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Non-tuberculous Mycobacterial Infections in Thoracic Transplant Candidates and Recipients

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Abstract

Purpose of Review To review and discuss the epidemiology, risk factors, clinical presentation, diagnosis, and treatment of non-tuberculous mycobacteria (NTM) in thoracic transplantation.

Recent Findings Non-tuberculous mycobacteria are ubiquitous but are an uncommon cause of disease after solid organ transplantation. The incidence of infection is higher in thoracic transplant recipients than in abdominal transplant recipients, with most cases seen after lung transplantation. It is associated with increased morbidity and, occasionally, mortality. Infection in the pre-transplant setting can occur in lung transplant candidates, often posing a dilemma regarding transplant listing. Disease manifestations are diverse, and pulmonary disease is the most common. Diagnosis requires a high index of suspicion. Treatment requires a multiple-drug combination and is limited by drug-drug interactions and tolerability. *Mycobacterium abscessus* is a challenge in lung transplant recipients, due to its intrinsic resistance and propensity to relapse even after prolonged therapy. *Mycobacterium chimaera* is an emerging pathogen associated with contamination of heater-cooler units and is described to cause disease months after cardiothoracic surgery.

Summary NTM infections in thoracic organ transplant recipients are uncommon but are associated with substantial morbidity and mortality. Data from larger multicenter studies is needed to better define the epidemiology of NTM in thoracic transplantation, best treatment options, and the management of infected transplant candidates.

Keywords Non-tuberculous mycobacteria · Transplantation · *Mycobacterium abscessus* · Thoracic transplantation

Introduction

Non-tuberculous mycobacteria (NTM) are a group of organisms that prevail ubiquitously in our environment, found in soil, water, plant material, and animal life. More than a hundred species of NTM exist of which *Mycobacterium avium-intracellulare* complex (MAC), *M. kansasii*, *M. marinum*, and *M. hemophilum* and the rapid growers *M. fortuitum*, *M. chelonae*, and *M. abscessus* complex cause the majority of human disease. Herein, we will discuss the epidemiology, risk factors, clinical presentation, diagnosis, and treatment of NTM in thoracic transplantation. Special consideration will be given to lung transplant candidates and recipients.

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Epidemiology and Risk Factors

The most common NTM species to cause disease in thoracic organ recipients are MAC and *M. abscessus*. *M. abscessus* has been recognized to be a complex of three closely related subspecies, with the use of 16S ribosomal RNA gene sequencing, *M. abscessus* (sensu stricto), *M. bolletii*, and *M. massiliense*. Very few reports differentiate the subspecies; therefore, we will refer to the *M. abscessus* complex as *M. abscessus* in this text.

NTM are an uncommon cause of disease. The true incidence of NTM infections in organ transplant recipients is not well understood, with most data being limited to single-center

studies [1]. The incidence of NTM infection is higher in thoracic organ recipients than in abdominal organ recipients [2••]. NTM infections have been reported in 0.24–2.8% of heart transplant recipients and 0.46–8% of lung transplant recipients [2••,3–6].

Environmental exposure to NTM by way of contact with soil or water is a natural risk factor for acquisition of infection. In the pre-transplant population, certain primary immune defects, such as genetic syndromes affecting the interlukin-12/interferon γ pathways, treatment with antitumor necrosis factor α agents, and structural lung disease due to chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), or bronchiectasis, confer susceptibility to NTM disease [7]. NTM infection occurs in 13–28% of patients with CF [8,9], and in 3–10% of patients with bronchiectasis [10].

Among organ transplant recipients, iatrogenic immunosuppression along with procedural disruption of the mucocutaneous barrier and exposure of the graft to the environment (in the case of lungs) are factors that possibly contribute to susceptibility. Lung transplantation is the strongest risk factor for NTM disease after organ transplantation, with most of infections occurring in the first 8 months post-transplant [2••]. Risk factors have been better studied in lung transplantation and CF as the underlying diagnosis, use of antithymocyte globulin (ATG) for induction, NTM disease or colonization pre-transplant, and single lung transplantation have been identified as independent risk factors for NTM disease [11].

Clinical Manifestations and Diagnosis

NTM can cause pulmonary and extrapulmonary clinical disease syndromes. Pulmonary manifestations are variable and have been reported to occur as either a solitary pulmonary nodule, pulmonary infiltrates, abscesses, or cavitary nodules, with symptoms including chronic cough, sputum production, dyspnea, and hemoptysis. These may be accompanied by nonspecific constitutional symptoms such as fatigue, fever, and weight loss [4,12,13].

Extrapulmonary syndromes can involve skin and soft tissue, musculoskeletal system, the lymphatics, catheter-related infection, or disseminated disease. Of the extrapulmonary manifestations, cutaneous disorders occur more frequently than others. Rapidly growing species may cause single or multiple skin lesions on the extremities, chest, back, or abdomen [14].

Establishing a diagnosis of NTM disease requires a high index of suspicion. The American Thoracic Society and Infectious Diseases Society of America have laid clinical and microbiological criteria for diagnosis of NTM lung disease [12], which are listed in Table 1 and are often extrapolated to the thoracic organ transplant (SOT) population. When NTM pulmonary disease is suspected, clinical and radiographic examination should be followed by sputum or bronchoalveolar lavage specimen submission for mycobacterial stain and culture along with antimicrobial susceptibility and histopathology. Extra pulmonary specimens from a skin or lymph node biopsy should also be submitted for the same. The incubation period can vary depending on species, ranging from a few days, in the case of rapid growers, to a few weeks, for slowly growing mycobacteria [15]. 16s rRNA sequencing may be employed for mycobacterial detection. More recently, *rpoB* gene sequencing has been tested and applied for NTM detection [16,17]. NTM colonization must be distinguished from disease before committing to treatment. Only a quarter of the lung transplant recipients who developed NTM infection post-transplant were felt to have had NTM disease while the rest were classified to have had NTM colonization in a study [11]. Knoll et al. suggest that episodic isolation of NTM from lung transplant recipients is common and most isolates occurring among asymptomatic patients are transient [6].

Table 1 Clinical and microbiologic criteria for diagnosing NTM lung disease

Clinical (both required)
1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules
AND
2. Appropriate exclusion of other diagnoses
Microbiologic
1. Positive culture results from at least two separate expectorated sputum samples. If the results from (1) are non-diagnostic, consider repeat sputum AFB smears and cultures.
or
2. Positive culture result from at least one bronchial wash or lavage
OR
3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM or biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM

Treatment

The treatment of NTM disease among thoracic organ transplant recipients and candidates involves multiple drug therapies guided by mycobacterial species identification. To date, there have been no randomized clinical trials and recommendations are based on existing literature, which is limited to case series and case reports [1,5,12,18,19] .

Tables 2 and 3 list the recommended and alternate treatment regimens for NTM in SOT recipients [1,12]. An important caveat to bear in mind during NTM therapy is the

Table 2 Recommended treatment agents and use of susceptibility testing for slow-growing and fastidious NTM in organ transplantation

Pathogen	Recommended regimen	Second-line agents	Routine susceptibility testing for initial treatment	Special considerations	Length of therapy
M. avium complex	Azithromycin Rifabutin Ethambutol	Clarithromycin Rifampin Amikacin or Streptomycin Clofazimine	Only for clarithromycin as class drug for macrolides	Never use macrolides alone.	At least 12 months after negative cultures
M. kansasii	Rifabutin Ethambutol Isoniazid plus pyridoxine	Rifampin Clarithromycin or azithromycin Sulfamethoxazole Moxifloxacin Amikacin or streptomycin	Rifampin	May be reported as resistant to isoniazid but inhibited by achievable concentrations	18 months with at least 12 months of negative cultures
M. marinum	Azithromycin Ethambutol Consider adding rifabutin for extensive disease	Rifampin Clarithromycin or azithromycin Sulfonamides Doxycycline or minocycline	Not unless patient is failing treatment	Some strains are resistant to ciprofloxacin; moxifloxacin may have better in vitro activity	3–4 months with at least 2 months after symptoms resolve
M. hemophilum	Azithromycin Rifabutin Ciprofloxacin	Rifampin Clarithromycin or azithromycin Sulfonamides Doxycycline	Use with caution as methods not standardized	All resistant to ethambutol. For doxycycline and sulfonamides susceptibility is variable	Unknown

interaction between immunosuppressive agents and rifamycins and macrolides. Rifampin is a potent CYP 450 3A4 inducer and can decrease calcineurin inhibitor (CNI) and sirolimus levels, which can cause graft rejection. Rifabutin is a less potent inducer and is hence the preferred rifamycin for transplant recipients. Clarithromycin is an enzyme inhibitor and azithromycin is preferred over it to minimize drug-drug interactions. Of note, recommended therapies also have associated side effects including ototoxicity and nephrotoxicity due to aminoglycosides, ocular toxicity due to ethambutol, gastrointestinal distress due to macrolides, and hepatotoxicity due to isoniazid. Clofazimine can be used in case of failure or intolerability to standard drugs [20•]. Surgery may be considered for source control, depending on the extent and location of infection. Duration of therapy will depend on the organ affected, time to microbiologic clearance, clinical response, and tolerability. Pulmonary specimen collection for mycobacterial stain and culture during follow-up is warranted, when feasible.

Special Considerations

Transplant Candidacy

Screening for NTM is not recommended for heart transplant candidates [21]. Screening for NTM is recommended for all patients with CF being referred for lung transplantation, but not for patients with other underlying illnesses [22]. The presence of progressive pulmonary or extrapulmonary disease despite maximal therapy or the inability to tolerate medications are contraindications to listing for transplantation.

Mycobacterium abscessus

M. abscessus is a challenging pathogen due to its poor antimicrobial susceptibility, toxicity of treatment regimens, and the risk of recurrence, even after prolonged therapy [23••]. The data on the impact of pre-transplant colonization or disease with *M. abscessus* on risk of disease after transplantation are limited and mostly derived from case series. In the post-transplant setting, surgical site, skin, and soft tissue infections are common [9,18,19,24,25].

When *M. abscessus* exists pre-transplant, the available data point toward a higher propensity of recurrence post-transplant. Patients with positive culture, regardless of smear positivity, are more likely to develop post-transplant disease [9,19]. This risk may be even higher with smear positivity, which signifies an increased bacterial load. There is a lot of controversy on whether patients with *M. abscessus* should be accepted for lung transplantation. The most recent International Society for Heart and Lung Transplantation (ISHLT) consensus document for the selection of lung transplant candidates states

Table 3 Recommended treatment agents for the treatment of rapid-growing NTM in organ transplantation

Pathogen	Regimens should be adjusted based on in vitro susceptibility results	Second-line or additional agents	Special considerations
M. abscessus	Azithromycin Plus amikacin, imipenem, or cefoxitin Or two parenteral agents	Clarithromycin Linezolid Tigecycline Clofazimine	Lung infection is difficult to cure May want to start 3 drug therapy until susceptibility available
M. chelonae	Two drugs Azithromycin Plus amikacin or tobramycin, linezolid, tigecycline, or imipenem	According to susceptibility results	Surgery should be considered for drainage of abscesses or resection of infected tissue. Infected foreign material should be removed
M. fortuitum	Amikacin Ciprofloxacin or other quinolones Sulfonamides	Sulfonamides Doxycycline or minocycline Imipenem Tigecycline	All isolates contain an inducible erythromycin methylase gene; use macrolides with caution

that infection with *M. abscessus* is a relative contraindication for lung transplant listing [22]. Patients can be considered for transplantation if the infection is sufficiently treated pre-operatively and there is reasonable expectation of adequate control post-operatively. It is recommended that these patients be evaluated by centers with significant experience in management of *M. abscessus*. Lung transplant candidates with *M. abscessus* should be started on therapy as soon as transplantation is being considered. The goals of therapy are to achieve smear and culture negativity, demonstrate ability to control the infection, and assess tolerability of an effective regimen [19,24,26]. Duration of therapy is difficult to predict, since conversion to culture or smear positivity after therapy discontinuation risks removal from the transplant list, relapse, and intra-operative contamination. Several measures to decrease intra-operative contamination are recommended, including chest cavity irrigation with an active anti-mycobacterial agent, close attention to surgical technique to avoid contamination, and continuation of anti-mycobacterials peri-operatively [19,25,27]. The post-transplant management should include close surveillance of wounds and the pleural space, sampling bronchoalveolar lavage specimens for acid fast bacillus (AFB) smear and culture when bronchoscopies are performed, and prolonged anti-mycobacterial therapy. The duration of therapy in the post-transplant setting has not been defined and relapse can occur even after prolonged therapy.

Mycobacterium chimaera

M. chimaera is a slow-growing mycobacterium which belongs to the *M. avium* complex. It is an emerging pathogen, which, in recent years, has been reported as a cause of disease in patients who underwent cardiac surgeries [28•,29•,30–32]. Sax et al. [29•] reported occurrences of prosthetic valve endocarditis and vascular graft infection among patients who underwent open-chest heart surgery on extracorporeal circulation in Switzerland. *M. chimaera* was isolated from cardiac tissue, blood, and biopsy specimens. It was also recovered from water circuits of heater-cooler units (HCUs) connected to cardiopulmonary bypass and air samples establishing airborne transmission of *M. chimaera* from contaminated HCUs to patients. Additional reports [28•,30–32] have described systemic and disseminated *M. chimaera* disease, all of which are notably healthcare-associated infections. Given its mode of transmission and the nature of cardiothoracic transplantation procedures, the clinician must be cognizant and wary about the possibility of occurrence of *M. chimaera* disease among the post heart and lung transplant patient populations. Signs of infection are nonspecific and may manifest after a prolonged incubation period of several months to years.

Conclusions

NTM infections in thoracic organ transplant recipients are uncommon, but are associated with substantial morbidity and mortality. The occurrence of NTM infection or disease in lung transplant candidates is associated with a higher risk of disease post-transplant. There is controversy in the field regarding the transplant candidacy of patients with a history of *M. abscessus* infection. *M. chimaera* is an emerging pathogen, associated with contaminated heater-cooler units used in cardiac surgery.

Compliance with Ethical Standards

Conflict of Interest Mana Rao and Fernanda P. Silveira declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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