



# Enfermedades Infecciosas y Microbiología Clínica

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## Tuberculosis in solid organ transplant patients

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### ABSTRACT

#### Keywords:

Latent tuberculous infection  
*Mycobacterium tuberculosis*  
Solid organ transplantation  
Tuberculosis

Tuberculosis is an opportunistic infection with high morbidity and mortality in solid organ transplant patients. The reasons for this high morbidity and mortality lie mostly in diagnostic difficulties, which cause delays in starting treatment, and associated pharmaceutical toxicity. There are still major issues and difficulties in managing tuberculosis in solid organ transplant patients. These include problems due to interactions between antituberculosis and immunosuppressant drugs, the high risk of toxicity of antituberculosis drugs (particularly in liver transplant patients) and the absence of clear indications for the treatment of latent tuberculous infection. This article updates current understanding of tuberculosis in solid organ transplant patients.

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### Tuberculosis en los pacientes trasplantados de órgano sólido

#### RESUMEN

#### Palabras clave:

Infección tuberculosa latente  
*Mycobacterium tuberculosis*  
Trasplante de órgano sólido  
Tuberculosis

La tuberculosis es una infección oportunista con una elevada morbimortalidad en los pacientes trasplantados de órgano sólido. Esta elevada morbimortalidad radica, sobre todo, en las dificultades en el diagnóstico, que condicionan un retraso en el inicio del tratamiento, así como en la toxicidad farmacológica asociada. En la actualidad continúan existiendo importantes dudas y dificultades en el manejo de la tuberculosis en los pacientes trasplantados de órgano sólido, como son las que se deben a las interacciones existentes entre fármacos antituberculosos e inmunosupresores, al elevado riesgo de toxicidad de los fármacos antituberculosos, particularmente en los trasplantados hepáticos o a la ausencia de indicaciones claras sobre el tratamiento de la infección tuberculosa latente. En este artículo se actualiza el estado del conocimiento sobre la tuberculosis en los pacientes trasplantados de órgano sólido.

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### Epidemiology and risk factors

Few studies have adequately described the incidence rate of tuberculosis in solid organ transplant (SOT) patients. Table 1 shows the prevalence and incidence rate of tuberculosis (TB) in SOT reported in most significant series in the medical literature. These data show the considerably greater risk of TB that SOT recipients present compared to the general population.<sup>1-7</sup> Most TB cases in SOT recipients are due to reactivation of latent infections after initiation of

immunosuppressive therapy. However, few risk factors have been clearly defined for developing tuberculosis in these patients. In 2009, the *Red de Estudio de la Infección en el Trasplante* (Network for the Study of Infection in Transplantation, RESITRA) published a prospective study of cohorts that, in addition to reporting the TB incidence rate in Spain for various types of solid organ transplants, identified two new previously unreported risk factors: recipient age and pulmonary transplantation.<sup>1</sup>

Table 2 shows the various post-transplant risk factors for TB reported in the medical literature. It is assumed that other factors that are associated with an increased risk of TB in the general population are also applicable to transplant recipients. Included in these factors are smoking, malnutrition and human immunodeficiency virus infection.<sup>8-15</sup>

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**Table 1**

Frequency and incidence of tuberculosis in solid organ transplantation

Measures of frequency	Type of solid organ transplantation					
	Total	Pulmonary	Cardiac	Renal	Hepatic	Renal-pancreatic
Prevalence, %						
Literature <sup>a</sup>	0.2-6.4 <sup>b</sup>	2-6.5	1-1.5	0.2-15	0.9-2.3	–
RESITRA (1997)	0.8	–	1	0.7	1	–
RESITRA <sup>c</sup> (2003-2006)	0.48	1.32	0.25	0.34	0.53	0.82
Incidence, cases per 10 <sup>5</sup> transplants/year						
Literature <sup>d</sup>	–	–	1300-1350	248	–	–
RESITRA <sup>c</sup> (2003-2006)	512	2072	255	358	541	1204

<sup>a</sup>Data collected from references 1, 3-5.<sup>b</sup>In developed countries; in countries with high endemicity of tuberculosis, prevalence may reach 15%.<sup>c</sup>Data collected from reference 1.<sup>d</sup>Data collected from references 6, 7, 11.**Table 2**

Risk factors for post-transplant tuberculosis described in the literature

Risk factors
Recipient characteristics
Blood group AB in kidney transplantation (evidence level 3)
Non-Caucasian (evidence level 2)
Age (evidence level 2)
Immunosuppressive therapy <sup>a</sup>
Muromonab-CD3 <sup>b</sup> o lymphocyte T antibodies (evidence level 3)
Intensification of immunosuppression secondary to rejection episode (evidence level 2)
Cyclosporine A versus azathioprine plus prednisone (evidence level 2)
Mycophenolate mofetil and tacrolimus versus azathioprine plus cyclosporine and prednisone (evidence level 3)
Rescue therapy with tacrolimus (evidence level 3)
History of prior exposure to <i>Mycobacterium tuberculosis</i>
Positive PPD (evidence level 3)
Radiological evidence of old untreated tuberculosis (evidence level 3)
Clinical conditions
Duration of haemodialysis before kidney transplantation (evidence level 2)
Diabetes mellitus (evidence level 2)
Systemic lupus erythematosus in kidney transplantation (evidence level 3)
Infection by hepatitis C virus in kidney transplantation (evidence level 3)
Chronic liver disease (evidence level 3)
Other coexisting infections: deep mycoses, cytomegalovirus, <i>Pneumocystis jiroveci</i> pneumonia or <i>Nocardia</i> (evidence level 3)
Number of rejection episodes post-transplant (evidence level 2)
Type of transplant
Kidney transplant, compared to other solid organ transplants (evidence level 2)
Pulmonary transplant, compared to other solid organ transplants (evidence level 2)

Note: Data collected from references 8-15. PPD: purified protein derivative (tuberculin test). Evidence levels: level 2, at least one non-randomised well-designed clinical study, cohort studies or case and control studies, uncontrolled experimental study but with conclusive results; level 3, expert opinions based on clinical experiences, descriptive studies or reports of expert committees.

<sup>a</sup>Information is not available on more recently introduced immunosuppressants, such as sirolimus, everolimus and the monoclonal antibodies daclizumab and basiliximab.

<sup>b</sup>Muromonab-CD3 is an anti-CD3 monoclonal antibody.

## Chronology, pathogenesis, clinical manifestations, diagnosis and prognosis

### Chronology

Between 45% and 63% of tuberculosis cases in SOT patients occur during the first year post-transplant, with an average onset time of nine months. In a smaller proportion of cases, the disease manifests after the first year, and is therefore referred to as a delayed form of tuberculosis. Patients subjected to kidney transplantation present the most delayed onset of symptoms when compared to other organ transplants. This may be due to the fact that after transplantation these patients receive a treatment regimen that entails less immunosuppression than with other types of solid organ transplantation.<sup>2-4,16</sup> It has therefore been determined that patients who receive immunosuppression with azathioprine and prednisone develop tuberculosis symptoms much later (26 months; range 0.1-94 months) than those who receive cyclosporine (11 months; range 0.1-94 months).<sup>13</sup> Another study showed a greater proportion of tuberculosis in the first six months following kidney transplantation in those patients whose immunosuppressive regimen included tacrolimus and/or mycophenolate (71.4% vs. 15.4%,  $P=.042$ ) compared to other transplant patients with regimens of lesser immunosuppressive capacity.<sup>17</sup> Similarly, patients with a history of exposure to *M. tuberculosis* (radiological findings of residual tuberculosis or positive PPD) prior to transplantation who did not receive appropriate tuberculosis treatment developed the disease earlier than patients without this history, regardless of the type of immunosuppression administered<sup>3</sup>.

### Pathogenesis

The most common form of developing tuberculosis after solid organ transplantation is by reactivation of latent infection in patients with prior exposure to bacillus. Another transmission mechanism is through the transplanted organ, but this is less frequent. Therefore, cases of tuberculosis have been reported in renal and pulmonary transplant patients whose grafts came from the same cadaver donor. Moreover, cases have been reported of transmission of tuberculosis through renal grafts and liver graft from living donors.<sup>3,4,18-22</sup> Nosocomial transmission is another recognised mechanism of transmission, as well as primary infection. This latter form of acquisition is very rare and is almost unique to paediatric patients.<sup>23</sup>

### Clinical manifestations

Tuberculosis that develops in SOT patients mainly affects the lungs. Nevertheless, it has to be taken into account that extrapulmonary involvement and disseminated involvement occur more frequently in this type of immunosuppressed patient than in the general population.<sup>2,4,24</sup>

The clinical presentation of tuberculosis in SOT patients is highly variable, may have no symptoms and may be accidentally diagnosed by routine surveillance cultures for mycobacteria.<sup>25</sup> When the disease is symptomatic, fever is the most frequent symptom, followed by constitutional symptoms such as asthenia, night sweats and weight loss. Coughing, dyspnoea, osteoarticular pain, abdominal pain and chest pain with pleuritic characteristics are other symptoms that occur relatively frequently. The onset of adenopathies is the most commonly observed sign.<sup>2,4</sup>

Tuberculosis with exclusive pulmonary involvement occurs in almost half of post-transplant tuberculosis cases. It usually presents with cough, fever, dyspnoea, haemoptysis and typical radiological images. Images of cavitation in the chest radiographs are usually very rare, as is the case with other patients with cellular immunosuppression (patients with HIV infection and patients subjected to biological therapies). Sometimes, radiological involvement may be atypical (miliary spread or solitary pulmonary nodule), and up to a third of patients may have normal chest radiographs. This makes diagnosis difficult and therefore the disease is not initially suspected in a significant number of cases.

Gastrointestinal involvement has a wide variety of presentations, including fever, abdominal pain, gastrointestinal bleeding, peritonitis and ulcerated lesions. The area most frequently affected is the ileocecal area. Isolated involvement of other parts of the digestive system, such as the pancreas and liver, is rare and generally appears in the context of disseminated tuberculosis.

Most patients with renal involvement present urinary symptoms, flank pain and fever. The development of these symptoms along with the presence of sterile pyuria should alert us to the possibility of urinary tuberculosis.

Lymph node tuberculosis develops with greater frequency in the pretransplant period, mainly presenting as mediastinal and cervical adenopathies. However, it can also develop after transplantation, forming part of disseminated tuberculosis. Likewise, cutaneous and osteoarticular involvement are often the result of disseminated tuberculosis, which is defined as TB that affects two or more noncontiguous organs. The most common presentation symptom is fever. The possibility of tuberculosis dissemination in transplanted patients should be considered when there are data on synchronous involvement of several organs. Respiratory symptoms in this presentation are common, since a high proportion of patients with disseminated tuberculosis present pulmonary involvement.<sup>2,4</sup>

### Diagnosis

The diagnosis of TB in transplanted patients is especially difficult, and it is not uncommon for it to be delayed since, as mentioned above, the disease is frequently asymptomatic or paucisymptomatic, which leads to low clinical suspicion. Moreover, it should be noted that thoracic radiography may be normal, and the tuberculin test may be negative in a large proportion, up to 70% of cases. This negativity in the tuberculin test is due to the cutaneous allergy caused by immunosuppression involved in the underlying disease motivating the transplantation, and by pharmaceutical immunosuppression started after transplantation.<sup>2,3,26</sup> Bacteriological diagnosis of tuberculosis in SOT patients does not differ much from the schedules and techniques used in the general population, although its performance is inferior due to the greater proportion of extrapulmonary tuberculosis.<sup>27</sup> This is due to the difficulty in

obtaining appropriate samples, and the organic and paucibacillary nature of these samples. Although a direct smear for bacilli using acid-alcohol resistant stainings is the fastest, simplest and cheapest method, its low sensitivity limits its usefulness, and must always be complemented with cultures.<sup>28</sup> Current automated systems for liquid medium cultures have improved the recovery and detection time of all types of mycobacteria compared to conventional methods in solid medium (Löwentein-Jensen). Cultures continue to be the reference microbiological method due to their cost-effectiveness and for allowing further studies on antimicrobial susceptibility and epidemiological typing.<sup>28</sup> However, in certain cases, a rapid and accurate diagnosis is required, which makes molecular techniques based on nucleic acid amplification the best option. Among them, the new real-time PCR methods (polymerase chain reaction) have proven very useful in direct detection of the *Mycobacterium tuberculosis* complex, in the general population and in immunosuppressed patients.<sup>29-32</sup> Therefore, this methodology may be applied in the same manner to SOT patients when a rapid diagnosis is required and there is a high clinical suspicion of tuberculosis.

In the case of pulmonary tuberculosis, the diagnostic techniques are, in most cases, direct smears for bacilli using acid-alcohol resistant stainings and sputum cultures. Three samples should be collected, preferably in the morning on three different days. In a study of HIV patients, analysis of two samples collected the same day gave similar results; however, there are no similar studies in transplanted patients.<sup>33</sup> In patients with suspicion of tuberculosis where valid sputum samples cannot be collected, obtaining respiratory samples through induced sputum (with hypertonic saline) or bronchoscopy should be assessed.

In patients with suspicion of disseminated tuberculosis, blood and urine cultures for mycobacteria may provide better performance.

In cases of suspected extrapulmonary disease, a sample of the affected organ should be obtained, usually by puncture or biopsy. In general, whenever possible it is important to obtain appropriate samples for pathological study to determine the presence of acid-alcohol resistant bacilli or caseating granulomas.

Due to the unique characteristics of transplanted patients, tuberculosis drug susceptibility testing should always be performed when obtaining positive cultures of the *M. tuberculosis* complex. Cases have been reported of multidrug-resistant tuberculosis in SOT recipients.<sup>34-36</sup>

### Prognosis

The development of tuberculosis in SOT patients has serious implications. In this population, tuberculosis is associated with high mortality, which is estimated between 15% and 30% (and up to 50% in some series), far higher than that caused in the immunocompetent population. This high mortality is due, at least in part, to the pharmaceutical interaction between immunosuppressants and tuberculosis treatment, which entails significant problems in clinical management and morbidity. This interaction often determines the onset of acute rejection, which is the most common cause for graft loss and death in the transplant population with tuberculosis.<sup>2-4</sup>

In a literature review that included 511 SOT patients with tuberculosis, the average mortality rate among transplant patients with tuberculosis was 29%. This is in contrast to reports from other authors who found lower mortality rates, between 9.5% and 20%.<sup>1-3</sup> In the same review, the greater mortality corresponded to patients who underwent kidney transplantation (30%), while lung transplantation presented the lowest mortality rate (17%). The review found that the following factors were not predictive of mortality: age, transplant patient's place of origin, prior history of exposure to *M. tuberculosis* complex, time of onset of disease after transplantation, immunosuppressive regimen, hepatotoxicity and rejection after tuberculosis treatment. In contrast, with disseminated tuberculosis,

prior rejection and administration of muromonab-CD3 were significant predictors of mortality. Along with these conditions, other factors associated with greater mortality have been reported, such as pre- and post-transplant diabetes mellitus, chronic liver disease, CMV infection and deep mycoses.<sup>8</sup>

## Latent tuberculosis infection

### *Diagnosis of latent tuberculosis infection*

The tuberculin test or the purified protein derivative (PPD) test, despite its limitations in terms of sensitivity and specificity, is still the test of choice for identifying latent tuberculosis infection (LTBI). One of the limitations of PPD is that it is an imperfect identifier for demonstrating the presence of latent tuberculosis infection in patients with anergy, which may affect up to 70% of candidates for solid organ transplantation.<sup>37,38</sup>

In the last decade, studies have been conducted aimed at validating new diagnostic techniques in SOT for latent tuberculosis infection based on the quantification of the release of interferon- $\gamma$  in response to *M. tuberculosis* antigens (interferon gamma release assays, IGRAs). These new methods may overcome some of the limitations of PPD. This would therefore reduce interobserver variability, obviate the need for a second visit and avoid a cross-reaction with the BCG vaccination or other nontuberculous mycobacteria. Additionally, IGRA results are affected to a lesser extent than those of PPD for patients with anergy, are obtained in a short time and may be useful in the diagnosis of LTBI in cadaveric donors and in emergency transplant situations.

The two most commonly used IGRAs are: QuantiFERON®-TB Gold In-Tube test (QFT-GIT) and T-SPOT®.TB test (T-Spot). One of the difficulties attributed to IGRAs is the proper interpretation of indeterminate results. This situation is rare and is minimised by repeating the test. IGRAs have also been deemed expensive. Although they are more costly than PPDs, they are not however inherently more expensive; PPDs are just very economical. IGRAs are not more expensive than other microbiological techniques applied to mycobacteria and especially to tuberculosis.

As of this writing, we cannot state that one technique is better than the other. At present, it would be more correct to say that using both techniques may increase the detection rate of latent tuberculosis infection.<sup>39-44</sup>

### *Treatment of latent tuberculosis infection*

TB in SOT recipients usually develops from a focus of latent infection, and therefore treatment of latent tuberculosis infection (TLTBI) should begin ideally before transplantation. If treatment cannot be finished before transplantation then it should be completed after the operation. Unfortunately, this treatment is not possible or is not performed before the transplantation, and it is therefore essential to perform it after the operation.

All patients on transplant waiting lists or who have been transplanted should receive TLTBI, provided they meet one or more of the following conditions: a) positive PPD skin test (induration greater than or equal to 5 mm, initially or after a booster shot); b) history of earlier improperly treated TB and c) history of contact with a patient with active TB. TLTBI is also recommended for patients with changes in thoracic imaging tests consistent with past untreated TB (apical fibronodular lesions, solitary calcified nodule, calcified lymph nodes and pleural thickening). The value of these radiological data as indications of prior TB is greater in countries such as Spain where there are regional mycoses (histoplasmosis, coccidioidomycosis, blastomycosis) that may cause similar lesions.<sup>45,46</sup>

It is common for patients on SOT waiting lists to present cutaneous anergy due mainly to their underlying disease. A cellular immunity

test is therefore recommended (Multitest® or other selected antigens, such as *Candida albicans* or tetanus toxoid) when carrying out the second PPD skin test, in order to determine the presence of anergy. The risk of developing active TB is not known in these patients, and some authors recommend treating them as if they had positive PPD until there are studies showing the actual risk in this situation. In these cases, the use of IGRAs may be helpful in establishing the definitive indication of treatment for latent tuberculosis infection.

Transmission of active TB from the donor is less common but has been reported. Generally, except in the case of living donors, clinical data may not be available that would reveal whether the donor had TB. It is therefore essential that biopsies and cultures be taken during transplantation in order to rule out active TB in the donor. It is recommended that TLTBI be performed on recipients of organs from donors who have histories or data indicative of untreated TB.<sup>45,46</sup>

The drug of choice in TLTBI is isoniazid (INH, 300 mg/day) supplemented with vitamin B6 for 6-9 months. In general, TLTBI should be performed ideally before transplantation. The duration and posology of TLTBI with INH are the same whether they are performed before or after transplantation.

The possibility of INH hepatotoxicity should be considered in these patients. In general, INH tolerance is good and interaction with calcineurin inhibitors is very limited. It is recommended that liver enzymes be monitored and INH discontinued if the enzymes rise three times above the baseline value and the patient is symptomatic, or if the enzymes rise five times in patients without accompanying symptoms.

In addition to the administration of INH, there are other alternatives such as rifampicin (with or without INH) for four months or rifampicin with pyrazinamide for two months. However, the latter combination has been associated with cases of severe hepatotoxicity and is generally not recommended, except when necessary for completing prophylaxis in a short time period, and always under strict supervision of an expert. This regimen is not recommended in patients with previous liver disease, who drink alcohol or who have a history of INH hepatotoxicity. Regimens that include rifampicin are only recommended when performing TLTBI before transplantation due to drug interactions.

In cases of severe toxicity, hepatic biopsy is recommended only when there is diagnostic uncertainty or lack of normalisation of readings after discontinuing TLTBI. In very high-risk patients, such as recent converters of the PPD skin test, attempts should be made to complete TLTBI with drugs other than INH. In these cases, levofloxacin plus ethambutol may be used for at least six months.<sup>45,46</sup>

Liver transplants present special problems in terms of TLTBI due to the risk of hepatotoxicity. Some authors believe that this risk outweighs the potential benefit, except in patients with greater risk of reactivation.<sup>14</sup> Other authors have not observed an increase in toxicity with the administration of INH to liver transplant candidates.<sup>47</sup> However, it is recommended that TLTBI be delayed in patients who will undergo liver transplantation until after the operation when hepatic function is stable. This strategy is justified because TLTBI may worsen hepatic function in patients still on waiting lists and may lead to emergency transplantation. The convenience of administering TLTBI to liver transplant patients is clearer when there are high-risk factors, such as a) recent conversion of the PPD skin test; b) history of improperly treated TB; c) direct contact with an untreated TB patient; d) residual tuberculous lesions in thoracic imaging tests and e) added immunosuppression factors, such as treatment of rejection episodes in patients with positive PPD skin tests who have not received TLTBI.<sup>14,45,46</sup>

### **Treatment of tuberculosis in solid organ transplant patients**

The recommendations for TB treatment in SOT patients are similar to those for the general population, with only two differences: a)

interaction of rifamycins (rifampicin, rifabutin and rifapentine) with immunosuppressants from the family of calcineurin inhibitors (cyclosporine, tacrolimus), with rapamycin and with steroids, and b) the duration of treatment.

#### Use of rifamycins

The inclusion of rifamycins, mainly rifampicin, in TB treatment regimens in transplant patients is the most controversial issue of treatment. There are arguments for and against its use, and the recommendations vary from one author to another.

Rifampicin has been widely used in transplanted patients. Some series, mainly those carried out in kidney transplants, have confirmed the success of regimens that include rifampicin while rigorously adjusting the concentrations of immunosuppressants, thus achieving a favourable response without an increase in rejection risk.<sup>48,49</sup> European guidelines for TB treatment in kidney transplant patients recommend a treatment similar to the general population: Two months treatment with INH, rifampicin and pyrazinamide, incorporating ethambutol if the rate of INH resistance in the community is greater than 4%, followed by INH with rifampicin for four more months.<sup>50</sup>

However, the rationale behind the final selection of this regimen, with an efficacy completely proven in the general population, leaves many grey areas for transplant patients. Rifampicin reduces serum concentrations of tacrolimus and cyclosporine. Although less studied, it also reduces concentrations of rapamycin, everolimus and corticosteroids. This has been associated in some series with increased rejection risk that is much higher than that observed in patients treated without rifampicin. Therefore, it is recommended that the dosage of calcineurin inhibitors be increased approximately three to five times when rifampicin is used simultaneously in these patients, and that immunosuppressant concentrations be closely monitored.

Not many studies have evaluated the role played by the use, or not, of rifampicin in the outcome of TB transplant patients. It has been documented that the combination of rifampicin with cyclosporine increases rejection rates, graft loss and mortality, both overall and when directly related to TB, despite increasing the dose of cyclosporine and performing appropriate monitoring of drug concentrations.<sup>2-4,51</sup> Recent studies on HIV patients have shown that rifampicin plays a key role in tuberculosis treatment in these patients, since recurrence rates two to four times higher have been observed when rifampicin was not included in the therapeutic regimen.<sup>52</sup> There is no similar information for transplant patients, which warrants more study in this population.

Rifabutin is a cytochrome p450 liver enzyme inducer, which is weaker than rifampicin. It is used as an alternative to rifampicin in patients with HIV infection and may also be an alternative in transplant patients, since it would require a smaller increase in the dose of calcineurin inhibitors. There are some positive experiences in the use of rifabutin in kidney transplant patients;<sup>53</sup> however, the collective experience is still limited and the capacity for interaction, although lower, persists.

#### Induction treatment and maintenance. Duration

There are two controversial issues: the duration and the type of drugs that should be used after the first two months, especially if rifampicin is not used in the first two months, or if rifampicin must be discontinued due to intolerance. Experience in the general population with TB regimens that do not include rifampicin should be cause for reflection on certain issues. For most patients, if there were a recurrence of TB during appropriate treatment that included rifampicin, the most likely explanation would be that this was a sensitive strain. However, with regimens that do not include

rifamycins, especially those that are unsupervised, the onset of resistance is frequent. In the general population, the regimen of INH, pyrazinamide and streptomycin administered for nine months has been shown effective, but parenteral drugs are difficult to maintain over long periods of time. Also, the use of aminoglycosides in transplant patients should be avoided given the renal toxicity risk associated with their use. There are no studies on the use of ethambutol instead of streptomycin in these situations. Nevertheless, in the general population, which is therefore also applicable to transplant patients, it is recommended that oral regimens without rifampicin be maintained for 12 to 18 months and that the benefit of injectable agents in the first two to three months should be assessed in the extensive or cavitary forms.

A Spanish study by the *Grupo de Estudio de las Infecciones en el Paciente Trasplantado* (Study Group on Infections in Transplant Patients, GESITRA) observed that treatment duration of less than nine months was a factor associated with increased mortality. In another study, the only factor significantly associated with greater recurrence of tuberculosis was treatment duration. No recurrence was observed in patients who received treatment for more than 12 months, regardless of whether rifampicin was included or not.<sup>3,54</sup>

A consensus document developed by GESITRA lists the management and treatment recommendations for tuberculosis treatment in SOT patients based on the available evidence.<sup>45,46</sup>

#### Conflicts of interest

The authors declare that they have no conflict of interest.

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#### References

- Torre-Cisneros J, Doblas A, Aguado JM, San Juan R, Blanes M, Montejo M, et al. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. *Clin Infect Dis.* 2009;48: 1657-65.
- Singh N, Paterson DL. *Mycobacterium tuberculosis* infection in solid-organ transplant recipients: impact and implications for management. *Clin Infect Dis.* 1998; 27:1266-77.
- Aguado JM, Herrero JA, Gavalda J, Torre-Cisneros J, Blanes M, Rufi G et al. Clinical presentation and outcome of tuberculosis in kidney, liver, and heart transplant recipients in Spain. Spanish Transplantation Infection Study Group, GESITRA. *Transplantation.* 1997;63:1278-86.
- Muñoz P, Rodríguez C, Bouza E. *Mycobacterium tuberculosis* infection in recipients of solid organ transplants. *Clin Infect Dis.* 2005;40:581-7.
- Morales P, Briones A, Torres JJ, Solé A, Pérez D, Pastor A. Pulmonary tuberculosis in lung and heart-lung transplantation: fifteen years of experience in a single center in Spain. *Transplant Proc.* 2005;37:4050-5.
- Muñoz RM, Pulpón LA, Yebra M, Segovia J, San Martín M, Salas C. Three cases of tuberculosis after heart transplantation in Spain. *Eur J Clin Microbiol Infect Dis.* 1998;17:801-6.
- Korner MM, Hirata N, Tenderich G, Minami K, Mannebach H, Kleesiek K, et al. Tuberculosis in heart transplant recipients. *Chest.* 1997;111:365-9.
- John GT, Shankar V. *Mycobacterial* infections in organ transplant recipients. *Semin Respir Infect.* 2002;17:274-83.
- Basiri A, Moghaddam SM, Simforoosh N, Einollahi B, Hosseini M, Foirouzan A et al. Preliminary report of a nationwide case-control study for identifying risk factors of tuberculosis following renal transplantation. *Transplant Proc.* 2005;37:3041-4.
- Basiri A, Hosseini-Moghaddam SM, Simforoosh N, Einollahi B, Hosseini M, Foirouzan A, et al. The risk factors and laboratory diagnostics for post renal transplant tuberculosis: a case-control, country-wide study on definitive cases. *Transpl Infect Dis.* 2008;10:231-5.
- Klote MM, Agodoa LY, Abbott K. *Mycobacterium tuberculosis* infection incidence in hospitalized renal transplant patients in the United States, 1998-2000. *Am J Transplant.* 2004;4:1523-8.
- John GT, Shankar V, Abraham AM, Mukundan U, Thomas PP, Jacob CK. Risk factors for post-transplant tuberculosis. *Kidney Int.* 2001;60:1148-53.

13. John GT, Vincent L, Jeyaseelan L, Jacob CK, Shastry JC. Cyclosporine immunosuppression and mycobacterial infections. *Transplantation*. 1994;58:247-9.
14. Benito N, Sued O, Moreno A, Horcajada JP, González J, Navasa M, et al. Diagnosis and treatment of latent tuberculosis infection in liver transplant recipients in an endemic area. *Transplantation*. 2002;74:1381-6.
15. Torres J, Aguado JM, San Juan R, Andrés A, Sierra P, López-Medrano F, et al. Hepatitis C virus, an important risk factor for tuberculosis in immunocompromised: experience with kidney transplantation. *Transpl Int*. 2008;21: 873-8.
16. Muñoz P, Palomo J, Muñoz R, Rodríguez-Creixems M, Peláez T, Bouza E. Tuberculosis in heart transplant recipients. *Clin Infect Dis*. 1995;21:398-402.
17. Atasever A, Bacakoglu F, Toz H, Basoglu OK, Duman S, Basak K, et al. Tuberculosis in renal transplant recipients on various immunosuppressive regimens. *Nephrol Dial Transplant*. 2005;20:797-802.
18. Rose G. The risk of tuberculosis transmission in solid organ transplantation: Is it more than a theoretical concern? *Can J Infect Dis Med Microbiol*. 2005;16:304-8.
19. Graham JC, Kearns AM, Magee JG, El-Sheikh MF, Hudson M, Manas D, et al. Tuberculosis transmitted through transplantation. *J Infect*. 2001;43:251-4.
20. Malone A, McConkey S, Dorman A, Lavin P, Gopthian D, Conlon P. Mycobacterium tuberculosis in a renal transplant transmitted from the donor. *Ir J Med Sci*. 2007;176:233-5.
21. Winthrop KL, Kubak BM, Pegues DA, Hufana C, Costamagna P, Desmond E, et al. Transmission of mycobacterium tuberculosis via lung transplantation. *Am J Transplant*. 2004;4:1529-33.
22. Transplantation-transmitted tuberculosis -Oklahoma and Texas, 2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:333-6.
23. Verma A, Dhawan A, Wade JJ, Lim WH, Ruiz G, Price JF, et al. Mycobacterium tuberculosis infection in pediatric liver transplant recipients. *Pediatr Infect Dis J*. 2000;19:625-30.
24. Skogberg K, Ruutu P, Tukiainen P, Valtonen V. Effect of immunosuppressive therapy on the clinical presentation and outcome of tuberculosis. *Clin Infect Dis*. 1993;17:1012-7.
25. Torre-Cisneros J, De la Mata M, Rufián S, Villanueva Marcos JL, Gutiérrez Aroca J, Casal M, et al. Importance of surveillance mycobacterial cultures after liver transplantation. *Transplantation*. 1995;60:1054-5.
26. Guidelines for the Prevention and Management of Infectious Complications of Solid Organ Transplantation. *Mycobacterium tuberculosis*. *Am J Transplant*. 2004;4 Suppl 10:37-41.
27. González-Martín J, García-García JM, Anibarro L, Vidal R, Esteban J, Blanquer R, et al. Consensus document on the diagnosis, treatment and prevention of tuberculosis. *Enferm Infecc Microbiol Clin*. 2010;28:297e1-20.
28. Alcaide F, Esteban J, González J, Palacios JJ. *Micobacterias*. En: Cercenado E, Cantón R, editores. *Procedimientos en microbiología clínica. Recomendaciones de la Sociedad de Enfermedades Infecciosas y Microbiología Clínica* [9a]. SEIMC, 2005. Available at: <http://www.seimc.org/documentos/protocolos/microbiologia/cap9a.pdf>
29. Moure R, Muñoz L, Torres M, Santín M, Martín R, Alcaide F. Rapid detection of Mycobacterium tuberculosis complex and rifampin resistance in smear-negative clinical samples by use of an integrated real-time PCR method. *J Clin Microbiol*. 2011;49:1137-9.
30. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011;377:1495-505.
31. Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? *J Clin Microbiol*. 2011;49:2540-5.
32. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363:1005-15.
33. Swaminathan S, Padmapriyadarsini C, Narendran G. HIV-associated tuberculosis: clinical update. *Clin Infect Dis*. 2010;50:1377-86.
34. Queipo JA, Broseta E, Santos M, Sánchez-Plumed J, Budia A, Jiménez-Cruz F. Mycobacterial infection in a series of 1261 renal transplant recipients. *Clin Microbiol Infect*. 2003;9:518-25.
35. Lee J, Yew WW, Wong CF, Wong PC, Chiu CS. Multidrug-resistant tuberculosis in a lung transplant recipient. *J Heart Lung Transplant*. 2003;22:1168-73.
36. Di Perri G, Luzzati R, Forni A, Allegranzi B, Cazzadori A, Bonora S, et al. Fatal primary multidrug-resistant tuberculosis in a heart transplant recipient. *Transpl Int*. 1998;11:305-7.
37. Richeldi L. An update on the diagnosis of tuberculosis infection. *Am J Respir Crit Care Med*. 2006;174:736-42.
38. Blumberg HM, Leonard MK, Jr., Jasmer RM. Update on the treatment of tuberculosis and latent tuberculosis infection. *JAMA*. 2005;293:2776-84.
39. Kim SH, Lee SO, Park JB, Park IA, Park SJ, Yun SC, et al. A prospective longitudinal study evaluating the usefulness of a T-cell-based assay for latent tuberculosis infection in kidney transplant recipients. *Am J Transplant*. 2011;11:1927-35.
40. Theodoropoulos N, Lanternier F, Rassiwal J, McNatt G, Preczewski L, Demayo E, et al. Use of the QuantiFERON-TB Gold interferon-gamma release assay for screening transplant candidates: a single-center retrospective study. *Transpl Infect Dis*. 2011 Aug 26. [Epub ahead of print].
41. Doblas A, Torre-Cisneros J. The current state of tuberculosis in solid organ transplantation: three principles for optimal management. *Am J Transplant*. 2011;11:1769-70.
42. Arias Guillén M, Palomar R, Arias M. Advances in the diagnosis of latent tuberculosis infection in patients receiving renal replacement therapy. *Nefrologia*. 2011;31:137-41.
43. Lavani A, Pareek M. Interferon gamma release assays: principles and practice. *Enferm Infecc Microbiol Clin*. 2010;28:245-52.
44. Casas S, Muñoz L, Moure R, Castellote J, Guerra M, González L, et al. Comparison of the 2-step tuberculin skin test and the QuantiFERON-TB gold in-tube test for the screening of tuberculosis infection before liver transplantation. *Liver Transpl*. 2011;17:1205-11.
45. Aguado JM, Torre-Cisneros J, Fortún J, Benito N, Meije Y, Doblas A, et al. Consensus document for the management of tuberculosis in solid organ transplant recipients. *Enferm Infecc Microbiol Clin*. 2009;27:465-73.
46. Aguado JM, Torre-Cisneros J, Fortún J, Benito N, Meije Y, Doblas A, et al. 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. *Clin Infect Dis*. 2009;48:1276-84.
47. Singh N, Wagener MM, Gayowski T. Safety and efficacy of isoniazid chemoprophylaxis administered during liver transplant candidacy for the prevention of posttransplant tuberculosis. *Transplantation*. 2002;74:892-5.
48. Sayiner A, Ece T, Duman S, Yildiz A, Ozkahya M, Kilicaslan Z, et al. Tuberculosis in renal transplant recipients. *Transplantation*. 1999;68:1268-71.
49. Al-Sulaiman MH, Dhar JM, Al-Khader AA. Successful use of rifampicin in the treatment of tuberculosis in renal transplant patients immunosuppressed with cyclosporine. *Transplantation*. 1990;50:597-8.
50. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.7.2. Late infections. Tuberculosis. *Nephrol Dial Transplant*. 2002;17 Suppl 4:39-43.
51. Chenhsu RY, Loong CC, Chou MH, Lin MF, Yang WC. Renal allograft dysfunction associated with rifampin-tacrolimus interaction. *Ann Pharmacother*. 2000;34:27-31.
52. Khan FA, Minion J, Pai M, Royce S, Burman W, Harries AD, et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. *Clin Infect Dis*. 2010;50:1288-99.
53. López-Montes A, Gallego E, López E, Pérez J, Lorenzo I, Llamas F, et al. Treatment of tuberculosis with rifabutin in a renal transplant recipient. *Am J Kidney Dis*. 2004;44:e59-63.
54. Park YS, Choi JY, Cho CH, Chang KH, Song YG, Kim YS, et al. Clinical outcomes of tuberculosis in renal transplant recipients. *Yonsei Med J*. 2004;45:865-72.