Management of Mycobacterium Other than Tuberculosis in Solid Organ Transplantation

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KEYWORDS

• Mycobacterium other than tuberculosis • Solid organ transplantation • Treatment

KEY POINTS

- Owing to immunosuppressive agents, impairment of host defenses in solid organ transplant recipients increases the risk of infections owing to mycobacteria other than tuberculosis.
- Mycobacteria other than tuberculosis is uncommon, but carries significant morbidity and mortality in the solid organ transplant population.
- Lung transplant recipients are at higher risk compared with other solid organ transplant recipients.
- Treatment of mycobacteria other than tuberculosis requires appropriate selection of antimicrobial agents, management of side effects, and consideration of drug–drug interactions.

INTRODUCTION

Mycobacteria other than tuberculosis (MOTT) are ubiquitous in the environment. To date, there are more than 150 different species of MOTT that have been described as a result of improved culturing and sequencing techniques and differentiation of species.[1] Owing to impaired T-cell–mediated immunity, solid organ transplant (SOT) recipients are at an increased risk for MOTT. The incidence of MOTT in SOT is low; however, it is essential to recognize the complexity of diagnosis and treatment of MOTT in this population. The latter involves awareness of drug combinations specific for MOTT species and drug–drug interactions between antimycobacterial drugs and immunosuppressive medications. This review focuses on relevant MOTT infections in SOT recipients and its management.

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OVERVIEW OF MYCOBACTERIUM OTHER THAN TUBERCULOSIS

Only about one-half of the MOTT infections can potentially cause disease in humans and animals. MOTT are classified by growth rate and colony pigmentation in culture media. MOTT are found in the soil, water, plant material, animals, and birds.[2] Only a few species that are known to cause disease have been recovered from the environment.[3,4] Tap water is considered a common reservoir for common human MOTT pathogens. Biofilm in pipes allows growth of MOTT and may render them less susceptible to disinfectants and antibacterial therapy.[5,6] MOTT have been implicated in healthcare-acquired outbreaks. A recent outbreak of *Mycobacterium abscessus* has shown that more than one-half of the patients who developed an infection or colonization were SOT recipients, with the majority being lung transplant recipients.[7] Person-to-person[8] and donor-derived transmission of MOTT are rare.[9,10]

SOT recipients with prior colonization or environmental exposure are at increased risk for clinical disease progression owing to T-cell–mediated immunity impairment and an overall net state of immunosuppression. **Table 1** summarizes the MOTT reported in SOT recipients. There are limited data on the incidence of infections owing to MOTT in SOT. The incidence is higher compared with the general population. He incidence of MOTT varies depending on type of organ transplanted, which are as follows: 0.1% in liver transplantation,[11] 0.16% to 0.55% in kidney transplantation,[12–20] 0.24% to 2.80% in heart transplant,[21,22] and 0.46% to 4.40% in lung transplantation.[23–26] To date, the incidence in the pancreas and small bowel transplant recipients is unknown. Lung transplant recipients, as expected, have a higher overall risk estimated at 1.1 per 100 person-years in contrast with non–lung transplant recipients at 0.02 per 100 person-years.[27] Factors that may predispose lung transplant recipients

Table 1
***Mycobacterium* species other than tuberculosis that cause infection in solid organ transplant recipients**

Slow-Growing Mycobacteria (Growth >7 d)	Rapid-Growing Mycobacteria (Growth <7 d)
M asiaticum	*M abscessus*[a]
M avium complex (includes avium and intracellulare)[a]	*M boletti*
M celatum	*M fortuitum*[a]
M gastri	*M chelonae*[a]
M genavense	*M mageritense*
M gordonae (commonly a contaminant)	*M massiliense*
M haemophilum	*M mucogenicum*
M kansasii[a]	*M neoaurum*
M malmoense	
M marinum[a]	
M scrofulaceium	
M simiae	
M szulgai	
M terrae	
M triplex	
M xenopi	

[a] Most common species.

Data from Patel R, Roberts GD, Keating MR, et al. Infections due to nontuberculous mycobacteria in kidney, heart, and liver transplant recipients. Clin Infect Dis 1994;19(2):263–73; and Doucette K, Fishman JA. Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. Clin Infect Dis 2004;38(10):1428–39.

to higher risk include direct exposure of transplanted organ to the environment, the presence of structural abnormalities that can interfere with host defenses against infection and the immunologic deficiencies from intense immunosuppression.[11] Mortality was demonstrated higher in lung transplant recipients[24,28] and any SOT recipient with MOTT infection during the first year of transplant.[29] Most infections present at the late posttransplant period with a median time of 10 months for liver transplants, 13 months for lung transplants, 15 months for heart transplants, and 20 months for kidney transplants.[30]

DIAGNOSIS

Clinical Presentation

MOTT can cause various types of infections. In immunocompetent individuals, common pulmonary infections are due to *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii*, whereas *Mycobacterium marinum* causes skin infections. In immunocompromised individuals, the spectrum of the presentation (**Table 2**) can be broad including pulmonary, skin/soft tissue infection, intestinal infection, hepatic abscess, pericarditis, graft infection, endophthalmitis, and bone/joint infections.[22,30–35] Clinicians should have a high index of suspicion for MOTT infections in SOT, especially in those who have a poor response to treatment and/or lack of an identifiable pathogen with conventional cultures.

Clinical Diagnosis

Skin and soft tissue infection is the most common type of infection owing to MOTT in SOT recipients. Certain MOTT have characteristic clinical findings and associated exposure history that raises clinical suspicion. Infection owing to *M marinum* can present as painful papules that progress to ulceration and scar formation, and occasionally similar to sporotrichoid disease (multiple ascending lesions) often occurring after water exposure (fish tank granuloma). Rapidly growing Mycobacteria, *M abscessus*, *Mycobacterium fortuitum*, and *Mycobacterium chelonae* can often cause skin and soft tissue infection in the setting of trauma, surgical procedures, or cosmetic-related procedures. The skin lesions can present as one of the following: sporotrichoid, localized nonlymphocutaneous, folliculitis, and furuncles. Both rapidly growing and slow growing mycobacteria can cause tenosynovitis or osteomyelitis, often with a history of previous traumatic injury or surgical procedure. Radiographic imaging is warranted if bone involvement is suspected.

Table 2
Clinical presentation of *Mycobacterium* species other than tuberculosis in solid organ transplant recipients

Skin Soft Tissue[22,30–32]	Pulmonary[22,30–32]	Disseminated
M avium complex	*M avium* complex	*M avium* complex[33–35]
M marinum	*M kansasii*	*M abscessus*[25,36–38]
M haemophilium	*M xenopi*	*M kansasii*[39,40]
M szulgai	*M malmoense*	*M haemophilium*[41–45]
M abscessus	*M szulgai*	*M chelonae*[46–48]
M chelonae	*M genavense*	*M immunogenum*[49]
M fortuitum	*M abscessus*	*M genavense*[50–54]
	M chelonae	*M lentifalvium*[55]
	M fortuitum	*M gordonae*[56]
		M marinum[57]

Pulmonary disease is the second most common presentation of MOTT infection in SOT. Patients can present with chronic cough with or without sputum production and fatigue. Infrequently, dyspnea, fever, hemoptysis, and weight loss can be present. However, in SOT, symptoms may be blunted owing to the degree of net immunosuppression. Radiographic imaging may range from bronchiectasis, to reticulonodular disease, to cavitary lesions.[58]

Disseminated disease in SOT can be due to various MOTT species (see **Table 2**). It is the second most common presentation in renal transplant recipients after skin/soft tissue infection and the third most common presentation in heart and lung transplant recipients after skin/soft tissue and pulmonary disease.[31]

Laboratory Diagnosis

Appropriate specimen should be obtained based on clinical presentation. The biopsied tissue, aspirated fluid, or respiratory specimen (expectorated sputum, bronchoalveolar lavage) should be sent for acid-fast staining, mycobacterial cultures, and pathology review. Individuals with MOTT infections may have positive tuberculin skin testing owing to shared protein components between mycobacterial species.[59] In contrast, interferon-gamma release assays for *Mycobacterium tuberculosis* complex use antigens that are present in *M marinum, M kansasii*, and *Mycobacterium szulgai*, resulting in cross-reactivity.[60] Of note, not all MOTT have been studied for cross-reactivity with interferon-gamma release assays. For pulmonary disease, diagnosis is difficult because one has to distinguish colonization or laboratory contamination from true disease. Guidelines published by the American Thoracic Society and Infectious Diseases Society of America set the microbiologic criteria for lung disease due to MOTT (**Box 1**).[58]

In the setting of suspected disseminated disease, mycobacterial isolator blood cultures should be collected. Certain mycobacterial species may require specific handling or processing. *Mycobacterium haemophilium* and *Mycobacterium genavense* require special supplementation such as iron-containing compounds and mycobactin J, respectively, in culture media to grow. The traditional method of MOTT species

Box 1
Summary of 2007 American Thoracic Society/Infectious Diseases Society of America Diagnostic Criteria for MOTT Lung Disease

Should meet clinical, radiographic, and microbiological criteria, and exclude other diagnoses
- Clinical symptoms
  - Based on the presence of pulmonary symptoms, which could be one of the following: chronic or recurring cough, sputum production, dyspnea, hemoptysis (less common), and chest pain
- Radiographic data
  - Presence of nodules or cavities, multifocal bronchiectasis with multiple small nodules in radiographic imaging (chest radiograph, computed tomography scan)
- Microbiologic data
  - At least 2 expectorated sputa or at least 1 bronchial lavage with positive culture for MOTT
  - Or
  - Transbronchial or lung biopsy showing the presence of granulomatous inflammation or acid-fast bacilli with 1 or more sputa or bronchial washings culture positive for MOTT

Abbreviation: MOTT, *Mycobacterium* species other than tuberculosis.

Adapted from Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175(4):379; with permission.

identification depends on phenotypic characteristics determined by biochemical testing, pigment production, growth characteristics, and colony appearance.[61] However, this process is limited by subjectivity and low specificity. Newer techniques such as molecular probes, high-performance liquid chromatography, and 16S rDNA sequencing[61,62] are currently in use to provide rapid and accurate identification of MOTT. More recently, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry is increasingly used to speciate mycobacteria.[63,64] Communication between the treating clinician and the microbiology laboratory is essential in determining the extent of identification analysis of a clinically relevant MOTT isolate.[58]

TREATMENT

Treatment of MOTT is species specific. Treatment of mycobacterial disease uses the fundamental principle of using more than 1 active agent for a prolonged duration to avoid the emergence of resistance. **Tables 3** and **4** summarize the standard therapy and dosing for MOTT based on the recommendations of the American Thoracic Society/Infectious Diseases Society of America.[58] Antimicrobial susceptibility testing can assist in therapeutic decision making for specific MOTT species. Guidelines recommended solely clarithromcyin susceptibility testing for either new, untreated MAC isolates or those who failed macrolided treatment or prevention. Newly diagnosed, untreated *M kansasii* should be tested in vitro to rifampin only. If it is rifampin resistant, other agents should be requested, which include rifabutin, ethambutol, isoniazid, clarithromycin, fluoroquinolones, amikacin, and sulfonamides. Only *M marinum* does not require routine testing given its consistent susceptibility to clarithromycin and ethambutol. Antimicrobial susceptibility testing may be warranted periodically in cases of persistent positive cultures after 6 months of treatment or in those with extended therapy.[65]

There are limited data in new treatment regimens for difficult-to-treat MOTT infections. Clofazimine as a salvage therapy has been used in 3 lung transplant, 1 kidney, and 1 liver transplant recipients after a standard course of MAC treatment was given.[66] Microbiological clearance and resolution of disease were documented in 2 of these 5 patients. Bedaquiline, an oral antimycobacterial drug belonging to the class diarylquinolines that have been approved for treatment of *M tuberculosis*, was used off-label for treatment failure of lung disease caused by MAC (n = 6), and *M abscessus* (n = 4).[67] Out of the 10 patients, 8 had macrolid-resistant isolates. All 10 patients received bedaquiline for 6 months, and 6 patients achieved the microbiologic response. This study suggests the potential of bedaquiline in those with advanced disease, but it remains to be validated in more extensive studies. Tedizolid, a new oxazolidinone, has better in vitro and intracellular activity against some MOTT species when compared with linezolid. Tedizolid was demonstrated to have equivalent or lower minimum inhibitory concentration $(MIC)_{50}$ and MIC_{90} values than linezolid for rapidly growing mycobacteria, including *M abscessus* and *M fortuitum*, *M marinum*, *MAC*, and *Mycobacterium simiae*.[68] Future studies are needed to evaluate its role as a potential treatment for MOTT. The combination of tigecycline and clarithromycin has synergistic activity against rapidly growing mycobacteria; however, its use might be limited by gastrointestinal side effects.[69] Novel delivery of the already established antimycobacterial drug, such as amikacin, has been shown to reduce potential drug toxicities. The addition of inhaled amikacin to standard drug therapy of refractory *M abscessus* and MAC improved symptoms and decreased both smear quantity and mycobacterial culture growth.[70] Inhalational liposomal amikacin seems to be promising, as demonstrated by the efficacy data in a murine mouse model for *M avium* and *M abscessus.*[71] Studies are needed to confirm its clinical efficacy and safety in humans.

Table 3
Treatment recommendations for *Mycobacterium* other than tuberculosis

Mycobacterial Species	Preferred[a]	Susceptibility Testing
M avium complex	Nodular/bronchiectasis Clarithromycin + Ethambutol + Rifampin Cavitary Clarithromycin + Ethambutol + Rifampin ± Streptomycin or amikacin Advanced or previously treated disease Clarithromycin or Azithromycin + Ethambutol + Rifampin + Streptomycin or amikacin for the first 2-3 months of therapy Disseminated disease Clarithromycin or + Ethambutol + Rifampin	Recommended for macrolides
M *kansasii*	Pulmonary Rifampin + Ethambutol + Isoniazid + Pyridoxine Rifampin-resistant: Alternative options include clarithromycin/azithromycin, moxifloxacin, ethambutol, sulfamethoxazole, or streptomycin	Recommended for rifampin
M xenopi	Isoniazid + Rifampin +Ethambutol + Clarithromycin ± Streptomycin	
M szulgai	Rifampin + Ethambutol + Clarithromycin or moxifloxacin	
M malmoense	Rifampin + Ethambutol + Isoniazid ± Clarithromycin or moxifloxacin	
M genavense	Optimal therapy not determined Multidrug therapy with clarithromycin has been reported effective Other drugs to consider: amikacin, rifampin, fluoroquinolones	
M marinum	Clarithromycin + Ethambutol Add rifampin for severe disease	Recommended only if failing treatment

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Table 3
(*continued*)

Mycobacterial Species	Preferred[a]	Susceptibility Testing
M haemophilum	Clarithromycin +Rifampin +Ciprofloxacin	No standardized method for susceptibility testing
M abscessus	Skin/soft tissue or bone infection Clarithromycin + One of the following: amikacin, cefoxitin, or imipenem Pulmonary Clarithromycin + Amikacin + Cefoxitin or imipenem Surgical debridement or resection of localized infection may offer best chance for cure	Recommended for amikacin, doxycycline, fluoroquinolones, sulfonamide or TMP-SMX, cefoxitin, clarithromycin, linezolid
M chelonae	Clarithromycin + One of the following: Amikacin/ tobramcycin, linezolid, tigecycline or imipenem	Recommended for amikacin, tobramycin, doxycycline, fluoroquinolones, sulfonamide or TMP-SMX, cefoxitin, clarithromycin, linezolid
M fortuitum	Minimum of 2 agents: Amikacin, fluoroquinolone, macrolide,[b] doxycycline, imipenem or sulfonamides Surgery is indicated for extensive disease, abscess	Recommended for amikacin, doxycycline, imipenem, fluoroquinolones, sulfonamide or TMP-SMX, cefoxitin, imipenem, clarithromycin, linezolid

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Rifabutin and azithromycin can be substituted for rifampin and clarithromycin, respectively.

[b] Macrolide should be used with caution owing to inducible erythromycin methylase (erm) gene.

Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175(4):367–416.

The duration of therapy is defined by organ involvement, MOTT species, the severity of illness, and the overall net state of immunosuppression. Certain MOTT infections, which are considered limited in immunocompetent patients such as *M marinum*, may have an aggressive clinical course and may warrant a longer course of antibiotic treatment in immunocompromised hosts.[72] The duration of therapy in immunocompromised hosts is extrapolated from current guidelines.[58] Pulmonary disease, in general, should be treated until sputum cultures are negative over a 12-month period. Skin and soft tissue infections are treated for a minimum of 4 months, and bone infection requires at least 6 months of therapy. The recommended treatment duration of disseminated disease in patients infected with the human immunodeficiency virus is 6 to 12 months after immune reconstitution. In contrast, treatment duration in SOT

Table 4
Dosing of anti-mycobacterial drugs and interaction with immunosuppressive drugs

		Drug–Drug Interaction	
Antimicrobial	**Dose**	**Calcineurin Inhibitor**	**mTOR Inhibitor**
Macrolides			
Azithromycin	250–500 mg PO daily 500–600 mg PO 3 times a week (MAC nodular/bronchiectasis)	↑	↑
Clarithromycin	250–500 mg PO BID 1000 mg PO 3 times a week (MAC nodular/bronchiectatic disease)	↑↑↑	↑↑↑
Ethambutol	15 mg/kg/day 25 mg/kg/day 3 times a week (MAC nodular/bronchiectatic disease)	No	No
Rifamycins			
Rifabutin	150–300 mg/day PO	↓↓	↓↓
Rifampin	450–600 mg/day PO 600 mg PO 3 times a week (MAC nodular/bronchiectatic disease)	↓↓↓	↓↓↓
Fluoroquinolones			
Ciprofloxacin	500 mg PO BID or 400 mg IV BID	↑	No
Levofloxacin	500–750 mg PO/IV daily	↑ (Cyclosporine only)	No
Moxifloxacin	400 mg PO/IV daily	No	No
Aminoglycosides			
Amikacin	10–15 mg/kg IV or IM daily or 25 mg/kg 3 times a week	No	No
Streptomycin	500–1000 mg IV or IM daily or 3 times a week	No	No
Tobramycin	5 mg/kg IV or IM daily or 3 times a week	No	No
Tetracyclines			
Doxycycline	100 mg PO or IV BID	No	No
Minocycline	100 mg PO daily	No	No
Tigecycline	Loading dose 100 mg IV followed by 50 mg IV BID	↑	No
Beta-Lactams			
Cefoxitin	8–12 g/day IV in divided doses	No	No
Imipenem	500 mg IV every 6 h	No	No
Others			
Linezolid	600 mg PO or IV BID	No	No
Isoniazid	5 mg/kg/day up to 300 mg PO daily with pyridoxine 50 mg PO daily	No	No
Trimethoprim/ sulfamethoxazole	800–1600 mg (sulfa component) PO/IV BID	No	No

Abbreviations: BID, twice a day; IM, intramuscular; IV, intravenous; MAC, *Mycobacterium avium* complex; mTOR, mammalian target of rapamycin; PO, oral; ↑, slight potential for increased immunosuppressive drug level owing to CYP inhibition; ↑↑↑, severe interaction resulting in increased immunosuppressive drug level owing to CYP inhibition; ↓↓, moderately decreases immunosuppressive drug level owing to CYP induction; ↓↓↓, severe interaction resulting in decreased immunosuppressive drug level owing to CYP induction.

Data from Refs.[58,75,76]

recipients is not well-defined given their need for long-term immunosuppression to preserve the allograft. In the setting of severe disease, reduction of immunosuppression may be warranted. However, caution should be exercised as potential immune reconstitution inflammatory syndrome can occur.[73] Adjunct treatment such as surgical intervention may be necessary in certain instances to decrease the microbial burden in the setting of abscesses or bone and joint infections. Of note, treatment outcomes in SOT recipients have been variable. Cure rates of MOTT infections were estimated as 42% in lung, 47% in heart, 62% in kidney, and 64% in liver transplantation.[32] Secondary prophylaxis in SOT is not well-studied, and no expert consensus has been made to recommend this as the standard of care. However, experts have suggested suppression for those with severe disseminated or recurrent disease.[31]

Treatment of MOTT can be complicated owing to potential toxicities that warrant close monitoring of patients. Adverse effects may include but not limited to nephrotoxicity (aminoglycosides), ototoxicity or vestibular dysfunction (aminoglycosides), hepatotoxicity (isoniazid), peripheral neuropathy (linezolid, isoniazid), optic neuritis (ethambutol), myelosuppression (linezolid), tendonitis (fluoroquinolones), and gastrointestinal intolerance (macrolide, tetracycline). An additional complexity to the treatment of MOTT in SOT is the consideration of drug–drug interactions with immunosuppressive drugs, particularly the rifamycins and macrolides (see **Table 4**). Rifampin is a potent inducer of the CYP3A4 enzyme that can decrease the level of the calcineurin inhibitor and sirolimus and consequently cause rejection. An alternative drug for rifampin is rifabutin, which is a less potent inducer of the CYP3A4 enzyme and has less of an effect on the metabolism of the calcineurin inhibitors, tacrolimus and cyclosporine A, and sirolimus. Clarithromycin, in contrast, is a moderate to strong inhibitor of CYP3A4 and decreases metabolism of the calcineurin inhibitors and sirolimus. A high level of calcineurin inhibitors has consequential nephrotoxicity. Azithromycin is a less potent inhibitor and preferred over clarithromycin for treatment of MOTT. If either or both a macrolide and rifamycin will be used for MOTT treatment, drug level monitoring of immunosuppressive agents is warranted to avoid rejection or drug toxicity. Modification of immunosuppression may be required if drug–drug interactions cannot be avoided. The use of belatacept in kidney transplant recipients instead of calcineurin inhibitors may be an option to consider.[74]

SUMMARY

MOTT are important pathogens to consider in SOT recipients. A delay in recognition and treatment may incur significant morbidity and mortality. Management of MOTT infections requires knowledge of treatments specific for each species, interpretation of drug susceptibility testing, and drug–drug interactions between antimicrobial and immunosuppressive drugs. Therapy in SOT recipients can be prolonged and may require a reduction in immunosuppression to improve outcomes.

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