Mycobacterium tuberculosis Infection in Recipients of Solid Organ Transplants

Patricia Muñoz, Claudia Rodríguez, and Emilio Bouza
Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario “Gregorio Marañón,” Madrid, Spain

Tuberculosis is a serious opportunistic infection that may affect transplant recipients. The incidence of tuberculosis among such persons is 20–74 times higher than that for the general population, with a mortality rate of up to 30%. The most common form of acquisition of tuberculosis after transplantation is the reactivation of latent tuberculosis in patients with previous exposure. Clinical presentation is frequently atypical and diverse, with unsuspected and elusive sites of affection. Manifestations include fever of unknown origin and allograft dysfunction. Coinfection with other pathogens is not uncommon. New techniques, such as PCR and quantification of interferon-γ, have been developed to achieve more-rapid and -accurate diagnoses. Treatment requires control of interactions between antituberculous drugs and immunosuppressive therapy. Prophylaxis against latent tuberculosis is the main approach to treatment, but many issues remain unsolved, because of the difficulty in identifying patients at risk (such as those with nonreactive purified protein derivative test results) and the toxicity of therapy.

EPIDEMIOLOGY AND RISK FACTORS

The frequency of Mycobacterium tuberculosis disease among recipients of SOTs in most developed countries is 1.2%–6.4%, but among transplant recipients living in areas of high endemicity, it might reach 15% [1]. For any given country, the incidence of tuberculosis among transplant recipients seems to be directly associated with the specific incidence in the general population, but the former is usually 20–74 times higher than the latter [1–3, 5].

The incidence of tuberculosis is 0.7%–2.3% among adult liver transplant recipients, 2.5% among pediatric liver transplant recipients, 0.5%–15% among kidney transplant recipients, 1%–1.5% among heart transplant recipients, and 2%–6.5% among lung transplant recipients [1, 6, 7]. For bone marrow transplant (BMT) recipients, the reported incidence is 0.23%–0.79% [8–10].

Several trials have described risk factors for the development of tuberculosis in transplant recipients. Among the risk factors are immunosuppressive treatment with OKT3 or anti–T cell antibodies [1], diabetes mellitus, chronic liver disease (in kidney transplant recipients), coexisting infections (e.g., cytomegalovirus infection, deep mycosis, Pneumocystis jiroveci pneumonia, and Nocardia infection), and lesions on a chest radiograph suggestive of previous tuberculosis infection [4, 7, 11]. In one study involving kidney transplant recipients, older age and...
cyclosporine used in the first year after transplantation increased the risk of developing tuberculosis [12]. Among BMT recipients, risk factors include graft-versus-host disease and total body irradiation [8].

**PATHOGENESIS**

The most common form of acquisition of tuberculosis after transplantation is the reactivation of latent infection in patients with previous exposure. These patients tend to have an earlier disease onset, as mentioned in Epidemiology and Risk Factors.

A possible yet less common mechanism of transmission is via the transplanted organ, as proven in cases in which the same *M. tuberculosis* strain was recovered from persons who received kidney and lung transplants from the same donor [1, 13, 14]. Transmission of tuberculosis from a living donor has been reported in cases of liver [15] and kidney transplantation [5]. Active tuberculosis should be excluded for potential living donors by means of all available diagnostic techniques, including PCR.

Nosocomial transmission has also been described in a renal transplant program, in which epidemiological data and restriction fragment–length polymorphism analysis of the strains identified an outbreak of tuberculosis among 10 kidney transplant recipients who developed the disease over a period of 11 months (onset occurred in 8 patients during a 5-month period) [16]. Five cases were associated with an index patient who had had posttransplantation exposure to tuberculosis at another hospital. Jereb et al. [16] state that bronchoscopy, intubation of that patient, and, remarkably, inadequate ventilation of the renal transplant unit possibly increased the risk of transmission of *M. tuberculosis* during the outbreak.

It is clear from the literature that primary infection is not frequently reported in this population. In pediatric cases, family screening detected infected relatives for 4 of 6 patients [10].

**TIME OF ONSET**

Tuberculosis frequently develops within the first year after surgery in SOT recipients, including pediatric patients [10]. The 2 largest series published that involved patients with all types of SOT described a median time to tuberculosis onset of 9 months (range, 0.5–13 months) in 61%–63% of patients. The remaining patients developed tuberculosis ≥2 years after transplantation [1, 4]. Although uremia in renal transplant recipients interferes with T cell function, which has an important role in immunity against mycobacteria [17], onset of tuberculosis in these patients is usually later, when renal function is often normal. A possible explanation is that renal transplant recipients are less immunosuppressed than recipients of other transplants [1].

Risk factors for early onset tuberculosis are receipt of nonrenal transplants, allograft rejection, immunosuppressive ther-

apy with OKT3 or anti–T cell antibodies, and previous exposure to *M. tuberculosis* [1]. The most important single factor that predisposes transplant recipients to early onset tuberculosis is the detection of lesions suggestive of tuberculosis (such as calcified hilar lymph nodes or granulomas) by pretransplantation chest radiography, particularly in countries where mycoses are not endemic and where, as a result, such lesions should yield a high suspicion of latent tuberculosis and warrant further evaluation of the patient [1, 4, 6]. We are not aware of solid data that demonstrate whether these suggestive radiological lesions should be considered as indications for prophylaxis in patients with nonreactive and/or anergic purified protein derivative (PPD) test results. Our opinion is that, at least for recipients of nonliver transplants, such lesions should be considered as such.

**CLINICAL MANIFESTATIONS**

A large series involving transplant recipients with tuberculosis described pulmonary involvement in 51% of patients, extrapulmonary tuberculosis in 16%, and disseminated infection in 33% [1]. In the lung, radiographic findings may vary among focal or diffuse interstitial infiltrates, nodules, or cavitary lesions. Fever is almost always present, particularly among those with disseminated disease, and constitutional symptoms are also common [1]. Cough, pyrexia, and poor appetite were the most common presentation symptoms in children [10].

It is worth noting that diverse, unsuspected, and elusive sites of tuberculosis infection have also been described. Gastrointestinal disease presents in a wide variety of forms, including gastrointestinal bleeding, peritonitis, and ulcers. Tuberculosis may also affect the pancreas and the liver. In transplant recipients, *M. tuberculosis* infection was also described in skin, muscle, the osteoarticular system, the CNS, the genitourinary tract, lymph nodes, the larynx, adrenal glands, and the thyroid gland [1, 4, 10]. Ocular lesions may be early indicators of dissemination [18].

We feel that tuberculosis should be considered in all SOT recipients with fever of unknown origin [2]. Some authors also recommend that, for most types of infection in this population, samples for detection of mycobacteria should be obtained even before transplantation, when the patient is being evaluated as a transplantation candidate [2, 19]. Respiratory samples of either sputum or bronchoalveolar lavage fluid (if the sputum specimen was negative for *M. tuberculosis* and radiological signs were present), urine, or blood samples could be used. In certain cases, it might be necessary to perform a biopsy (of the lymph nodes, liver, or pleura, for example) to obtain the correct diagnosis [19]. Allograft rejection may also appear simultaneously. In an Australian series involving 23 patients with mycobacterium infection from a population of 261 lung and
heart-lung transplant recipients, Malouf and Glanville [20] found that 15 of the patients for whom bronchoalveolar lavage fluid tested positive for mycobacterial isolates had evidence of graft dysfunction. However, there was no significant difference in the rate of rejection between patients with and patients without mycobacterial infection. In this trial [20], enrollment criteria included infection with any kind of mycobacteria, and only 2 cases were due to M. tuberculosis.

**DIAGNOSIS**

The suspicion of tuberculosis in transplant recipients may be delayed, because paucisymptomatic, extrapulmonary disease is not uncommon. Another factor that makes tuberculosis in transplant recipients difficult to diagnose is its frequent association with other infections (in up to 23% of cases in some series [4]), such as cytomegalovirus infection, Nocardia infection, community-acquired pneumonia, urinary tract infection, and aspergillosis, that modify the already nonspecific symptomatology. A high index of suspicion is required to successfully achieve a positive diagnosis, and it is advisable to routinely consider or even perform mycobacterial cultures when evaluating an infectious complication in this population. This recommendation would apply even if other agents had already been isolated or because a positive culture result might have been achieved accidentally as part of routine evaluations or even during necropsy [4].

After transplantation, PPD testing has a low efficacy, justifying more-aggressive diagnostic techniques, such as fiberoptic bronchoscopy, mediastinoscopy, laparoscopy, and tissue biopsy [2]. Despite this fact, PPD testing continues to be the first step in the evaluation of M. tuberculosis infection. The use of anergy skin testing to validate negative PPD test results in immunocompromised patients has been found to be ineffective, although very few transplant recipients are included in these series [21, 22].

An interesting diagnostic tool for the screening of tuberculosis is the recently developed Quantiferon-TB test (Cellestis), a whole-blood IFN-γ in vitro assay. It is based on the quantification of IFN-γ released from sensitized lymphocytes when incubated with PPD from M. tuberculosis and control antigen [23]. At the time of writing, it is comparable to the PPD test in its ability to detect latent tuberculosis, but details about the performance and potential advantages of this test in the transplant population are lacking.

The definitive diagnosis of tuberculosis involves isolation of M. tuberculosis from clinical samples, but this may take up to 6 weeks. In recent years, the introduction of new, automated liquid culture methods have resulted in more-rapid diagnoses [24].

One test that reduces the time required to diagnose tuberculosis is the amplification of genetic material from M. tuberculosis, which can detect mycobacterial rRNA in clinical samples in a few hours. RNA amplification products are hybridized to complimentary acridinium ester–labeled DNA probes that are subsequently depredated, resulting in luminescence that is measured in relative light units. Luminescence of >30,000 relative light units is considered to be indicative of M. tuberculosis. These molecular techniques may be used to identify M. tuberculosis in cultures as well as in direct clinical samples. The sensitivity and specificity of the test are not homogeneous, and its usefulness for SOT recipients is not yet clear, although information that has been reported is promising [15, 25–28]. In theory, the test is affected neither by the immune status of the patient nor by the presence of nontuberculous mycobacteria [29]. This kind of test has specificities close to 100% but has variable sensitivities, especially in cases of smear-negative disease, and there is still uncertainty about how it should be used. The Centers for Disease Control and Prevention (CDC; Atlanta, GA) recommends testing the very first sputum specimens collected [30], and other authors suggest that it should not be used for patients with low clinical suspicion of tuberculosis [31, 32]. However, this test has become an important part of the evaluation process for patients for whom tuberculosis diagnosis is difficult, and in any case, confirmatory cultures are necessary. Experience with transplant recipients is scarce, but the efficacy of molecular techniques seems to be similar to that for the population without transplants [10, 25–28].

Another application of molecular biology techniques for the diagnosis and treatment of tuberculosis is the ability to detect multidrug-resistant M. tuberculosis strains earlier than conventional methods do and to sequence such strains with real-time PCR assays [33]. Finally, it is important to mention the contribution of molecular techniques as epidemiological markers.

Some authors have found positron emission tomography with 18fluorodeoxyglucose, a nuclear medicine technique, to be useful for diagnosing tuberculosis. This technique is used for diagnosing malignancy and active inflammatory processes (granulomatous processes, in particular). Although this technique is not specific for tuberculosis, it might be suggestive and helpful in guiding biopsy procedures when conventional images, such as ultrasonograms, CT scans, or MRIs, are not enough [34, 35].

**TREATMENT**

There is still controversy regarding the most appropriate therapy for transplant recipients with tuberculosis. The practice guidelines of the Infectious Diseases Society of America and the CDC recommend treatment of tuberculosis in the general population with isoniazid, rifampin, and pyrazinamide; a fourth drug—ethambutol or streptomycin—is recommended, depending on local resistance patterns [36]. However, in the population of transplant recipients, this treatment poses a special problem, because of significant interactions between rif-
ampin and immunosuppressive agents. Rifampin substantially decreases serum levels of cyclosporine and tacrolimus, and we do not recommend its use. In extreme situations, the benefits of rifampin must be balanced against the risk of rejection. Some authors [4] have found that up to 25% of grafts were lost because of the interference between cyclosporine and rifampin. If rifampin use is mandatory, the cyclosporine or tacrolimus dose should be increased 3–5 fold, and serum levels should be closely monitored [2]. Other authors [37] have found it useful to use rifabutin instead of rifampin, which is reported to cause less enzyme induction and to make interaction more manageable, but in our opinion, many of the concerns associated with the use of rifampin remain when rifabutin is used.

Isoniazid should be included in the treatment of all SOT recipients with tuberculosis, unless there is a resistant strain or toxicity that makes its use impossible. Pyrazinamide is another first-line antituberculous drug. Frequently, it is used as elective therapy in transplant recipients, but careful follow-up should be performed because of the potential risk of hepatotoxicity, especially in liver transplant recipients. Streptomycin and, alternatively, other aminoglycosides can be used in transplant recipients, with special attention given to drug interactions. Nephrotoxicity and ototoxicity should be carefully monitored.

Quinolones have been studied as an alternative treatment for tuberculosis for nearly 20 years. In their 2003 guidelines on tuberculosis treatment, the CDC and the American Thoracic Society considered these drugs specifically as not being first-line agents [38]. In our opinion, quinolones should have first-line status for the treatment of tuberculosis in SOT recipients because of the inconveniences associated with both rifampin and aminoglycoside therapy in this situation. Agents from this class are recommended in cases of resistance or intolerance to first-line drugs and have been proven to be effective alternatives that would also permit shorter treatment periods [38]. However, as the frequency of treatment with quinolones increases, selective pressure may result in the emergence of quinolone-resistant M. tuberculosis; therefore, education regarding appropriate use is necessary [39]. Another problem that could arise from widespread use of quinolones involves false-negative culture results for patients previously treated with these drugs [39]. In these cases, when a strong clinical suspicion is present, new diagnostic tools, such as PCR, should be considered to clarify the situation. Linezolid has been shown to have high in vitro activity against M. tuberculosis [40], but the potential for untoward effects, such as the recently reported cases of peripheral neuropathy in patients who received long-term treatment [41], precludes its use.

In our practice, stable patients without evidence of disseminated disease and without suspicion of multidrug-resistant tuberculosis are usually treated with a combination of isoniazid, ethambutol, and pyrazinamide. For patients with more-severe clinical conditions, we add a fourth drug, usually levofloxacin, to avoid increases in aminoglycoside levels. In cases in which multidrug-resistant tuberculosis is suspected, streptomycin or amikacin therapy should be included in the regimen. Treatment with this combination is usually maintained during the initial 2 months after transplantation, until results of microbiological tests are received and the patient’s condition has stabilized.

Up to now, multidrug-resistant tuberculosis has rarely been reported in transplant recipients [37], but this is expected to change with time and with the development of transplant programs in developing countries. In our institution, the incidence of multidrug-resistant tuberculosis has been reported to be <2% among transplant recipients, and at the time of writing, none of the transplant recipients we have treated have had multidrug-resistant tuberculosis. When multidrug-resistant tuberculosis is a possibility, we prefer the de-escalating approach, which involves starting with 4 or 5 drugs (isoniazid, pyrazinamide, ethambutol, streptomycin, and/or levofloxacin) and reducing the number of agents on the basis of results of susceptibility tests.

The length of therapy and the type of drugs to be used after the initial 2-month period of treatment are far from clear. In stable patients without extrapulmonary disease, combinations of isoniazid and ethambutol may be used for up to 18 months. Treatment for patients for whom shorter treatment durations are desirable could include a third drug, such as pyrazinamide or levofloxacin. In our experience, long-term use of levofloxacin is well tolerated for periods of up to 1 year, but arthralgias frequently develop after 12 months of use. In our patients, arthralgias responded well to discontinuation of the drug, without further sequelae. The duration of treatment for patients who receive 3 drugs is ∼1 year.

Most authors, including us, do not recommend reducing immunosuppression if correct treatment is promptly started [4, 42–44]. However, in particularly severe cases involving kidney transplant recipients, immunosuppression may be considered. Besides, it has not been established whether a specific immunosuppressive drug predisposes to tuberculosis. It has been suggested that suppression of macrophage function by steroid therapy would be more important in triggering mycobacterial infections than IL-2 suppression achieved with more-selective immunosuppressive drugs [45].

Another problem associated with antituberculous therapy is its potential toxicity, which mainly affects the liver. In a large Spanish series, 16 of 46 patients developed some degree of toxicity [4]. Few patients presented with neurotoxicity (n = 2) or cutaneous toxicity (n = 1), but 15 developed some degree of liver damage. Patients receiving 4 drugs were more frequently and more severely affected. According to the type of transplantation, 12 (50%) of 24 of liver transplant recipients and 33 (37%) of 89 kidney transplant recipients developed hepatotoxicity. Of interest, none of the 6 heart transplant recipients
developed toxicity [4]. Kunimoto et al. [46] have reported severe hepatotoxicity in association with rifampin-pyrazinamide combination therapy; therefore, for patients for whom rifampin therapy is imperative, closer monitoring of liver function parameters would be necessary.

**OUTCOME**

The mortality rate among patients with SOT and tuberculosis may reach 30% in both adults and children, and it is also associated with a high morbidity rate, because antituberculous therapy may produce alterations in the metabolism of immunosuppressive drugs [10]. This may lead to allograft rejection, which is severe in many cases [1]. Death in conjunction with tuberculosis is more frequent among patients associated with graft rejection, receipt of steroid therapy, antilymphocyte antibody treatment, and presence of other opportunistic infection concomitant with tuberculosis. Disseminated disease does not seem to predispose to an unfavorable outcome [4].

In a study involving 66 kidney transplant recipients with tuberculosis, John et al. [12] also found that diabetes and chronic liver disease increased the risk of death. In our experience, no single case of death attributable to tuberculosis has occurred after the initiation of appropriate treatment.

**PROPHYLAXIS**

As mentioned, transplantation is associated with an increased risk of developing active tuberculosis from an old, latent infection, and general treatment recommendations for transplant recipients include prophylaxis with isoniazid. PPD testing is currently the standard method for identifying patients at risk. However, this test is a relatively imperfect screening tool for transplant recipients, because up to 70% of transplant candidates could be anergic [1]. A second PPD test performed 1 week after an initial test (the results of which were negative) can lead to the identification of an additional 10% of patients, because of the booster phenomenon [2]. This second test should always be performed in case the first reaction was negative.

Radiographic changes also provide valuable information, because patients with lesions suggestive of a previous history of tuberculosis have a higher risk of developing active disease [1, 6]. These radiographic changes are more-specific indications of tuberculosis in areas where other forms of chronic granulomatous diseases, such as endemic mycoses, are uncommon. The presence of such lesions is a compelling indication to obtain samples for cultures, and, in our opinion, to seriously consider initiation of prophylaxis.

Indications for prophylaxis also include a history of tuberculosis contact before transplantation, patients who have been newly infected with *M. tuberculosis* (i.e., those with a recent PPD conversion), and recipients of transplants from donors with a history of untreated tuberculosis [1]. Patients for whom tuberculosis was correctly treated in the past do not need new treatment courses or prolonged prophylaxis [47].

To date, isoniazid is the agent of choice for tuberculosis prophylaxis, and it was proven to be effective in liver, renal, and heart transplant recipients [1, 6, 48]. To the best of our knowledge, there have been no reports of tuberculosis in patients who received appropriate isoniazid prophylaxis. However, this is not a guarantee of unlimited protection. The American Thoracic Society and the CDC now recommend at least 9 months of prophylaxis with isoniazid. Other alternatives for tuberculosis prophylaxis include 2 months of rifampin-pyrazinamide [36], but as mentioned above in Treatment, this combination is associated with a increased number of hepatotoxic reactions, compared with other prophylaxis regimens, and is no longer recommended [49].

For patients in whom active infection is possible, we recommend initiating treatment with 3 drugs (isoniazid, ethambutol, and pyrazinamide), followed by de-escalation. When the hypothesis of active disease is rejected (after 8 weeks of sample incubation) and chest radiograph findings are stable, a prophylaxis regimen with isoniazid may be completed.

Some authors believe that the risk of isoniazid hepatotoxicity for liver transplant recipients overwhelms the benefit of its use, because these patients are believed to be more susceptible to drug toxicity [6]. Our opinion is that prophylaxis should be initiated after liver transplantation has been performed and when liver function is stable, but we usually do not provide prophylaxis to transplantation candidates, to avoid inducing emergent transplantation-related comorbidities if liver toxicity develops. In other types of transplantation (including lung transplantation [50]), we begin prophylaxis as soon as possible, and we do not preclude placement of the patient on the waiting list or performance of the transplantation itself, because we have not found problems associated with completing prophylaxis after the procedure. Liver enzyme levels should be monitored, in accordance with CDC recommendations, and therapy should be suspended if a 3-fold increase is detected and the patient has symptoms or if a 5-fold increase is observed and the patient is asymptomatic [51].

In cases of severe liver toxicity, liver biopsy is only performed when there is diagnostic doubt or if enzyme levels have not normalized after discontinuation of therapy. Once prophylaxis is suspended, we recommend close observation of the patient, and if risk is considered to be high (e.g., for patients with a recent PPD conversion), we suggest use of levofloxacin and ethambutol for at least 6 months. However, this latter option is based on our opinion, and no evidence of its utility is available.

To exclude the diagnosis of genitourinary tuberculosis in living kidney donors, urine analysis, 3 cultures of urine to test for *M. tuberculosis*, echography, and pyelography should be performed. In Spain, a 3-month course of isoniazid therapy is
recommended for living kidney donors with a positive PPD reaction [52]. For living liver donors, the risk of hepatotoxicity should be carefully considered.

Diagnosis of and prophylaxis against tuberculosis in transplant recipients are still controversial issues that deserve further investigation. The low incidence of this disease stresses the potential utility of multicenter international trials that address, among other things, the efficacy of shorter prophylaxis or therapeutic schemes, the utility of anergy tests for validating PPD results, or the necessity of providing prophylaxis to patients with old lesions (detected by radiography) and negative results of PPD tests.

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