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Mycobacterial infections in solid organ transplant recipients

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Abstract

Mycobacterial infections represent a growing challenge for solid organ transplant recipients (SOT). The adverse effects of tuberculosis (TB) therapy present a major difficulty, due to the interactions with immunosuppressive drugs and direct drug toxicity. While TB may be donor-transmitted or community-acquired, it usually develops at a latent infection site in the recipient. Pre-transplant prevention efforts will improve transplant outcomes and avoid the complications associated with post-transplant diagnosis and treatment. The present review and consensus manuscript is based on the updated published information and expert recommendations. The current data about epidemiology, diagnosis, new regimens for the treatment of latent TB infection (LTBI), the experience with rifamycins for the treatment of active TB in the post-transplant period and the experience with isoniazid for LTBI in the liver transplant population, are also reviewed. We attempt to provide useful recommendations for each transplant period and problem concerning mycobacterial infections in SOT recipients.

Keywords: Latent tuberculosis infection, mycobacteria, non-tuberculous mycobacteria, solid organ transplantation, tuberculosis
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Hot Topics

- Because active tuberculosis (TB) is associated with high mortality in solid organ transplant (SOT) recipients, all transplant candidates should undergo evaluation for latent TB infection (LTBI) AII.
- The tuberculin skin test (TST) is currently the standard method for identifying subjects at risk. The TST is considered positive if there is ≥5 mm of induration at 48–72 h (AI).
- Whenever possible, patients with either positive or negative TST results should undergo an IGRA test interpreted according to the manufacturer's instructions (BIII).
- Before initiation of treatment for LTBI, patients with positive immunological test results (TST and/or IGRA) should be evaluated so as to rule out active TB (AI).
- A diagnosis of TB can only be confirmed by culturing MTC or by identifying specific nucleic acid sequences in a clinical specimen collected from the suspected site of disease AII.
- Treatment for LTBI should be administered to patients on transplant waiting lists or to recipients after transplantation who have ≥1 of the following conditions: (i) a TST (initial or after a booster effect) with a 5-mm induration or positive IGRA result; (ii) a history of untreated TB; or (iii) a history of contact with a patient with active TB (AII).
- The drug of choice for LTBI is isoniazid (300 mg/day) supplemented with vitamin B6 for 9 months (AI).
- For localized, non-severe forms of TB and periods with high rejection rates, it may be advisable to avoid the use of rifamycins (B-II). Maintenance therapy with isoniazid and

ethambutol (or pyrazinamide) is recommended for 12–18 months (CIII).

- For severe forms or disseminated TB, the use of a TB regimen that includes rifampicin or rifabutin should be considered (B-II). Maintenance therapy with isoniazid and rifampicin or rifabutin is recommended for at least 9 months (BIII).

Introduction

Tuberculosis (TB) represents a growing challenge for SOT recipients, as it is associated with high transplant failure and mortality rates.

The epidemiology of TB in a country determines the risk of developing TB disease after transplantation, compounded by the increased risk among SOT recipients compared with the general population in a given area [1,2]. In addition, variability in the risk of TB is accounted for by centre-related differences in the management of LTBI and active TB [3].

The heterogeneity of TB epidemiology in Europe is high. The incidence of TB ranges from <20 to >75 per 100 000 people according to country and multidrug-resistant rates [4–7]. Few studies have adequately described the incidence rate in the transplantation setting. The incidence of TB in SOT recipients in Europe has previously been reported to be as high as 3.5% [8] although large current series suggest a lower rate (0.45–0.9%), [2,9,10]. The highest incidence (6.4–10%) is observed in lung transplant recipients [11–13].

Tuberculosis-related mortality in SOT recipients has been reported to be as high as 40% [14,15]. Although this mortality rate may have decreased due to better diagnostic techniques, it remains high (9.5–17%) [2,10]. In addition, there are no reports of the mortality rate in Eastern European countries, where the prevalence of TB is high.

Although the majority of patients develop pulmonary TB, the percentage of SOT recipients who develop extrapulmonary or disseminated TB is higher than in the general population [9,15–17]. Immune reconstitution and haemo-phagocytic syndrome associated with TB have also been reported in SOT recipients [9,18]. Most patients develop TB infection in the first year post-transplantation [2] but a bi-modal distribution has also been observed, with the incidence of TB at a peak 2 years after SOT [1,17].

The adverse effects of TB therapy present a major difficulty, due to the interactions with immunosuppressive drugs and direct drug toxicity. The current rise in drug resistance in the *Mycobacterium tuberculosis* complex (MTC) makes TB therapy even more challenging in some European areas.

While TB may be donor transmitted or community acquired, it usually develops at a latent infection site in the recipient, especially in Western Europe, where its prevalence is low [9,19]. Pre-transplant prevention efforts will improve transplant outcomes and avoid the complications associated with post-transplant diagnosis and treatment.

Diagnosis

Latent tuberculosis infection

Latent TB infection is defined as infection with MTC at an early stage with a viable organism in a dormant state. Although the diagnosis of LTBI is hampered by the lack of a reference standard, it is usually made by documenting a positive TST in a person who has no signs, symptoms or chest radiograph evidence of active TB disease [20]. Unfortunately, TST often gives false-negative results in anergic patients, such as those receiving immunosuppressive therapies and/or affected by chronic kidney and liver disease. It may also give false-positive results in areas in which BCG vaccination is prevalent or when there is accidental exposure to environmental non-tuberculous mycobacteria (NTM).

Novel blood tests have become available which detect gamma interferon production in response to antigens encoded by the RD-1 region of the MTC genome. These tests, now known as IGRAs (interferon gamma release assays), seem to be more specific (presenting no cross-reactivity with BCG and NTM) and less affected by immunosuppressive therapies, despite undergoing the same inhibition of immune mechanisms that is responsible for the impaired performance of TST.

Two commercially produced IGRAs are available, the QuantiFERON-TB Gold test (QFT-G; Cellestis Limited, Carnegie, Victoria, Australia), later replaced by the QuantiFERON-TB Gold In-Tube test (QFT-GIT; Cellestis), and the T-SPOT.TB (T-SPOT; Oxford Immunotec, Abingdon, UK). Both tests employ a mitogen-induced positive control able to differentiate between an anergic and a true negative response. With both tests, the result may be reported as qualitative (positive/negative) or quantitative according to defined cut-off values. Quantitative results seem more accurate in detecting the progression of TB infection. While the QFT-GIT test is technically easier to perform and is widely used in clinical laboratories, recent evidence suggests that the T-SPOT, less prone to indeterminate results, is the more sensitive and specific of the two tests, especially in immunosuppressed patients [21–24].

QFT-GIT presented higher positivity than TST and provided a more accurate reflection of the risk of LTBI among kidney transplant candidates [25]. QFT-GIT also showed a role in predicting subsequent TB development in kidney transplant recipients in whom TST did not detect LTBI [26]. In patients

awaiting liver transplantation, TST and QFT-G were comparable for the diagnosis of LTBI, presenting a reasonable concordance between tests [27]. Indeterminate results were more likely in patients with advanced liver disease, using either QFT-G or QFT-GIT [27–29].

As TB is a very serious complication in SOT recipients and both TST and IGRAs may have false-positive and negative results, their concurrent use would be the ideal approach for increasing diagnostic sensitivity [24]. However, this is not always feasible, either for financial reasons or due to the characteristics of specific centres. In our view, excellence not only means transferring new scientific data into daily practice, but, above all, carrying out ordinary tasks to perfection. In everyday practice, many patients undergo transplantation without a prior TST [30]. The scarcity of data in the transplant population and the lack of a reference standard make any definite recommendation difficult.

In addition, when transplants are carried out from deceased donors in whom laboratory investigations cannot be performed, TB transmission may represent an under-appreciated risk [31]. The value of IGRAs in this situation needs further investigation, particularly in lung transplantation [30].

Recommendations for diagnosing latent tuberculosis infection

- Because active TB is associated with a high mortality rate in SOT recipients, all transplant candidates should undergo evaluation for LTBI (AII).
- TST is currently the standard method for identifying subjects at risk; a test is considered positive if there is ≥5 mm of induration at 48–72 h (AI).
- Patients with either positive or negative TST results should undergo an IGRA test interpreted according to the manufacturer's instructions [32] (BIII).
- In the case of discrepant results, any positivity (unless related to a documented BCG vaccination) should be considered for the treatment of LTBI [32,33] (BIII).
- Before initiation of treatment of LTBI, patients with positive immunological test results (TST and/or IGRA) should be evaluated in order to rule out active TB (AI).
- Should IGRA tests be unavailable, a second TST (7–10 days after the first test) should be performed in patients with a negative reaction, in search of a boosting-related skin conversion (AIII).
- Living donors should undergo the same evaluation as transplant recipient candidates [34] (AII).
- When neither TST nor IGRA testing can be performed, as in the case of deceased donors, a history should be obtained from the donor's family of previous latent or active TB and any associated treatment [34] (AII).

Active tuberculosis

Active TB after solid organ transplantation may present at any time during the post-transplant period and is associated with extensive morbidity and mortality [35]. Because of its non-specific clinical manifestations, the lack of clear symptoms and in some cases the presence of extrapulmonary involvement, diagnosis may be problematic [18,36]. In addition, patients may often have coexistent infections and non-infectious complications that add new challenges to the diagnosis. Therefore, a high index of suspicion is of utmost importance for performing an appropriate diagnostic workup. Invasive procedures may be necessary to obtain specimens from the body sites most likely to yield mycobacteria [20].

Recommendations for diagnosing active tuberculosis

- A diagnosis of TB can only be confirmed by culturing MTC or by identifying specific nucleic acid sequences in a clinical specimen collected from the suspected site of disease (AII).
- Culture is the most sensitive detection method; growth is necessary for definitive species identification and full drug susceptibility testing (DST) [37] (AII).
- Today, a combination of liquid and solid culture gives the fastest and most accurate rates of mycobacterial recovery from clinical specimens [38] (AII).
- Smears for acid-fast bacilli (AFB) and mycobacterial culture should be required whenever TB is suspected (AII).
- In the case of pulmonary disease, invasive techniques such as bronchoscopy with bronchoalveolar lavage, transbronchial biopsy and/or mediastinoscopy should be performed as soon as routine sputum examination is found to be uninformative (AII).
- For extrapulmonary TB, a diagnostic approach aiming to obtain direct sampling from the involved site is recommended (Table 1) (AII).
- If an unexplained fever raises the suspicion of disseminated disease, mycobacterial blood cultures should be obtained (BIII).
- Amplification tests performed on respiratory and/or extrapulmonary specimens are required to confirm clinical diagnosis, but do not rule it out [39] (AII).
- When multidrug resistance (MDR) is suspected in a smear-positive patient, rapid molecular tests able to detect gene mutation(s) associated with drug resistance in MTC may be used [40] (BIII).
- Although TST and IGRAs are the cornerstone of the evaluation of MTC infection, they are complementary tests in the case of active TB and may be helpful only if positive (and especially if newly positive) [21] (AII).
- Surveillance cultures performed at fixed times during the post-transplantation period regardless of any clinical and/or radiological evidence produce very low yields and should be discouraged (DIII).

TABLE 1. Recommended site-specific investigations in the evaluation and diagnostic assessment of extrapulmonary TB [32]

Site	Clinical signs	Imaging	Biopsy	Culture
Lymph node	Lymph node enlargement	Ultrasound	Node	Biopsy or aspirate
Pleura	Pleural effusion	Plain X-ray and computed tomography (CT)	Pleura	Biopsy Sputum Pleural fluid
Bone/joint	Involvement of weight-bearing joints (spine, hip and knee)	Plain X-ray and computed tomography (CT) Magnetic resonance imaging (MRI)	Site of disease	Biopsy Site abscess Joint fluid
Gastrointestinal	Abdominal pain Symptoms of intestinal obstruction	Ultrasound CT abdomen Endoscopy	Omentum Bowel	Biopsy Ascites
Genitourinary	Local signs and symptoms	Intravenous urography Ultrasound	Site of disease	Early morning urine Biopsy Endometrial curetting
Disseminated	Involvement of 2 or more non-contiguous sites Miliary TB	High-resolution CT thorax Ultrasound abdomen	Lung Liver Bone marrow	Bronchial washing Liver Bone marrow Blood
Central nervous system	Meningitis Neurological abnormalities	CT brain MRI	Tuberculoma	Biopsy Cerebrospinal fluid
Skin	Ulcerative lesions Local signs and symptoms		Site of disease	Biopsy Site abscess
Pericardium	Pericardial effusion	Echocardiogram	Pericardium	Biopsy Pericardial fluid

Prevention (Treatment of Latent Tuberculosis Infection)

Pre-transplant

Treatment of latent TB infection (LTBI) should only be considered once active TB has been ruled out. Therefore, if clinical or radiological data suggest TB, sputa and/or other respiratory specimens (bronchoaspirate, BAL) must be collected to preclude active disease before initiating LTBI treatment [36]. This is even more important for lung transplant recipients in whom a high incidence of explant-associated TB has been documented [11].

The treatment of LTBI should start before transplantation. If it cannot be completed before the procedure, it should be continued afterwards. It should be provided to all patients on the waiting list for SOT who have ≥1 of the following conditions: [1] a TST (initial or after a booster effect) with an induration ≥5 mm and/or a positive IGRA; [2] a history of untreated TB or chest radiograph findings compatible with untreated TB (apical fibronodular lesions, calcified solitary nodule, calcified lymph nodes, or pleural thickening), especially in geographical areas such as Europe where endemic mycoses mimicking TB lesions do not occur; and/or [3] a history of contact with a patient with active TB [36,41,42].

The drug of choice for LTBI in the transplant recipient is isoniazid (300 mg/day), supplemented with vitamin B6, for 9 months [15,42,43]. Prophylaxis with isoniazid has been shown to prevent TB in randomized studies involving kidney recipients, both pre-transplant [44,45] and post-transplant [46,47]. A recent meta-analysis supported the value of isoniazid as a prophylaxis against TB in renal transplant recipients at risk of active infection in endemic areas [48].

Tolerance of isoniazid is generally good [49] with few reported complications [45]. However, isoniazid-induced hepatotoxicity is possible in these patients. Baseline hepatic measurements of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin levels should be recorded in all patients. Follow-up evaluations should be performed at least monthly and patients should be informed of the possibility of adverse effects [50]. Treatment of LTBI should be suspended if AST or ALT values increase three-fold in patients with symptoms or five-fold in patients without accompanying symptoms [42,51]. A liver biopsy is only recommended when diagnosis is doubtful or when laboratory values do not return to normal after treatment withdrawal.

When suspension of LTBI treatment is necessary, patients should be closely monitored. Treatment should be completed with drugs other than isoniazid in high-risk patients, such as those whose TST and/or IGRA results have changed from negative to positive or some lung transplant patients for whom high risk factors should be individualized. For patients at high risk of TB and isoniazid toxicity, we recommend treatment with levofloxacin (or moxifloxacin) for at least 6 months. However, there are no controlled trials that support this treatment [36].

Other prophylactic alternatives, for which only limited data are available in the SOT population, include isoniazid given twice weekly by directly observed therapy (DOT), rifampicin (with or without isoniazid) for 4 months [42,52,53] and weekly rifapentine and isoniazid for 3 months as DOT [54,55]. These latter alternatives have the benefit of a shorter regimen duration, greater likelihood of therapy completion before

transplant and potentially fewer side-effects. A less frequently recommended regimen of rifampicin with pyrazinamide for 2 months [56] has been associated with severe liver toxicity [57]. The choice of the agent depends on local rates of antituberculosis drug resistance, the recipient's country of birth and the type of transplant [58].

Liver transplant recipients may present a high risk of hepatotoxicity with isoniazid prophylaxis [59]. Some authors consider that this risk outweighs any potential benefits in relation to the fairly low frequency of TB reactivation [43,60,61] compared with the possibility of liver dysfunction and the need for emergency transplant [36]. Other authors did not report increased toxicity associated with isoniazid in the liver transplant population [62–64]. In their review, Holty *et al.* [65,66] reported a significant reduction in TB reactivation and minimal toxicity with isoniazid prophylaxis.

There is widespread agreement regarding the treatment of LTBI in liver recipients when risk factors such as a recent change in TST results, a history of incorrectly treated TB, direct contact with a smear-positive TB patient, residual TB lesions and immunosuppression factors are present [36,43,65]. It also seems reasonable to consider treatment only in patients with compensated cirrhosis and in whom hepatotoxicity is closely monitored [53,67]. For the remaining cases, we consider that the decision should be individualized. Other drugs such as fluoroquinolones may also be considered for LTBI treatment, although adverse effects associated with long treatment duration have been described [17].

Post-transplant

If the treatment of LTBI has not been conducted before transplant, it should be performed afterwards. The indication for and duration of isoniazid prophylaxis is the same as in the pre-transplantation period. Universal post-transplantation isoniazid prophylaxis is only warranted in high endemicity areas [68].

The interaction of isoniazid with calcineurin inhibitors is very limited [42,69]. Isoniazid may increase corticosteroid levels and, consequently, corticosteroid-mediated side-effects [58]. Regimens that include rifamycins are not generally recommended in the post-transplantation period because of drug interactions.

Except in the case of living donors [70], clinical data indicating whether the donor had TB may not be available. Treatment of latent TB infection must be administered to recipients of an organ whose donor has a history of, or data suggesting, untreated TB [15] or recent exposure to active TB [34], particularly in lung transplants [71]. Treatment of LTBI should also be considered for recipients if the donor TB screening test (TST or IGRA) was positive and the donor did not receive chemoprophylaxis [31,68].

Recommendations for treating latent tuberculosis infection

- Treatment of LTBI should be administered to patients on transplant waiting lists or to recipients after transplantation who have ≥1 of the following conditions: (i) a TST (initial or after a booster effect) with a 5-mm induration or positive IGRA result; (ii) a history of untreated TB; or (iii) a history of contact with a patient with active TB (AII).
- The drug of choice for LTBI is isoniazid (300 mg/day) supplemented with vitamin B6 for 9 months (AI).
- Alternatives to isoniazid include rifampicin for 4 months only in the pre-transplantation period (BII).
- Therapy for LTBI must be suspended if AST or ALT values increase three-fold in patients with symptoms or five-fold in patients without accompanying symptoms (BII).
- When isoniazid is suspended, LTBI treatment should be completed with drugs other than isoniazid for patients with a high risk of TB, such as those whose TST result has recently become positive or some high-risk lung transplant patients. Treatment with levofloxacin or moxifloxacin for at least 6 months may be an option (CIII).
- Liver transplant recipients: treatment before transplantation should be considered in patients with compensated cirrhosis, a recent change in TST, a history of incorrectly treated TB, or direct contact with an untreated person with TB (BII).

Treatment of Active Tuberculosis

Pre-transplant

When active TB cannot be ruled out, we recommend initiation of TB treatment with the standard three drugs. Treatment can be completed with isoniazid alone if cultures for MTC are negative after 8 weeks of incubation [36].

In general, patients with active TB should not undergo transplantation. Possible exceptions are patients with well-controlled infections and non-pulmonary SOT [36,67,72].

Post-transplant

The Guidelines of the Expert Group in Renal Transplantation [73] recommend a standard 6-month regimen including rifampicin for TB treatment, in accordance with the currently available guidelines for the general population [41].

In our view, it is reasonable to use a prolonged course of treatment in the immunosuppressed SOT population [36]. A higher risk of death and relapse with short duration treatments has also been reported [1,74,75]. However, there are no

controlled trials assessing the optimal schedule and duration of TB therapy in SOT recipients.

The ideal length of therapy remains controversial. Decisions regarding the duration and the type of drugs to be used, especially if rifampicin is not administered, are based on case series, general population guidelines and expert recommendations.

Recommendations for treating active TB in transplant recipients also differ from those applied to the general population, because of the interactions between rifamycins and immunosuppressants mentioned above, and the potential for hepatotoxicity associated with first-line TB therapy [36]. Additionally, many first-line anti-TB drugs (isoniazid, streptomycin and ethambutol) warrant dose adjustment in renal transplant patients.

The use of rifamycins remains controversial. The interaction between rifampicin and calcineurin inhibitors, inhibitors of the mammalian target of rapamycin (mTOR) and corticosteroids is known to increase the risk of acute rejection [76–80]. The use of rifampin has been identified as a risk factor for immune reconstitution syndrome (IRS) related to changes in immunosuppressive treatment [18]. However, studies in populations other than SOT recipients have shown an increased risk of TB recurrence and high TB resistance rates when rifamycin-sparing regimens are used [41,81].

Some authors have reported difficulties adjusting immunosuppressive drug serum levels and a high graft failure rate with rifampicin usage [82–84]. However, recent series have observed no difference in post-tuberculosis rejection rate or mortality between patients who did or did not receive rifampicin-based regimens [2,85]. Other series have also demonstrated that these drugs may be safe with rigorous control of immunosuppressive drug levels [8,74,86].

Rifabutin may be an alternative, as it appears to be as efficacious as rifampicin in HIV patients and has shown fewer interactions with immunosuppressive drugs [36]. Favourable experiences with rifabutin have been described in small series of kidney and lung transplant patients [87–89]. However, other authors have reported a similar need to increase immunosuppressive drug doses for rifabutin in liver transplant patients [65].

Therefore, the benefits of rifamycins must be balanced against the risk of rejection. Their recommendation for patients with severe or disseminated forms of tuberculosis or with suspicion of resistance to isoniazid seems reasonable. On the other hand, for localized, non-severe forms of tuberculosis and transplantation periods with a high rejection rate, physicians may weigh up the risks and benefits before including rifamycins in the anti-TB regimen.

If rifampin use is mandatory, the dose of calcineurin inhibitors and mTOR should be increased between three- and five-fold (increasing the frequency of administration from twice to three times daily) and the corticosteroid dose should be doubled [1,15,71,76,90–92]. Levels of immunosuppressants should be closely monitored for both kinds of rifamycins and their dose may need to be increased even in the case of rifabutin.

Regimens including rifamycins

If the anti-TB regimen chosen includes rifampicin or rifabutin, a standard treatment based on a three-drug regimen (with the exception of high rates of isoniazid-resistant TB countries) may be considered. We recommend completing treatment with isoniazid and rifampicin or rifabutin in the maintenance phase for at least 9 months [36].

The administration of treatment for less than 9 months has been associated with an increased mortality rate [1]. In addition, it has been shown that a 9–12 month period of anti-tuberculosis treatment reduces the risk of recurrence or treatment failure rates [74,75].

As the standard regimen of isoniazid, rifampin and pyrazinamide may cause significant hepatotoxicity [1,41,75,93,94], monitoring of the liver enzyme is mandatory. The development of liver toxicity is of particular concern for liver transplant patients [1,94]. Although some short series have reported good outcomes [75,86], the standard three-drug regimen has been more frequently associated with high percentages of histologically confirmed hepatotoxicity [95]. Alternatively, pyrazinamide could be replaced with a fluoroquinolone.

Some authors suggest that extrapulmonary TB presentations and patients with cavitary pulmonary TB who remain culture-positive after 2 months require 12–18 months of treatment [34,36,66,67,86].

Regimens that do not include rifamycins

Because of the interactions of transplant drugs with rifamycins, many clinicians opt to avoid these medications if alternative regimens are feasible. If rifampicin therapy is not used, prolonged treatment has been considered for SOT patients due to the experience gained in the general population. Regimens should be continued for at least 12–18 months [15].

In rifamycin-free treatment regimens, some authors recommend a combination therapy with isoniazid and ethambutol for 18 months with the addition of pyrazinamide for the first 2 months [71]. In our view, maintenance agents may include isoniazid and pyrazinamide or ethambutol, and the possible addition of levofloxacin/moxifloxacin should be considered; a three-drug regimen may reduce the treatment length [36]. Some studies have reported favourable experiences with the

use of isoniazid, pyrazinamide and ethambutol for the first 2 months, followed by a 12- to 18-month course of complete therapy [74,96].

In the general population, isoniazid, pyrazinamide and streptomycin have proven to be effective when the regimen is administered for 9 months [41], although it is difficult to maintain injected therapy for long periods because of the risk of ototoxicity and renal toxicity. Little information in the transplant setting is available [97].

Fluoroquinolones (FQs) are an alternative for transplant patients because of the disadvantages associated with rifamycins and aminoglycosides [98]. They can be used as first-line agents [41]. In the transplant setting, good outcomes with FQs in the initial four-drug regimen for kidney and lung transplant recipients have been described [11,99,100].

Current clinical trials are in progress to test the effectiveness of 4-month FQ-containing regimens in the general population. The preliminary results of two of these studies, the RIFAQUIN trial (moxifloxacin and rifapentine twice weekly in place of rifampicin and isoniazid) [101] and the OFLOTUB trial (gatifloxacin instead of ethambutol), showed the inferiority of 4-month TB regimens for outcome [102]. In addition, the possibility that the widespread use of FQs for other infections could lead to a high prevalence of FQ-resistant TB is a matter for concern [103]. Other studies suggest that the prevalence of FQ-resistant TB is still low [104].

Prolonged use of fluoroquinolones may be associated with arthralgias [17]; it may enhance the risk of tendon-related side-effects of corticosteroids, and a combination may decrease mycophenolate levels. An additional effect of levofloxacin is to increase cyclosporine levels [58] and its combination with pyrazinamide is associated with poor digestive tolerance [105].

Linezolid has proven to be effective for patients with TB [106]. However, prolonged use of this drug has been associated with thrombopenia, anaemia and polyneuropathy, especially in patients with diabetes or kidney disease.

Recommendations for treating active tuberculosis

- For localized, non-severe forms of TB and periods with high rejection rates, it may be advisable to avoid the use of rifamycins (B-II).
- For severe forms of or disseminated TB, the use of a TB regimen that includes rifampicin or rifabutin should be considered (B-II).
- When rifamycins are used, levels of immunosuppressive drugs should be closely monitored, and the dose of calcineurin inhibitors, mTOR and corticosteroids should be increased (A-II).
- In regimens that include rifamycins, maintenance therapy with isoniazid and rifampicin or rifabutin is recommended for at least 9 months (B-III).
- In regimens that do not include rifamycins, maintenance therapy with isoniazid and ethambutol (or pyrazinamide) is recommended for 12–18 months (C-III); the incorporation of a third drug, such as pyrazinamide or levofloxacin, could reduce this period to 12 months (C-III).

Drug-resistant Tuberculosis

Multidrug-resistant (MDR) TB is defined as resistance to both isoniazid and rifampin and extremely drug-resistant (XDR) TB is defined as resistance to isoniazid, rifampin, fluoroquinolones and at least one injectable drug (i.e. amikacin, kanamycin and capreomycin) [107].

Drug-resistant TB is not a major health problem in Western Europe at present. However, the finding of substantial MDR-TB among isolates from previously treated patients, combined with the evidence that immigrants from areas where isoniazid resistance is endemic contribute substantially to the number of new TB cases every year, strongly suggests that public health action is needed to improve treatment outcomes [108]. The situation in Eastern Europe is more worrying, as this is one of the areas with the highest proportions of TB patients with MDR-TB in the world [7].

Only a few case reports of MDR-TB in SOT recipients have been published [109–111]. In non-SOT individuals with MDR-TB infection, treatment with second-line anti-TB therapy for 18–24 months achieved a 75% long-term success rate [112]. If isoniazid and rifamycins cannot be used, induction treatment should include four to six drugs, including injectable antimicrobials (e.g. streptomycin, amikacin, kanamycin or capreomycin), linezolid or other second-line drugs, for a prolonged period of time and should be managed only in consultation with an infectious diseases specialist [36,67]. Although evidence is lacking, the recommended treatment duration for these regimens is up to 2 years following MTC culture conversion [113].

Non-Tuberculous Mycobacteria (NTM)

Introduction

Non-tuberculous mycobacteria (NTM) are ubiquitous environmental organisms commonly found in soil and water, whose human-to-human transmission has never been demonstrated [114]. In SOT recipients, the incidence of NTM

infections is much higher than in the general population due to impaired cell-mediated immunity.

The incidence ranges between 0.16% and 0.38% in kidney transplant recipients and is higher in heart and lung transplants (0.24–2.8 and 0.46–2.3, respectively). The data available on liver transplants are limited and show an incidence of 0.04%, which may reflect local epidemiology, misdiagnosis or a genuine reduced susceptibility of liver transplant recipients to NTM infections [115–118].

With the exception of lung transplant recipients, in whom pleuropulmonary NTM disease is the predominant manifestation, the majority of SOT patients develop cutaneous lesions of the extremities, tenosynovitis and arthritis. Over half of these patients exhibit disseminated involvement of non-contiguous areas [115–118].

Diagnosis

Diagnosis of NTM infection. Pulmonary infection with NTM is more frequent in individuals with a pre-existing condition of impaired lung function, which provides a favourable environment for colonization and subsequent invasive disease [114]. Unfortunately, these conditions (pneumoconiosis, COPD, cystic fibrosis (CF) and bronchiectasis) are the leading indications for receipt of a lung transplant. SOT recipients going into surgery colonized with NTM, such as end-stage CF patients with severe bronchiectasis [119], may develop post-transplant infection, and around half of them undergo host vs. graft reaction at the time of diagnosis.

Transmission of NTM infection by the transplanted organ, though rare, has also been reported.

Recommendations for diagnosing NTM infection.

- The recognition of NTM as lung pathogens may be under-appreciated in CF patients whose airways are chronically infected with Gram-negative bacteria, as the latter may conceal the presence of mycobacteria for a long time [119] (BIII).
- In CF patients, a proactive pre-transplant surveillance for respiratory NTM is recommended (AII).

TABLE 2. Non-tuberculous mycobacteria species involved as cause of infection in solid organ transplant recipients

Slowly growing mycobacteria	Fast growing mycobacteria
M. asiaticum	*M. abscessus*
M. avium	*M. bolletti*
M. celatum	*M. chelonae*
M. genavense	*M. fortuitum*
M. haemophilum	*M. mageritense*
M. intracellulare	*M. massiliense*
M. gastri	*M. mucogenicum*
M. gordonae	*M. neoaurum*
M. kansasii	
M. malmoense	
M. marinum	
M. scrofulaceum	
M. szulgai	
M. terrae	
M. thermoresistibile	
M. triplex	
M. xenopi	

Diagnosis of NTM disease. In SOT recipients, due to the effects of immunosuppressive therapy on cell-mediated immunity, NTM infections, though uncommon, are much more frequent than in the general population. NTM infections generally occur late, up to 10 years after transplantation, and the causative agents vary depending on the type of transplant. To date, at least 20 different species have been implicated in these infections (Table 2). The clinical relevance of NTM may differ according to species including organisms with a higher rate of pathogenicity (*M. kansasii*, *M. xenopi*, *M. szulgai*, and *M. malmoense*) and others with a lower rate (*M. fortuitum, M. peregrinum*) [115,116,118]. Although infections caused by NTM can increase morbidity and possibly mortality in SOT recipients, the criteria for firm diagnosis may be uncertain and may vary according to the site involved.

Recommendations for diagnosing NTM disease.

- Isolation of an NTM organism from a normally sterile body site (blood, cerebrospinal fluid and other sterile fluids) provides conclusive proof of invasive disease (AII).
- Local disease is fully explained when skin, soft tissue and lymph node lesions showing granulomata on biopsy yield an NTM species on culture (AII).
- The diagnosis of significant pulmonary infection is more difficult because of the ubiquitous nature of the organisms (AII).
- According to the American Thoracic Society [114], diagnosis of significant pulmonary infection is firmly established when all the following criteria are fulfilled: (i) a compatible clinical presentation; (ii) radiographic images consistent with the diagnosis of NTM; (iii) exclusion of other diagnoses; and (iv) the NTM species was either recovered from respiratory specimens (one bronchoalveolar lavage or two consecutive sputa) or was cultivated from pulmonary tissue (AII).
- Although the above criteria have been developed for immunocompetent individuals with respiratory isolates of *M. avium* complex, they are also believed to provide a useful guide for assessing whether an isolate may be clinically significant in SOT recipients (BIII).
- Failure to respond to standard antimicrobial therapy may provide the first clue that the organism is unusual (BIII).
- A high index of suspicion combined with invasive procedures and prompt transfer to the laboratory of relevant clinical

specimens are essential for rapid and accurate diagnosis [115,116,118] (AIII).

- Clinical specimens must be cultured on both solid and liquid media and all joint fluid, skin and bone specimens incubated at 35°C and 30°C (range 28–32°C) [38] (AII).
- If the clinical information suggests the presence of *M. haemophilum*, *M. genavense* or other fastidious NTM species, the laboratory should be promptly alerted (AII).
- Species identification is essential for choosing effective therapy and deciding whether DST may be performed [37] (AII).
- The correlation between *in-vitro* DST and the clinical outcome has been demonstrated for a limited number of species [114] (AII).

Prevention

Lung transplant. Non-tuberculous mycobacteria colonization has been described as a risk factor for NTM disease and it has been associated with an increased risk of mortality independent of bronchiolitis obliterans syndrome [120]. As *M. abscessus* disease is difficult to cure, the prevalence of *M. abscessus* in colonized patients with cystic fibrosis or chronic lung diseases who may become transplant candidates is a matter of particular concern. Some guidelines recommend that patients with cystic fibrosis colonized with rapidly growing mycobacteria (RGM) should be considered for post-transplant chemoprophylaxis to prevent surgical site infections; in addition, patients infected or colonized with *M. avium* complex (MAC) should be considered for multidrug MAC therapy prior to lung transplantation [121].

Treatment

Non-tuberculous mycobacteria therapy is a challenge, because NTM are inherently resistant to the majority of first-line tuberculostatic therapies; in addition, there are major secondary effects with the active drugs as well as interactions with immunosuppressive drugs. What is more, controversy exists regarding the clinical utility of susceptibility testing. The correlation between *in vitro* data and clinical outcome has been demonstrated for a limited number of species. It is generally recommended for all species of RGM [122].

Because the development of resistance is a regular problem, therapy based on at least two or three active agents, including one injectable drug, is recommended for patients with severe infection. In general, treatment of NTM disease may require a combination of antimicrobial therapy, surgical excision and/or the reduction of immunosuppressive drugs [117].

The optimal duration of therapy in SOT recipients is not known. Pulmonary disease due to NTM should usually be treated until sputum cultures obtained over 12 consecutive months are negative. Skin and soft tissue infections require at least 3–6 months [123]. No data are available for disseminated NTM infection. Close clinical follow-up after discontinuation of antimicrobial agents is important in all cases. The recommended drugs for treating the most common NTM infections are listed in Tables 3 and 4.

TABLE 3. Recommended drugs for slow-growing non-tuberculous mycobacteria (NTM) species involved in solid organ transplant (SOT) recipient infections [117]

NTM species	First-line treatment	Second-line drugs	Validated DST[a]
M. avium complex	Azithromycin Rifabutin Ethambutol	Rifampicin Clarithromycin Amikacin Moxifloxacin	Clarithromycin
M. kansaii	Rifabutin Ethambutol Isoniazid	Rifampicin Clarithromycin Azithromycin Amikacin Moxifloxacin Sulfamethoxazole	Rifampicin
M. marinum	Azithromycin Ethambutol	Rifampicin Rifabutin Clarithromycin Cotrimoxazole Doxycicline Sulfonamides	Rifampicin Ethambutol

[a]Drugs for which a correlation between *in-vitro* results and clinical outcome has been demonstrated.

TABLE 4. Recommended drugs for fast-growing non-tuberculous mycobacteria (NTM) species involved in solid organ transplant (SOT) recipient infections [117]

NTM species	First-line treatment	Second-line drugs	Validated DST[a]
M. abscessus	Amikacin Clarithromycin	Cefoxitin Imipenem Linezolid	All first- and second-line drugs
M. chelonae	Clarithromycin Tobramycin	Azithromycin Amikacin Imipenem Linezolid	All first- and second-line drugs
M. fortuitum	Ciprofloxacin Cefoxitin Clarithromycin	Azithromycin Imipenem Amikacin Moxifloxacin Doxycicline Cotrimoxazole	All first- and second-line drugs

[a]Drugs for which a correlation between *in-vitro* results and clinical outcome has been demonstrated.

Recommendations for treating NTM disease.

- NTM disease usually requires antimicrobial therapy, surgical excision and/or the lessening of immunosuppressive drugs (BIII).
- Therapy should be started with at least two active agents due to the high risk of development of resistance (BIII).
- A life-threatening illness or high infectious burden should be treated with three or more active drugs (BIII).

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Transparency Declaration

The authors have no conflicts of interest to declare.

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