Prevention and Treatment of Mycobacterial Infections

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14.1 Tuberculosis

14.1.1 Epidemiology

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. The incidence of TB ranges from <20 to >125 per 100,000 people according to country and multidrug-resistant rates [1]. The incidence of TB in SOT ranges from 0.45% in low-endemic countries to 15.2% in high-endemic countries [2, 3]. The highest incidence (6.4–10%) is observed in lung transplant recipients [4].

Although mortality rate in SOT recipients may have decreased due to better diagnostic techniques, it remains high (9.5–17%) [2, 3]. In addition, there are scarce reports of the mortality rate in countries with high prevalence of TB. Most patients develop TB infection in the first year posttransplantation [2], but a bimodal distribution has also been observed, with the incidence of TB at a peak 2 years after SOT [5].

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14.1.2 Diagnosis

14.1.2.1 Latent Tuberculosis Infection

Documenting a positive tuberculin skin test (TST) in a person who has no signs, symptoms, or chest radiograph evidence of active TB disease usually makes the diagnosis of LTBI, but this diagnosis is usually hampered by the lack of a reference standard test [6]. 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 [7]. Two commercially produced IGRAs are available, the QuantiFERON-TB Gold In-Tube or Gold Plus (QFT; Qiagen, Germantown, USA) 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.

Both tests, TST and IGRAs, may have false-positive and false-negative results; their concurrent use would be the ideal approach for increasing diagnostic sensitivity [8, 9]. However, this is not always feasible, either for financial reasons or due to

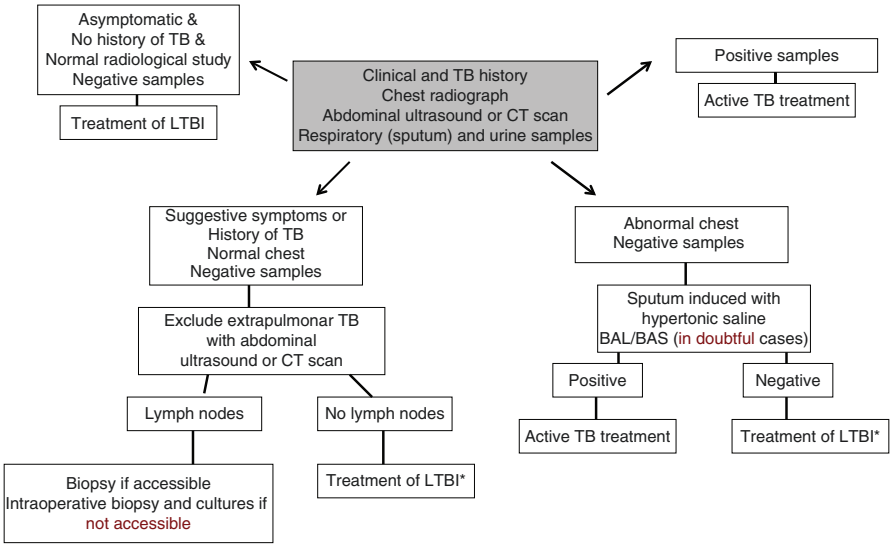

Fig. 14.1 Diagram to rule out active TB. *If urgent transplant, perform treatment of LTBI after transplantation

the characteristics of specific centers. In everyday practice, many patients undergo transplantation without a prior TST [10].

All living donors should also undergo TST and/or IGRA [11–14]. If the result of one of the assays is positive, active TB should be ruled out (see Fig. 14.1) [12, 14]. Treatment of latent TB infection must be administered to recipients of an organ whose donor has a history of, or data suggesting, untreated TB or recent exposure to active TB [14], particularly in lung transplants recipients.

14.1.2.2 Active Tuberculosis

Diagnosis of tuberculosis is challenging due to the non-specific clinical manifestations, the lack of specific radiological findings, and the presence of frequent extrapulmonary involvement [13]. The presence of fever, night sweats, weight loss, lymphadenopathy, or radiographic abnormalities should raise suspicion of TB, especially in patients with a history of contact with *M. tuberculosis* [13].

The first step in diagnosing TB is to obtain specimens for acid-fast bacilli (AFB) stains and mycobacterial culture. If pulmonary disease is suspected, three induced sputums should be collected, and/or invasive techniques, including bronchoalveolar lavage, transbronchial biopsy, and/or mediastinoscopy, should be performed. For extrapulmonary TB, a diagnostic approach aiming to obtain direct sampling from the involved site is recommended. If an unexplained fever raises the suspicion of disseminated disease, mycobacterial blood cultures should be obtained. Definitive diagnosis requires AFB cultures or the use of PCR to identify specific nucleic acid sequences in a clinical specimen collected. In addition to their sensitivity, AFB cultures allow for definitive species identification and full drug susceptibility testing. Although TST and IGRAs are the cornerstone of the evaluation of latent infection, they are not typically helpful in ruling out active TB, and positive testing may not indicate active infection [8].

14.1.3 Prevention

14.1.3.1 Pretransplant

The treatment of LTBI should start before transplantation. If it cannot be completed before the procedure, it should be continued afterward. It should be provided to all patients on the waiting list for SOT who has ≥1 of the following conditions [11, 12]:

- A TST (initial or after a booster effect, with a second TST performed 1–2 weeks later) with an induration ≥5 mm and/or a positive IGRA
- 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
- A history of contact with a patient with active TB

The drug of choice for LTBI in the transplant recipient is isoniazid, supplemented with vitamin B6, for 9 months [15, 16] (See Table 14.1). Other prophylactic alternatives for which only limited data [17, 18] are available in the SOT population are shown in Table 14.1. Isoniazid is generally well tolerated, although

Table 14.1 Suggested regimens for the treatment of LTBI

Drug	Duration	Recommendations
INH (5 mg/kg) (maximum of 300 mg)	Daily, 9 months	Combine with pyridoxine, 25–50 mg/day
INH (15 mg/kg) (maximum of 900 mg)	Twice weekly, 9 months DOT	Combine with pyridoxine, 25–50 mg/day
Rifampin (10 mg/kg) (maximum of 600 mg)	Daily, 4 months	Used preferably before transplantation due to interaction with immunosuppressive drugs
INH (15 mg/kg); (maximum of 900 mg) plus RFP (<50 kg, 750 mg; >50 kg, 900 mg)	Once weekly, 3 months, DOT or WR	Combine with pyridoxine, 25–50 mg/day Used preferably before transplantation due to interaction with immunosuppressive drugs

NH isoniazid, *RFP* rifapentine, *DOT* direct observed therapy, *WR* weekly reminders

isoniazid-induced hepatotoxicity may occur, especially in pre-liver candidates. Recent data showed that rifampicin has similar efficacy and reduced toxicity as compared to isoniazid [19], although data on the use of rifampicin in SOT candidates is scarce. Aminotransferases should be monitored closely [14]. Treatment of LTBI should be suspended if AST or ALT values increase threefold in patients with symptoms or fivefold in patients without accompanying symptoms.

In case of discontinuation of LTBI treatment, patients should be closely monitored, and treatment should be completed with drugs other than isoniazid in high-risk patients or could be deferred to posttransplant in lower-risk patients. Alternative regimens include rifampin or fluoroquinolones [12].

When active TB cannot be ruled out in an SOT recipient, it is recommended to start treatment with three drugs (INH, ethambutol, and pyrazinamide) [11]. A fourth drug, e.g., a fluoroquinolone, should be added if the disease is severe or until susceptibilities are known. Treatment can be completed with only INH if, after 8 weeks, cultures are negative for *M. tuberculosis* and the chest radiograph is considered normal [11].

Liver transplant recipients may present a high risk of hepatotoxicity with isoniazid prophylaxis. Some authors consider that this risk outweighs any potential benefits in relation to the fairly low frequency of TB reactivation compared with the possibility of liver dysfunction and the need for emergency transplant [15]. Other authors did not report increased toxicity associated with isoniazid in the liver transplant population [20].

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 [11, 20]. It also seems reasonable to consider treatment only in patients with compensated cirrhosis and in whom hepatotoxicity is closely monitored [12]. 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 [21].

14.1.3.2 Posttransplant

If the treatment of LTBI has not been conducted before transplant, it should be performed afterward. The indication for and duration of isoniazid prophylaxis is the same as in the pretransplantation period. The interaction of isoniazid with calcineurin inhibitors is small [69]. Isoniazid may increase corticosteroid levels and, consequently, corticosteroid-mediated side effects [58]. Regimens that include rifamycins are not generally recommended in the posttransplantation period because of drug interactions.

14.1.4 Treatment

14.1.4.1 Pretransplant

When active TB cannot be ruled out, we recommend initiation of TB treatment with the standard three/four drugs. Treatment may be completed with isoniazid alone if cultures for MTC are negative after 8 weeks of incubation [12]. In general, patients with active TB should not undergo transplantation. Possible exceptions are patients with well-controlled infections and non-pulmonary SOT [11, 12].

14.1.4.2 Posttransplant

Recommendations for treating active TB in transplant recipients also differ from those applied to the general population, because of the interactions between rifamycins and immunosuppressive drugs, and the potential for hepatotoxicity associated with first-line TB therapy [11]. 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 [22, 23]. 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 [24].

Some authors have reported difficulties adjusting immunosuppressive drug serum levels and a high graft failure rate with rifampicin usage [25]. Other authors have demonstrated that these drugs may be safe with rigorous control of immunosuppressive drug levels [26]. Favorable experiences with rifabutin have been described in small series of kidney and lung transplant patients [27]. However, other authors have reported a similar need to increase immunosuppressive drug doses for rifabutin in liver transplant patients [20].

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 [11–13]. See Table 14.2.

Table 14.2 Tuberculosis treatment options

Situation	Initial treatment	Maintenance treatment
Patients with localized and no severe TB and non-suspicion or evidence of resistance to isoniazid	• Avoid the use of rifamycins • INH, ethambutol, and pyrazinamide (or levofloxacin)	• Isoniazid and ethambutol (or pyrazinamide) are recommended for 12–18 months • The incorporation of a third drug, such as pyrazinamide or levofloxacin, could reduce this period to 12 months[a]
Severe forms or disseminated forms of TB or suspicion or evidence of resistance to isoniazid[b]	• Consider adding rifampicin or rifabutin to the regimen[c] • Levels of immunosuppressors should be closely monitored	• Complete treatment with isoniazid and rifampicin or rifabutin for at least 9 months
Multidrug-resistant TB or when there is some limitation for the use of the aforementioned drugs	• If isoniazid and rifamycins cannot be used, induction treatment should include 4–6 drugs • Possible drugs: injectable antimicrobials (e.g., streptomycin[d] amikacin, kanamycin, or capreomycin), linezolid, or other second-line drugs[e]	• The duration of treatment and the types of drugs should be individualized

[a]Prolonged use of fluoroquinolones can be associated with arthralgias; it may enhance the risk of tendon-related side effects of corticosteroids, may decrease mycophenolate levels, and may increase cyclosporine levels, and the combination with pyrazinamide is poorly tolerated by the digestive system

[b]If isoniazid cannot be used, induction and maintenance treatment that includes four drugs for at least 18 months is recommended

[c]A standard treatment based on a three-drug regimen may be considered (isoniazid, rifampicin or rifabutin, and pyrazinamide). Monitoring of the liver enzyme is mandatory and of particular concern for liver transplant patients. Alternatively, pyrazinamide could be replaced with a fluoroquinolone. The dose of calcineurin inhibitors and mTOR should be increased between three- and fivefold (increasing the frequency of administration from twice to three times daily), and the corticosteroid dose should be doubled. 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. Resistance to rifampin is almost systematically associated with cross-resistance to rifabutin and rifapentine; therefore, these drugs are not suitable alternatives

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

[e]There is no experience with the use of intermittent regimens, which, in any case, are not recommended for the management of multidrug-resistant TB, with the injectable drugs after a period of at least 2–3 months of daily therapy

14.1.4.3 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. Complete treatment with isoniazid and rifampicin or rifabutin in the maintenance phase for at least 9 months is recommended [11, 12]. 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 [11, 14, 20].

14.1.4.4 Regimens That Do Not Include Rifamycins

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 [24]. In rifamycin-free treatment regimens, the combination therapy with isoniazid and ethambutol for 12–18 months with the addition of pyrazinamide for the first 2 months is an option [28]. 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 [12].

In the general population, isoniazid, pyrazinamide, and streptomycin have proven to be effective when the regimen is administered for 9 months [24], 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.

Fluoroquinolones (FQs) are an alternative for transplant patients because of the disadvantages associated with rifamycins and aminoglycosides. In the transplant setting, good outcomes with FQs in the initial four-drug regimen for kidney and lung transplant recipients have been described [4]. 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.

Linezolid has proven to be effective for patients with TB [29]. However, prolonged use of this drug has been associated with thrombopenia, anemia, and polyneuropathy, especially in patients with diabetes or kidney disease.

14.1.5 General Approach

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). The tuberculin skin test (TST) and/or an IGRA test are currently the standard methods for identifying subjects at risk. Before initiation of treatment for LTBI, patients with positive immunological test results (TST and/or IGRA) should be evaluated to rule out active TB. 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. Treatment for LTBI should be administered to patients on transplant waiting lists or to recipients after transplantation who have ≥1 of the following conditions: (1) a TST with a 5-mm induration or positive IGRA result, (2) a history of untreated TB, or (3) a history of contact with a patient with active TB. The drug of choice for LTBI is isoniazid (300 mg/day) supplemented with vitamin B6 for 9 months or rifampicin for 4 months. For localized, non-severe forms of TB and periods with high rejection rates, it may be advisable to avoid the use of rifamycins. Maintenance therapy with isoniazid and ethambutol (or pyrazinamide) is recommended for 12–18 months. For severe forms or disseminated TB, the use of a TB regimen that includes rifampicin or rifabutin should be considered. Maintenance therapy with isoniazid and rifampicin or rifabutin is recommended for at least 9 months.

14.2 Non-tuberculous Mycobacteria

Introductory Abstract
Non-tuberculous mycobacteria (NTM) are uncommon causes of human disease despite their ubiquity in the environment including soil and water [30] but are increasingly recognized as significant pathogens in solid organ transplant (SOT) recipients as opportunistic agents. NTM disease progression is facilitated by impaired cell-mediated immunity in this population and, in the case of lung transplant candidates and recipients, by structural disease promoting airway colonization [31]. High index of suspicion is required for timely diagnosis and treatment. On the other hand, a subset of NTM isolated from the lungs may represent colonization or early subclinical infection, for which watchful observation without therapy is reasonable. Given the complicated and prolonged treatment regimens for the majority of NTM, which can adversely interact with immunosuppressive medications, true therapeutic need should be established before initiation of treatment for pulmonary NTM. Treatment is usually given for 12–18 months or longer, with regimen tailored to speciation and sensitivity testing results [32]. In recent years, *M. abscessus* infection in lung transplant candidates has emerged as a major therapeutic challenge due to its propensity to cause early surgical site infection posttransplant.

14.2.1 Epidemiology

NTM are a heterogeneous group of organisms numbering >125 species and growing, over half of which have the potential to cause human infections. However, majority of NTM infections are caused by approximately 20 common pathogens [33]. NTM are broadly classified as rapidly growing mycobacteria (RGM) vs. the rest, based on the speed of growth of the organism on the culture media once incubated. RGM typically grow within 7 days of incubation and include *Mycobacterium abscessus*, *M. fortuitum*, and *M. chelonae*. The rest of NTM such as *Mycobacterium*

avium complex (MAC) or *M. kansasii* take longer to grow, although time to culture positivity is also impacted by the inoculum size. While the source of most NTM infections is believed to be environmental, possibility of person-to-person transmissions has been raised recently with *M. abscessus*, with the conjectured route of spread via fomite or aerosol [34]. True incidence of NTM in SOT recipients is difficult to determine due to its lack of reporting requirement, but literature suggests relatively low incidence of <1% in abdominal transplant recipients and up to 2.8% in heart transplant recipients. The incidence is by far the highest in lung transplant recipients, varying widely and ranging from 0.5% up to 18% [35], with higher rates seen in centers that perform routine surveillance bronchoscopies.

As with their presentation in immunocompetent hosts, pulmonary disease is by far the most frequent site of NTM infection in SOT recipients, followed by skin and soft tissue infections (SSTI). While MAC causes the majority of NTM disease overall, RGM are mostly frequent etiological agent for SSTI, which typically presents as erythematous to violaceous subcutaneous nodules or ulcerative lesions that occur at a surgical site or in extremities, often in clusters or along a lymphangitic spread [33]. Other less common manifestations include osteoarticular infections such as vertebral osteomyelitis, catheter-associated mycobacteremia, lymphadenitis, and disseminated disease involving two or more organ systems.

SOT recipients are at increased risks for more severe infections by NTM due to their compromised cell-mediated immunity. Specific risk factors for different NTM species have been elucidated for certain subsets of patients: Pulmonary infections with MAC are increased in subjects with impaired lung architectures and function, such as emphysema and bronchiectasis. *M. abscessus* has emerged as a major pathogen in patients with cystic fibrosis (CF) and other immunodeficiencies associated with recurrent pulmonary infections and bronchiectasis [36]. All three RGM species have been linked to foreign body/prosthetic infections. Certain species have specific risk factors, such as *M. marinum* and its close association with injuries from marine life or contact with contaminated seawater or fish tank.

NTM infection can occur at varying times from transplant, from early postoperative period to years after the transplant. A recent single-center study suggested a bimodal distribution, with the first peak at median of 2.2 months and second at 7.5 years. Early NTM infections occurring <1 year posttransplant was significantly associated with increased mortality compared to matched control [37]. A specific subset of early posttransplant NTM infection of note is *M. abscessus* surgical site infection that occurs in lung transplant recipients colonized with the organism pretransplant, usually within the first few weeks to months during wound healing. Management of *M. abscessus* infection in this scenario has posed significant therapeutic challenges.

14.2.2 Diagnosis

Diagnosis of NTM in SOT patient requires a high index of suspicion and prompt submission of appropriate specimen for mycobacterial cultures. NTM should be

high on the list of differential diagnosis in any SOT recipients with unexplained febrile illness, atypical pulmonary radiological abnormalities, subacute SSTI with nodular or ulcerative components, surgical site infections, or foreign body-associated infections. For extrapulmonary infections, delay in diagnosis is common due to frequently omitted request for mycobacterial cultures during the processing of clinical samples. Once an NTM is isolated in mycobacterial blood or tissue cultures, the diagnosis is relatively unambiguous, although sampling error or low bacterial inoculum may lead to falsely negative culture results, necessitating repeated attempts at fluid or tissue cultures.

For pulmonary infection, diagnosis of NTM is a more layered topic. Isolation of NTM from a respiratory sample might represent colonization of the airways or environmental contamination rather than an invasive disease. Lung transplant recipients have a particularly high rate of isolation of NTM from respiratory samples, due to their abnormal airway anatomy and impaired ciliary function facilitating NTM colonization, as well as frequent submission of respiratory samples. The American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guideline for diagnosis of pulmonary disease by NTM [32] attempts to distinguish symptomatic infections from asymptomatic colonization or early subclinical disease, by considering clinical, radiological, and microbiological criteria as a whole (Table 14.3). While this provides a useful reference, clinicians should be advised that these diagnostic criteria were devised with largely immunocompetent hosts in mind. Early invasive NTM infections that do not meet the criteria may progress more rapidly than expected in SOT recipients. Close follow-up with repeated respiratory cultures and serial imaging is warranted for patients at high risk for invasive NTM disease.

Once an NTM was isolated, precise speciation is needed for the clinicians to choose optimal combination therapy. DNA probes and other molecular-based assays are frequently employed for rapid diagnosis of common mycobacteria such as *M. tuberculosis* and MAC. Speciation of less common NTM species may require DNA sequencing or for the isolates to be sent to a reference testing laboratory. Identification down to the subspecies level is of particular importance for *M. abscessus*, as

Table 14.3 ATS/IDSA diagnostic criteria of NTM lung diseases

Clinical
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiographs, or a high-resolution scan that shows multifocal bronchiectasis with multiple small nodules
2. Appropriate exclusion of other diagnoses
Microbiological
1. Positive culture results from at least two separate expectorated sputum samples
2. Positive culture results from at least one bronchial wash or bronchoalveolar lavage
3. Transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathological features and one or more sputum or bronchial washings that are culture-positive for NTM

Adapted from ATS/IDSA guideline [32]

subspecies *M. massiliense* is associated with better sensitivity profile and a more favorable response to therapy [38]. In case of positive AFB stain seen in histopathologic examination without corresponding positive cultures, direct detection of AFB DNA from tissue may be attempted using broad-range, multi-locus PCR [39].

14.2.3 Prevention

Many NTMs are ubiquitous in the environment and difficult to avoid. Transplant recipients are advised to refrain from cleaning aquariums or, if unavoidable, to use gloves during the cleaning to minimize the exposure to *M. marinum* [40]. Gloves should also be used during gardening. Insufficiently heating in household water systems has been associated with increased number of NTM [41]; thus at-risk patients such as transplant candidates or recipients should ensure adequate water heater temperatures. In contrast to *M. tuberculosis*, pharmacological prophylaxis has not been well established in NTM prevention in SOT recipients. The closest analog would be rifabutin or azithromycin chemoprophylaxis against MAC, reserved for patients with advanced AIDS [32]. However, the rate of MAC infection across SOT populations is not consistent or high enough to warrant therapy with agents that carry significant GI side effects or interact with immunosuppressive medications.

14.2.4 Treatment

14.2.4.1 General Considerations

In-depth discussion of various regimen used for NTM is beyond the scope of this review, but Table 14.4 lists first-line therapy for several medically significant NTMs, the majority of which requires multidrug combinations for ≥12 months. In general, susceptibility testing is recommended for RGM to guide therapy, whereas its utility is more debated for slower-growing NTM species. MAC isolates should be tested for macrolide sensitivity; testing of MAC sensitivities for other agents such as rifabutin, ethambutol, amikacin, and quinolones may be requested, but correlation with clinical response is more questionable. Rifampin sensitivity testing should be performed on *M. kansasii*, with further testing for secondary agents to be considered for rifampin-resistant isolates [32].

If feasible, reduction in immunosuppression is recommended for severe or disseminated disease. Rifamycins are strong inducers of CYP3A4 enzymes through which calcineurin inhibitors and mTor inhibitors are metabolized, and coadministration results in reduction of exposure for these immunosuppressive agents. Rifabutin is a weaker inducer compared to rifampin and is the preferred agent in NTM therapy among transplant patients, although dose adjustment in CNI and mTor inhibitors is still necessary in most cases. Similarly, while the ATS/IDSA guideline lists clarithromycin as the major macrolide backbone in most NTM

Table 14.4 First-line therapy for several medically significant NTMs

Organism	Susceptibility testing	Recommended regimen	Comments
MAC	Clarithromycin; correlation between susceptibility and clinical response not well established for other agents	Azithromycin + rifabutin + ethambutol for at least 12 months after microbiological clearance	Induction with amikacin may be considered for severe or disseminated infection
M. kansasii	Rifampin; if resistant, consider testing for additional agents	Isoniazid with pyridoxine + rifabutin + ethambutol for 18 months (≥12 months after microbiological clearance)	Isoniazid may be active even if in vitro resistance is reported
M. haemophilum	No standardized susceptibility testing available	Azithromycin + ciprofloxacin + ethambutol	Resistant to ethambutol
M. marinum	Routine susceptibility testing not recommended	Azithromycin + ethambutol ± rifabutin	Shorter course of therapy, e.g., 6 months, might be adequate
M. abscessus	Amikacin, cefoxitin, imipenem and/or meropenem, quinolones, clarithromycin, doxycycline, minocycline, sulfonamide, linezolid	Based on susceptibility data, ≥3 active drug combination preferred including macrolide backbone if susceptible	Induction with parenteral antibiotics recommended; for MDR pathogens, test for tigecycline and clofazimine sensitivities
M. chelonae	Amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, sulfonamides, linezolid	Based on susceptibility data, two active drugs including a macrolide recommended	For localized infection, consider surgical debridement
M. fortuitum	Same as *M. chelonae*	Based on susceptibility data, two active drugs recommended	Contains inducible macrolide resistance via methylase gene; use macrolides with caution

treatment regimen, substitution with azithromycin is recommended in SOT recipients due to its minimal interaction with transplant medications compared to clarithromycin, which inhibits CYP3A4 [42].

The ATS/IDSA guideline recommends minimum of 12 months of therapy for NTM after microbiological clearance. Longer therapy of ≥18 months may be needed for osteoarticular or disseminated infections. For disease limited to the skin and soft tissue, a shorter duration of therapy such as 3–6 months may be acceptable provided there is clinical resolution.

14.2.4.2 Special Consideration: Lung Transplant and NTM

Patients with structural lung disease awaiting lung transplant, especially those with CF, are one of the highest risk groups for NTM infection. While severe MAC infection may contribute to respiratory insufficiency in rare instances, in majority of cases, isolation of MAC pretransplant represents colonization, and MAC colonization pretransplant has not been associated with increased posttransplant morbidity or mortality [43]. That said, once listed, most clinicians would opt to treat MAC until transplant with combination therapy [44], although treatment is not usually extended posttransplant once colonized lungs have been explanted. On the other hand, infection with *M. abscessus* has posed a major clinical challenge in this population, especially in cystic fibrosis patients. Since the early 2000s, multiple published case reports and case series brought attention to the tendency of *M. abscessus* to cause aggressive early recurrent infections in the surgical sites associated with poor outcome [45–48], prompting the majority of lung transplant centers to consider *M. abscessus* infection a relative, if not absolute, contraindication for transplant listing. In contrast, a cohort study from a large US lung transplant center showed *M. abscessus*-colonized CF patients may still be transplanted with comparable survival to CF patients without the infection [49]. Further reports suggest that, while surgical site infection remained a major issue, *M. abscessus* infection needs not be an absolute contraindication for lung transplant [50–52]. However, these reports come with several caveats: (1) eradication attempts should be made prior to transplant; (2) aggressive treatment for *M. abscessus* is needed pre- and posttransplant; (3) consider further methods to minimize contamination of the surgical space during transplant surgery, including antibiotic irrigation, lymphadenectomy, and changing of surgical gloves prior to handling donor organs. The optimal duration of *M abscessus* therapy posttransplant has not been well established.

For lung transplant recipients developing NTM infection past early postoperative period, the decision to treat depends on a variety of clinical factors, such as extent of symptoms and radiological abnormalities, number/persistence of positive cultures, concomitant rejection, and anticipated medication toxicities. Moreover, NTM isolation in this population is often transient and may not require therapy and has not been associated with increased posttransplant mortality [53]. Even for difficult pathogens such as *M. abscessus*, the ATS guideline appears useful in determining significant infection warranting therapy [54].

14.2.5 General Approach

NTM should be considered for subacute respiratory infections associated with atypical pulmonary radiological presentation in SOT patients. Nodular or ulcerative SSTI, indolent osteoarticular infections, chronic wasting illness, and persistent or recurrent foreign body-associated infections should also raise a suspicion of NTM. Repeated sampling may be needed to establish the diagnosis. Once NTM has been isolated, extensive susceptibility testing should be performed on all clinically significant RGM, whereas more limited testing is recommended for MAC and *M. kansasii*. With frequent respiratory sampling, NTM may be isolated incidentally. As treatment is usually complex and prolonged, therapeutic necessity should be established in each individual case based on clinical signs and symptoms and radiological progression. Reduction in immunosuppression is recommended for severe and/or disseminated disease. Lastly, *M. abscessus* infection in lung transplant candidates is a complex topic that requires a multidisciplinary approach. Every attempt should be made to eradicate the organism pretransplant, although final decision whether to list these patients remains up to the practice of individual institution, given the high risk of aggressive early recurrence.

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