonary TB usually mimics that in the nontransplant population, including cough, fever, dyspnea, chest pain, and weight loss (100, 112). The classic pulmonary findings, such as apical cavitation or infiltration, however, are typically lacking. Instead, nonspecific imaging findings with diffuse lobar-segmental infiltration, interstitial pneumonitis, adult respiratory distress syndrome, peripheral pulmonary nodules, and diffuse alveolar hemorrhage may occur (107). Clinical and radiological manifestations can resemble invasive fungal pulmonary

<table>
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<th>TABLE 5</th>
<th>Risk factors of TB in HSCT recipients</th>
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<td><strong>Allogeneic transplantation</strong></td>
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<td>Unrelated donor</td>
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<td>Mismatched allograft</td>
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<td>T-cell-depleted allograft</td>
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<td>Pretransplant conditioning therapies</td>
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<td>Total-body irradiation</td>
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<td>Chronic myeloid leukemia</td>
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<td>Myelodysplastic syndrome</td>
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<td>Bronchiolitis obliterans</td>
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<td>History of <em>M. tuberculosis</em> infection</td>
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<td>Use of monoclonal antibodies, e.g., rituximab</td>
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infection, or TB may coexist with fungal pathogens (113). On rare occasions, pulmonary TB may present with completely unremarkable computed tomography (CT) of the chest (111).

Up to 15% of the patients may have extrapulmonary TB involving the liver, spleen, kidney, bone, bone marrow, CNS, and joints (85, 94, 96, 111, 114, 115). One-third of the patients have disseminated TB with predominantly extrapulmonary involvement (83, 96, 116, 117). CNS disease can manifest as space-occupying lesions (115). On rare occasions patients may present with fever of unknown origin or acute abdomen secondary to abdominal mass or intestinal obstruction (118, 119). Notably, TB in umbilical cord blood transplant recipients may manifest as bacteremia with a fulminant course (94, 105, 120).

Diagnostic Considerations
Nonspecific clinical and radiological findings often necessitate invasive procedures, including tissue biopsy for establishment of diagnosis. Although CT-guided biopsy has been reported to be safe and efficacious, the risk associated with bleeding may preclude invasive diagnostic procedures (100, 121). The diagnostic yield of culture was 56% in one study, followed by microscopy for acid-fast bacilli (26%) and histology (20.3%) (107).

EVALUATION OF CANDIDATES AND DONORS
Candidates for HSCT
Based on the American Society for Blood and Marrow Transplantation guidelines, assessment of HSCT candidates should include history of prior active TB, prior exposure to high-priority contacts per Center for Diseases Control and Prevention (CDC) guidelines, and result of previous TST or IGRA. However, there was no agreement on the need and benefit of universal screening for HSCT candidates or on the superiority of TST versus IGRA for evaluation (103). On account of prior chemotherapy-induced immunosuppression, TST in HSCT candidates might not be as sensitive as in the healthy population or in SOT recipients. Although IGRA is more specific for TB, a negative test does not rule out the latent infection (122). Based on a meta-analysis, IGRA may have higher positive predictive value and negative predictive value for progression to active TB than those of the TST in high-risk patients (123). HSCT candidates with negative IGRA on pre-transplant testing had a very low risk for subsequent development of TB, with negative predictive values ranging from 95 to 100%, although they were predictors of active TB (87, 124–126).

Management of Candidates with a Positive TST
HSCT candidates with positive TST or IGRA or with history of a positive test should be evaluated for active TB. A chest X ray should be obtained. If active TB is detected or suspected, the patient should be isolated and treated. HSCT should be delayed until control of active TB has been achieved (103). Patients with positive TST and/or IGRA but without evidence of TB should be treated for latent TB and the HSCT need not be delayed (103).

Evaluation of HSCT Donors
The risk of donor-derived TB in HSCT recipients appears to be insignificant. Therefore, the American Society for Blood and Marrow Transplantation does not recommend screening for latent TB in the donor. If the donor is diagnosed with active TB, HSCT should be deferred until the donor is no longer infectious and is deemed to be medically fit (103).

Treatment of Latent M. tuberculosis Infection in HSCT Candidates and Recipients
Indications and recommendations for treatment of latent TB are the same as for SOT recipients. The treatment for latent M. tuberculosis infection should be initiated prior to conditioning therapy, if feasible, or upon completion of conditioning therapy as clinically indicated when the risk for disease is high (103).

Treatment of TB in HSCT Recipients
Management of active TB in the HSCT setting is the same as in the SOT population.

CONCLUSION
TB remains an important opportunistic infection in transplant recipients, although the mortality rates appear to have declined in the current era. Improvement in outcomes in transplant recipients with TB is a consequence largely of enhancement of our knowledge base due to data and experience accrued over the years. Novel assays that do not rely on T-cell immune response could facilitate rapid and reliable detection of latent M. tuberculosis infection. Finally, newer anti-TB agents that incur a lower risk for drug-drug interaction and shorten and simplify treatment regimens have the potential for further optimizing the management of TB in this immunocompromised host population.
REFERENCES


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Tuberculosis and Transplantation


