

# Tuberculosis in Solid-Organ Transplant Recipients: Consensus Statement of the Group for the Study of Infection in Transplant Recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology

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Tuberculosis is a particularly important condition in solid-organ transplant recipients because of the delay in treatment caused by the difficulties involved in its diagnosis and because of the pharmacological toxicity associated with this treatment. Both treatment delay and toxicity are responsible for the many clinical complications of and high mortality associated with tuberculosis in this population. The Consensus Statement from the Spanish Group for the Study of Infectious Diseases in Transplant Recipients defines the indications for treatment of latent tuberculosis infection in solid-organ transplant recipients, especially in patients with a high risk of pharmacological toxicity, as is the case with liver recipients. We established a series of recommendations regarding the types of drugs and the duration of treatment of tuberculosis in solid-organ recipients, giving special attention to pharmacological interactions between rifampin and immunosuppressive drugs (cyclosporine, tacrolimus, rapamycin, and corticosteroids).

## RATIONALE FOR AND TIMING OF THE CONSENSUS DOCUMENT

Tuberculosis (TB) is one of the most important opportunistic infections affecting solid-organ transplant (SOT) recipients [1–4] because of the high associated morbidity and mortality. Complications of TB therapy include interactions with immunosuppressors, lack of clear guidelines for the treatment of latent TB infection, and high risk of toxicity, particularly among liver recipients. Therefore, a goal of the Spanish Group for Study of Infectious Diseases in Transplant Recipients, as part of the Spanish Society of Infectious Diseases and Clinical Microbiology, was to unify the indications for and improve the management of TB in SOT recipients.

## DEFINITIONS AND METHODOLOGY

This article was written in accordance with the international recommendations on consensus statements (table 1) [5, 6]. The authors and coordinators agree on the content and conclusions.

## EPIDEMIOLOGY AND RISK FACTORS

The exact incidence of disease caused by *Mycobacterium tuberculosis* in SOT recipients is unknown. Although the literature mentions prevalence, this cannot be converted to or compared with incidence. Table 2 shows the prevalence and incidence rates of TB in SOT recipients in the most numerous series in the literature and compares them with information available (unpublished data) to the Spanish Group for Study of Infectious Diseases in Transplant Recipients and collected by the Spanish Network for the Study of Infection in Transplant Recipients. These data reveal a considerably higher risk of TB among SOT recipients, compared with the general population.

Most cases of TB in SOT recipients are caused by reactivation of a latent infection after immunosuppressive therapy is started. However, few risk factors have been clearly defined for these patients [7, 8]. This is mainly because most series are retro-

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**Table 1. Classification of the recommendations in this article, based on the strength and quality of the evidence analyzed.**

Category, grade	Definition
Strength of the evidence	
A	Solid evidence for efficacy and clinical benefit
B	Solid or moderately solid evidence for efficacy, but clinical benefit is limited
C	Insufficient evidence for efficacy, or the possible benefits in terms of efficacy do not outweigh the cost or risks (toxicity and medication interactions); valid alternatives are available
D	Moderately solid evidence for a lack of efficacy or poor outcome
E	Strong evidence for a lack of efficacy or poor outcome
Quality of the evidence	
I	Evidence from at least 1 well-designed and performed trial
II	Evidence from at least 1 well-designed nonrandomized clinical study, cohort study, or case-control study, or a noncontrolled experimental study with nonconclusive results
III	Expert opinion based on clinical experience, descriptive studies, or reports from expert panels

spective or small and lack control transplant recipients without TB. Furthermore, most of the available information refers to kidney recipients and cannot necessarily be applied to recipients of other organs. Table 3 shows the risk factors for TB that have been reported in the literature [7–10]. It seems reasonable to assume that other factors associated with increased risk of TB in the general population can also be applied to transplant recipients. These include smoking, malnutrition, and HIV infection.

## EVALUATION OF CANDIDATES AND DONORS

### Evaluation of Candidates for SOT

Evaluation for TB in an SOT candidate must include recording of any history of infection or disease and, if there is a history, determination of whether treatment was administered, which drugs were used, and the duration of treatment. It is important to know whether there has been contact with patients with active TB in the family or workplace and whether the patient has undergone purified protein derivative skin testing (PPD; B-III). History should include possible institutional exposure and travel to areas where TB is highly endemic. All candidates should undergo PPD testing, even patients who have been vaccinated against bacille Calmette-Guérin infection (A-II). PPD tests should be repeated 7–10 days after the first test (booster effect). The only reason for not performing PPD testing would be if the patient had already had a positive PPD result or a history of TB [12]. Correct interpretation of the PPD test result necessarily involves knowledge of whether the transplantation candidate has received treatment against latent TB infection [11, 12]. The PPD test result should be interpreted independent of the bacille Calmette-Guérin vaccination status [13].

Active TB infection should always be ruled out by a chest

radiograph. In symptomatic patients, active TB must be ruled out, because it is a contraindication for transplantation [11]. A patient with active pulmonary TB could be considered to be a candidate for nonpulmonary SOT if the patient is receiving anti-TB treatment and if results of stains for the detection of acid-fast bacilli in sputum are negative shortly before transplantation.

### *Treatment of candidates with a positive PPD test result.*

It is extremely important to rule out active TB in patients who have a positive PPD test result (A-II). If clinical or radiological data suggest TB, sputum smears and culture must be performed or, if this is not possible, bronchoscopy and culture of the bronchoalveolar aspirate and/or lavage fluid specimen should be performed. Additional clinically guided examinations may be necessary, such as abdominal ultrasound (to detect enlarged abdominal lymph nodes) or biopsy and lymph node culture. For an asymptomatic patient whose chest radiograph reveals residual lesions, sputum samples should be cultured, and in specific cases, bronchoscopy and culture of aspirate or lavage fluid specimens should be performed.

When active TB has been ruled out, treatment of latent TB infection should be considered. The transplantation candidate could initiate treatment of latent TB infection, be registered on the waiting list, and, if possible, continue treatment after the transplantation.

### *Treatment of candidates with a negative PPD test result.*

If the initial PPD test result is negative, PPD testing should be repeated 7–10 days after the initial test (booster effect). According to the recommendations of the American Thoracic Society, an induration of  $\geq 5$  mm indicates a positive test result (B-III) [14]. Patients waiting for an SOT often experience cutaneous anergy because of their underlying disease. Cellular

**Table 2. Frequency of tuberculosis among solid-organ transplant recipients.**

Variable	Solid-organ transplantation type					
	Overall	Pulmonary	Cardiac	Renal	Hepatic	Renal-pancreatic
Prevalence, %						
Literature <sup>a</sup>	1.2–6.4 <sup>b</sup>	2–6.5	1–1.5	0.5–15	0.7–2.3	...
GESITRA	0.45	1.15	0.26	0.35	0.47	0.85
Incidence, cases per 10 <sup>5</sup> inhabitants per year (95% CI 95): GESITRA	512 (317–783)	2072 (565–5306)	255 (6.5–1421)	358 (144–728)	541 (269–1065)	1204 (30.5–6710)

**NOTE.** Data from the Network for the Study of Infection in Transplant recipients (GESITRA) are from 2008.

<sup>a</sup> Data are from [1–4].

<sup>b</sup> Data shown are for developed countries; the prevalence in countries where tuberculosis is highly endemic was 15%.

immune testing (multitest or specific testing for selected antigens, such as *Candida albicans* or tetanus toxoid) could be performed at the time of the second PPD skin test to determine the presence of anergy. Unfortunately, there is not enough data on the use of these tests in SOT recipients.

**Treatment of candidates with cutaneous anergy.** The real risk of TB among patients with cutaneous anergy is unknown. It is probable that not all anergic patients require treatment, particularly if they have a low risk of acquiring primary infection. If there is a high risk for primary infection, these patients should be treated as if they had a positive PPD test result until more data are available [11].

New techniques, such as measurement of the release of IFN- $\gamma$  in response to *M. tuberculosis* antigens (QuantiFERON TB Gold Test), are being developed and validated, and these could help improve the diagnosis of latent TB infection in transplantation candidates. Figures 1, 2, and 3 provide our approach to the diagnostic management of TB in candidates for SOT [15].

### Evaluation of Solid Organ Donors

TB has been transmitted through kidney, lung, and liver grafts [14]. Latent infection with *M. tuberculosis* in the donor could be reactivated in the transplant recipient. Therefore, all living donors should undergo PPD skin testing. If the result is positive, active TB should be ruled out (A-II) [12]. The situation is more complex in cadaveric donors, because there is often not enough information to rule out the existence of latent TB infection or active TB. Therefore, in principle, not only active TB, but also a well-founded suspicion of it should contraindicate SOT (A-II). Biopsy samples must be obtained, and cultures must be performed at the time of transplantation to rule out active TB in the donor.

Residual pulmonary lesions in the donor contraindicate lung transplantation; however, this is not true for other organs. For lung transplantation, a histopathological and microbiological study of the donor lung should be performed to rule out active infection. Techniques that amplify the nucleic acids of *M. tuberculosis* in respiratory samples are highly sensitive and specific

and could prove to be useful in the evaluation of donors [16]. Disseminated TB is an absolute contraindication for the use of any organ for transplantation [17].

### Emergency Transplantation

When the transplantation is urgent, respiratory and urine samples must be obtained for culture for *M. tuberculosis*. Similarly, samples should be obtained from both the donor and the recipient during surgery of any enlarged lymph nodes from the surgical bed. A positive culture result would indicate the need to start specific treatment (figure 3) [15].

### Lung Transplantation

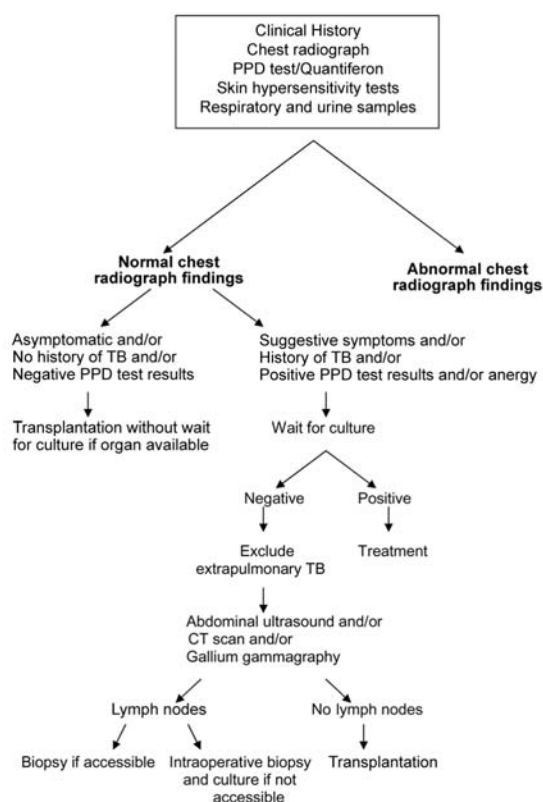
Although there may be extrapulmonary or pulmonary (single-lung transplantation) reactivation in the recipient, the main

**Table 3. Risk factors for tuberculosis (TB) after transplantation.**

Risk factor
Immunosuppressive therapy <sup>a</sup>
OKT3 or anti-T lymphocyte antibodies (III)
Intensification of immunosuppression associated with graft rejection (II)
Cyclosporine A vs. azathioprine plus prednisone (II)
Mycophenolate mofetil and tacrolimus vs. azathioprine, cyclosporine, and prednisone (III)
History of exposure to <i>Mycobacterium tuberculosis</i>
Positive PPD test result (III)
Radiological evidence of previous untreated TB (III)
Clinical condition
Chronic renal insufficiency or hemodialysis (kidney transplantation; II)
Diabetes mellitus (II)
Hepatitis C virus infection (kidney transplantation; III)
Chronic liver disease (III)
Other coexisting infections: profound mycoses, cytomegalovirus, or <i>Pneumocystis jiroveci</i> or <i>Nocardia pneumonia</i> (III)

**NOTE.** Roman numerals indicate the degree of evidence (table 1). PPD, purified protein derivative.

<sup>a</sup> No information was available on recently introduced immunosuppressors, such as sirolimus, everolimus, or monoclonal antibodies (daclizumab and basiliximab).



**Figure 1.** Flow diagram of the approach to the diagnosis of tuberculosis (TB) in patients undergoing nonurgent transplantation and in patients with normal chest radiograph findings. PPD, purified protein derivative.

risk for lung recipients is pulmonary reactivation from the graft (especially in double-lung transplantations). As mentioned above, residual pulmonary lesions contraindicate lung transplantation, although they do not contraindicate transplantation of other organs. For lung transplantation, a histopathological and microbiological study of the lung should be performed to rule out active infection.

#### Treatment of Latent TB Infection in SOT Recipients or Candidates

**Indications for treatment of latent TB infection.** In SOT recipients, TB usually develops from a site of latent infection in the recipient. Ideally, treatment of latent TB infection should start before transplantation. If treatment cannot be completed before the procedure, it should be completed after the procedure. Treatment of latent TB infection should be provided for all patients on the waiting list for a transplantation or for recipients who have  $\geq 1$  of the following conditions: (1) a PPD skin test (initial or after a booster effect) with an induration  $\geq 5$  mm, (2) a history of untreated TB, or (3) a history of contact with a patient with active TB. Patients with chest radiograph findings compatible with untreated TB (apical fi-

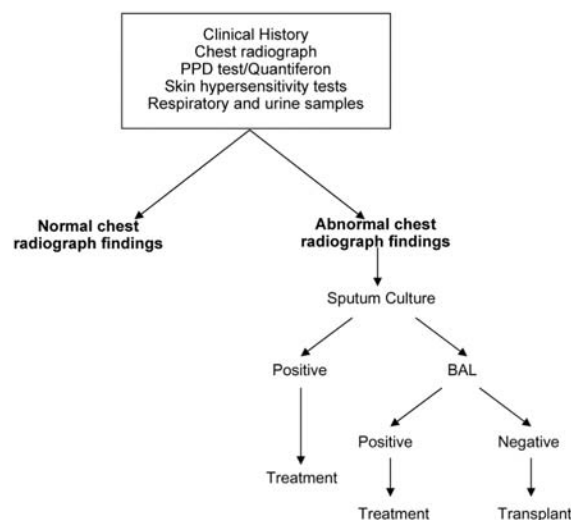
bronodular lesions, calcified solitary nodule, calcified lymph nodes, or pleural thickening) should also receive therapy for latent TB infection (A-II) [18]. The value of such radiological data as an indication of a history of TB is greater in areas such as Europe, where there are no regional mycoses (e.g., histoplasmosis, coccidioidomycosis, or blastomycosis) that could cause similar lesions.

Transmission of active TB from a donor is less common, although it has been reported [19]. In general, except in the case of living donors [20, 21], clinical data indicating whether the donor had TB may not be available. Therefore, as stated above, biopsies and cultures must be performed at the time of transplantation to rule out active TB in the donor. Treatment of latent TB infection must be administered to recipients of an organ whose donor has a history of or data that suggest untreated TB [3].

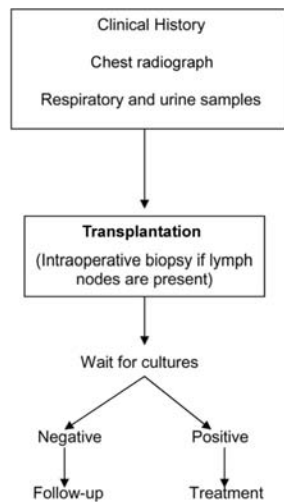
Before initiation of treatment of latent TB infection, patients should undergo a thorough evaluation to rule out active TB (culture and PCR for mycobacteria in blood, sputum, and urine samples) [3,10, 20]. For patients with radiological alterations who are unable to expectorate, sputum should be induced with hypertonic saline, or fiberoptic bronchoscopy should be performed. Patients whose previous case of TB was properly treated do not require treatment for latent TB infection [22].

#### Recommendations for the treatment of latent TB infection.

The drug of choice for treatment of latent TB infection is isoniazid (300 mg/day), supplemented with vitamin B<sub>6</sub> for 9 months [3, 10, 23–26]. Prophylaxis with isoniazid was proven



**Figure 2.** Flow diagram of the approach to the diagnosis of tuberculosis in patients undergoing nonurgent transplantation and in patients with abnormal chest radiograph findings. BAL, bronchoalveolar lavage; PPD, purified protein derivative.



**Figure 3.** Flow diagram of the approach to the diagnosis of tuberculosis in patients undergoing urgent transplantation.

to prevent TB in randomized studies involving kidney recipients (A-I) [23, 27, 28].

The ideal approach is to treat latent TB infection before transplantation, except possibly in the case of liver transplantation. The duration and dose of isoniazid therapy are the same, irrespective of whether it is administered before or after transplantation. Patients who have completed therapy before transplantation do not need to repeat it after the procedure.

The possibility of isoniazid-induced hepatotoxicity is possible in these patients. Tolerance to isoniazid is generally good [29, 30], and the interaction with calcineurin inhibitors is very limited [31, 32]. All patients should have baseline hepatic measurements of serum aspartate aminotransferase, alanine aminotransferase, and bilirubin levels. They should receive follow-up evaluations at least monthly. Patients should be educated about the adverse effects associated with treatment of latent TB infection and should be advised to stop treatment and promptly seek medical evaluation when adverse effects occur [13]. Treatment of latent TB infection must be suspended if aspartate aminotransferase or alanine aminotransferase values increase 3-fold in patients with symptoms or 5-fold in patients with no accompanying symptoms [34].

Alternatives to isoniazid include rifampicin (with or without isoniazid) for 4 months (B-II) [31] or rifampicin and pyrazinamide for 2 months (C-III) [33]. However, this last combination has been associated with severe liver toxicity and is generally not recommended (except when prophylaxis must be completed over a short period) and must always be administered under expert supervision [34]. This regimen is not recommended for patients with previous liver disease, consumers of alcohol, or patients who have developed isoniazid-induced hepatotoxicity [18]. The regimens that include rifampicin are

only recommended for pretransplantation treatment of latent TB infection because of the medication interactions that affect this drug.

For severe toxicity, a liver biopsy is only recommended when there is a doubtful diagnosis or when laboratory values do not return to normal after treatment is suspended. When suspension of treatment of latent TB infection is necessary because of toxicity, the patient should be closely monitored, and treatment of latent TB infection should be completed with drugs other than isoniazid, although only in patients at high risk of TB, such as those who recently had a positive PPD result after having had a negative result. For patients at high risk of TB, we recommend treatment with levofloxacin and ethambutol for at least 6 months (B-III).

When active TB cannot be ruled out in a transplant recipient, we recommend initiation of treatment with 3 drugs (isoniazid, ethambutol, and pyrazinamide). Treatment can be completed with only isoniazid if, after 8 weeks of incubation of samples, cultures are negative for *M. tuberculosis* and the chest radiograph findings remain normal.

**Exclusions from treatment of latent TB infection and precautions.** Liver transplant recipients present special problems when they receive treatment for latent TB infection because of the high risk of hepatotoxicity. Some authors consider that this risk outweighs any potential benefits, because the frequency of reactivation is not excessively high [10]. However, other authors have not observed increased toxicity associated with isoniazid in liver transplant recipients [35].

We recommend delaying the administration of treatment for latent TB disease in liver recipients until after the transplantation, when liver function is stable, because administration of therapy when the patient is still on the waiting list (which is recommended for recipients of other organs) can cause liver dysfunction and lead to the need for an emergency transplantation (B-III). The convenience of treating latent TB infection in liver recipients is clearer when there are risk factors, such as a recent change in PPD results from negative to positive, a history of incorrectly treated TB, direct contact with an untreated person with TB, residual TB lesions on the chest radiograph, and added immunosuppression factors (e.g., treatment of graft rejection episodes in patients with a positive PPD result who have not received treatment for latent TB infection).

**Isolation measures for the prevention of nosocomial TB.** There have been reports of isolated cases and outbreaks of nosocomial TB after diagnostic or therapeutic maneuvers among patients with smear-positive pulmonary TB. The maneuvers that are most likely to lead to nosocomial TB transmission include orotracheal intubation, fiberoptic bronchoscopy, and induction of sputum.

Patients with pulmonary TB and especially those with laryngeal TB should be isolated, because these are the most trans-

**Table 4. Tuberculosis (TB) treatment options, recommended doses, alternative dosing regimens, and drug interactions and contraindications.**

Situation	Initial treatment	Maintenance treatment
Patients with localized, nonsevere forms of TB, without suspicion or evidence of resistance to isoniazid	Avoid the use of rifamycins; if rifamycins are used, the levels of immunosuppressors should be closely monitored, and the dose of cyclosporine or tacrolimus should be increased (A-II); if treatment is started early, it is not necessary to reduce the level of immunosuppression (C-III)	Isoniazid and ethambutol (or pyrazinamide) are recommended for 12–18 months (C-III); the incorporation of a third drug, such as pyrazinamide or levofloxacin, <sup>a</sup> could reduce this period to 12 months (C-III)
Severe forms or disseminated forms of TB or suspicion or evidence of resistance to isoniazid <sup>b</sup>	Consider adding rifampicin or rifabutin to the regimen (B-III) <sup>c</sup>	Complete treatment with isoniazid and rifampicin or rifabutin for at least 9 months
Multidrug-resistant TB or when there is some limitation for the use of the aforementioned drugs	If isoniazid and rifamycins cannot be used, induction treatment should include 4–6 drugs, including injectable antimicrobials (e.g., streptomycin, <sup>d</sup> amikacin, kanamycin, or capreomycin), linezolid, or other second-line drugs (C-III) <sup>e</sup>	The absence of isoniazid and rifampicin in the initial treatment makes it difficult to calculate the duration of treatment and the types of drugs to be used; therapy should be individualized

<sup>a</sup> Prolonged use of fluoroquinolones can be associated with arthralgias, and the combination of pyrazinamide and levofloxacin is poorly tolerated by the digestive system.

<sup>b</sup> If isoniazid cannot be used, induction and maintenance treatment that includes 4 drugs for at least 18 months is recommended (C-III).

<sup>c</sup> Use of rifampicin or rifabutin would require an increased dose of cyclosporine or tacrolimus and closer monitoring of the levels of these drugs (A-II). Resistance to rifampicin is almost systematically associated with cross-resistance to rifabutin and rifapentine; therefore, these drugs are not suitable alternatives (D-II).

<sup>d</sup> In cases of resistance to streptomycin, there is no cross-resistance with other injectable drugs (e.g., amikacin, kanamycin, and capreomycin); however, cross-resistance between amikacin and kanamycin is universal. The combination of injectable drugs is not recommended because of their intolerance and the association of adverse effects (D-II).

<sup>e</sup> There is no experience with the use of intermittent regimens, which, in any case, are not recommended for the management of multidrug-resistant TB, with the use of injectable drugs after a period of at least 2–3 months of daily therapy (D-II).

missible forms of TB. International recommendations state that (1) isolation should be maintained until it has been shown that the patient does not have TB (if the isolation occurs because of suspected disease); (2) isolation should be suspended for patients with TB who receive treatment, are improving clinically, and have 3 consecutive negative sputum smear results; and (3) the patient can be discharged from the hospital if it can be guaranteed that he or she will not be in contact with patients who are particularly susceptible to infection, such as small children and immunodepressed patients.

Patients with smear-positive TB should be placed in individual rooms with negative pressure (compared with the corridor). The windows and doors should remain closed, except when persons are entering or leaving the room [36].

## TREATMENT OF TB IN SOT RECIPIENTS

The recommendations for treatment of TB in transplant recipients are similar to those for treatment of the general population [18], with the exception of the 2 following differences: (1) the treatment regimen, because of the interaction between rifamycins (rifampicin, rifabutin, or rifapentine) and immunosuppressors of the calcineurin inhibitor family (cyclosporine and tacrolimus), rapamycin, and corticosteroids; and (2) the duration of treatment. The decision to use a determinate num-

ber of drugs for treatment of SOT recipients is driven by the rate of drug resistance in each country and is based on the epidemiology in individual cases. Mycobacterial susceptibility testing is currently critical for the determination of treatment of TB in SOT recipients, especially because of the eventuality of multidrug-resistant and extensively drug-resistant TB. Our recommendations with regard to the type of regimen and duration of treatment are based fundamentally on the opinion of the panel of experts (table 4).

**Use of rifamycins in transplant recipients.** Although rifampicin has been widely administered to SOT recipients (mainly kidney recipients), the need for the drug in all cases is controversial [37, 38]. European kidney transplantation guidelines recommend 2 months of isoniazid, rifampicin, and pyrazinamide therapy (with the addition of ethambutol when there is >4% isoniazid resistance), followed by isoniazid and rifampicin for an additional 4 months (B-III) [25].

Rifampicin reduces the seric levels of tacrolimus, cyclosporine, rapamycin (sirolimus), everolimus, and corticosteroids (although there is less information about corticosteroids). The reductions in these levels have been associated with a high risk of graft rejection [39, 40]; therefore, the dose of calcineurin inhibitors should be increased 3–5-fold, and levels should be closely monitored [1, 2]. Even with suitable monitoring, com-

binning rifampicin and cyclosporine increases the frequency of graft rejection, graft loss, and overall TB-related mortality [1–3].

Rifabutin could be an alternative, because it is a weaker inducer of cytochrome P450, compared with rifampicin. There have been favorable experiences with rifabutin in kidney recipients [41–43], but data are limited. It is worth remembering that, as occurs in HIV-infected patients, SOT recipients with TB can develop an immune reconstitution syndrome related to changes in immunosuppressive treatment and to interactions with immunosuppressors and the medication used to treat TB, especially the rifamycins.

**Use of other anti-TB drugs in transplant recipients.** Isoniazid and pyrazinamide have been widely used in transplant recipients with TB. Because of the risk of hepatotoxicity, close monitoring of liver enzyme values is necessary, especially in patients undergoing liver transplantation.

The administration of streptomycin and aminoglycosides to transplant recipients should be considered carefully because of the risk of boosting the nephrotoxicity of these drugs with calcineurin inhibitors. Fluoroquinolones are an alternative for these patients because of the disadvantages associated with rifamycins and aminoglycosides, and they can sometimes be used as first-line agents [44]. Nevertheless, indiscriminate use of fluoroquinolones in the general population has been associated with an increase in resistance of *M. tuberculosis* to these drugs in recent years [45]. Combined and prolonged use of levofloxacin and pyrazinamide has been associated with poor tolerance in SOT recipients, mainly in the digestive system [46].

In special cases of drug resistance or drug-related toxicity, linezolid has proven to be effective for patients with TB [47]. However, prolonged use of this drug is associated with frequent development of thrombopenia and anemia and, in some cases, polyneuropathy, especially in patients with other associated conditions, such as diabetes or kidney disease. Therefore, use of linezolid in transplant recipients is limited.

**Tolerance of anti-TB treatment by the transplant recipient.** For liver recipients, the development of liver toxicity is of particular concern during the treatment of TB [1]. In recipients of other organs, isoniazid is generally well tolerated, although the risk of hepatotoxicity has also been reported in kidney recipients [3, 48].

As mentioned above, rifampicin must be used with extreme caution when treating TB in transplant recipients. When combined with isoniazid, rifampicin has led to a considerable increase in the frequency of hepatotoxicity, especially in liver recipients [48]. Initial treatment with isoniazid, rifampicin, and pyrazinamide in liver recipients with TB has been associated with histologically confirmed hepatotoxicity in 88% of cases [49]. A particularly high risk of hepatotoxicity has also been

reported with the combination of rifampicin and pyrazinamide for the treatment of latent TB infection [50].

**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 [51, 52]. The main problems that can occur after transplantation are drug interactions and recurrence of hepatitis C virus infection, which may increase the risk of TB [8] and favor toxicity.

Although reported experience is scant, the standard regimen used for treatment of TB in HIV-infected transplant recipients seems to be as effective as the regimen used for treatment of TB in other HIV-infected patients [51]. Rifamycins may lead to greater hepatotoxicity in HIV-infected patients (compared with HIV-uninfected patients) and jeopardize antiretroviral therapy because of their interaction with protease inhibitors and nonnucleoside reverse-transcriptase inhibitors. All 3 groups of drugs can inhibit or induce the isoenzyme family of cytochrome P450, thus leading to interactions that are difficult to manage. We recommend the combination of isoniazid, pyrazinamide, and ethambutol, in addition to a quinolone. The use of aminoglycosides is limited by the risk of nephrotoxicity induced by calcineurin inhibitors.

**Duration of anti-TB treatment in transplant recipients.** The duration of treatment and type of drugs used after the first 2 months of treatment are very controversial issues, especially if rifampicin therapy was not used during the first 2 months or was suspended because of intolerance. Experience in the general population with anti-TB regimens that do not include rifampicin should be considered. Most patients who receive suitably managed rifamycin therapy and who experience relapse are usually infected with a rifamycin-susceptible strain. However, in rifamycin-sparing regimens, especially if these are not supervised, drug resistance occurs more frequently [18].

In the general population, isoniazid, pyrazinamide, and streptomycin have proven to be effective when the regimen is administered for 9 months [18], although it is difficult to maintain injected therapy for long periods because of the risk of ototoxicity and renal toxicity. Furthermore, the use of injectable drugs in transplant recipients should be avoided because of the risk of nephrotoxicity. 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 12–18 months (C-III), and the benefit of treatment with injectable agents should be evaluated during the first 2–3 months in extensive or cavitary forms.

One Spanish study [1] observed that administration of treatment for <9 months was associated with greater mortality. Another study [53] observed that the only factor that was signif-

icantly associated with greater recurrence of TB was duration of treatment: no recurrence was observed in patients who received >12 months of treatment, irrespective of whether the treatment regimen included rifampicin [53].

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