

Mycobacteria: Selection of Transplant Candidates and Post-lung Transplant Outcomes

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Abstract

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- ▶ *Mycobacterium chelonae*
- ▶ *Mycobacterium avium* complex

Mycobacterium is a large, clinically relevant bacterial genus made up of the agents of tuberculosis and leprosy and hundreds of species of saprophytic nontuberculous mycobacteria (NTM). Pathogenicity, clinical presentation, epidemiology, and antimicrobial susceptibilities are exceptionally diverse between species. Patients with end-stage lung disease and recipients of lung transplants are at a higher risk of developing NTM colonization and disease and of severe manifestations and outcomes of tuberculosis. Data from the past three decades have increased our knowledge of these infections in lung transplant recipients. Still, there are knowledge gaps to be addressed to further our understanding of risk factors and optimal treatments for mycobacterial infections in this population.

Lung transplantation provides a therapeutic option for many patients with end-stage lung disease. The outcomes of lung transplantation continue to improve due to optimized pre-transplant patient selection; novel surgical techniques, including ex vivo lung perfusion; and a better understanding of strategies to prevent rejection.¹ Increasing numbers of successful lung transplants and improved longevity of recipients have presented new challenges with infections and chronic lung allograft dysfunction (CLAD).

Of significant importance is the impact of mycobacterial infections on lung transplant candidates and recipients. In 2019, more than 10 million people worldwide were diagnosed with active tuberculosis (TB), and many more are silently harboring latent infections.² Migration significantly impacts both organ donors as well as transplant candidates and recipients with infections occurring even in low-prevalence countries.³ In regions with a low prevalence of TB, such as North America, Western Europe, and Australia, nontuberculous mycobacteria (NTM) are more frequently encountered and pose unique challenges in the lung transplant

patient.⁴ Unlike TB, there is a lack of robust evidence for the optimal approach for managing NTM infections, and practices vary considerably between transplant centers.⁵

This review highlights recent studies and summarizes important findings of tuberculous and NTM infections' impact on lung transplant candidate selection and recipient outcomes, focusing on NTM infections.

Microbiology and Pathogenicity of *Mycobacterium* spp.

The bacterial genus *Mycobacterium* is composed of more than 200 species that, despite sharing some common features, are heterogeneous in their pathogenicity, epidemiology, and management. As with other genera within the family *Mycobacteriaceae*, *Mycobacterium* spp. have a cell wall with a high mycolic acid content that resists decolorization with acid alcohols and provides the characteristic positive acid-fast staining. These bacteria are aerobic, non-spore-forming, and weak gram-positive bacilli.⁶

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The genus is further divided into several species complexes. The most well-recognized, the *Mycobacterium tuberculosis* (MTB) complex, comprises a group of pathogenic bacteria that cause TB in humans and other mammals. The most commonly implicated human pathogens include *M. tuberculosis*, *M. bovis* bacillus Calmette-Guérin (BCG) strain, *M. africanum*, and *M. canetti*. Zoonotic pathogens include *M. bovis*, *M. pinnipedii*, *M. caprae*, and *M. microti*. These are primarily transmitted by respiratory aerosols between persons or animals; although these are not considered sapro-rotic, species of the MTB complex have been recovered from environmental surveys.^{7,8} Of global importance, another group of pathogenic mycobacterial species includes the three causative species of leprosy. *M. leprae* is the most commonly implicated organism, with sporadic leprosy cases being caused by *M. lepromatosis*. *M. lepraemurium* is the cause of leprosy in murine hosts.⁹

The other hundreds of mycobacterial species not included in these complexes are known collectively as NTM. NTM are ubiquitous environmental bacteria that, for the most part, are opportunistic pathogens or commensal bacteria, although exceptions do exist. To date, more than 150 NTM species have been recognized, and due to the advent of molecular techniques, such as 16S rRNA and heat shock protein sequencing, new species are being rapidly identified.^{10,11}

One of the first methods of characterizing NTM species dates back to 1959 and focuses on colony growth characteristics. This Runyon classification categorizes species by the colonies' growth rate, morphology, and pigmentation pattern. While newer molecular diagnostic techniques are increasingly utilized to speciate NTM, the speed of colony growth remains a significant clinical distinction. Rapidly growing mycobacteria (RGM), such as *M. abscessus*, *M. fortuitum*, and *M. chelonae*, typically produce visible colonies on solid media within 7 days, whereas slowly growing mycobacteria (SGM) may take up to 2 to 3 weeks. Common SGM species include those in the *M. avium* complex (MAC; *M. avium*, *M. intracellulare*, *M. chimera*, etc.), *M. kansasii*, *M. xenopi*, and *M. haemophilum*. Intermediate-growing mycobacteria, for example, *M. marinum* and *M. goodii*, represent a small subgroup of SGM that requires anywhere from 7 to 10 days for colony production. Although the ability for a colony to produce pigment in both light and dark environments (scotochromogens), in light only (photochromogens), or not at all (nonchromogens), may help further differentiate mycobacterial species, this property is seldom used to identify species in modern microbiology laboratories.

The virulence factors and reasons for variable pathogenicity of NTM species are not entirely understood, although studies have identified which species are more likely to produce invasive pulmonary disease. In a multicenter Belgian cohort of 384 patients with pulmonary NTM infections, Vande Weygaerde and colleagues evaluated the clinical significance of individual species on the development of NTM disease.¹² They found that more than 60% of those infected with *M. abscessus*, *M. malmoense*, *M. intracellulare*, and *M. kansasii* had disease. *M. goodii* was among the

most common nonpathogenic species and almost exclusively represented colonization. *M. fortuitum* was occasionally implicated in pulmonary disease, whereas *M. avium* and *M. xenopi* caused pulmonary disease approximately 50% of the time.

Some species, such as *M. abscessus* and *M. avium*, display two colonial morphotypes. The smooth morphotype has been associated with increased bacterial motility and biofilm formation, allowing them to persist in the environment. The rough morphotype is associated with severe or disseminated infections, likely due to mechanisms that bypass macrophage activity, such as the ability to form extracellular cording and induction of strong humoral immune response.¹³ The ability to transition between these two morphotypes may, in part, explain some species' increased pathogenicity.¹³⁻¹⁶ *M. abscessus* can also be highly resistant to macrophages' bactericidal activity, allowing it to persist and multiply intracellularly, unlike less pathogenic species, whose ability to divide and survive in a host is readily halted by the macrophage.¹⁴

Tuberculosis

Latent Tuberculosis—Diagnostic and Therapeutic Challenges

Active TB following solid-organ transplantation (SOT) can be challenging to diagnose and treat due to altered inflammatory response, atypical radiographic findings, and drug-drug interactions. TB is associated with mortality as high as 10 to 20%, although rates are decreasing possibly due to heightened clinical suspicion and optimization of treatment approaches to minimize and manage drug-drug interactions.^{17,18} The American Society of Transplantation recommends that all transplant candidates be screened and treated for latent TB infection (LTBI) before transplant.¹⁹ As outlined in these guidelines, an assessment should include symptom inquiry, a review of epidemiological risk factors, chest radiography, and either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA). The sensitivity of the TST and IGRA is affected by systemic immunosuppression or chronic disease, and there is a risk of false-negative results after transplant.²⁰ No studies have investigated whether treatment of LTBI before versus after transplant is associated with better patient and graft outcomes, but the guidelines recommend treatment begin before transplant when possible.¹⁹ Improved treatment adherence is anticipated when therapy is completed before transplant, because of lower pill burden, less drug interactions, and better tolerability.^{21,22} First-line therapy for LTBI is either 9 months of isoniazid, 4 months of rifampin, or 3 months of combination therapy with isoniazid and rifapentine. The use of rifampin and rifapentine is best avoided after transplant due to interactions with several classes of drugs, including immunosuppressants (– **Table 1**). Because treatment is several months in duration, the urgency of transplant may preclude a full course before transplant, necessitating a change in treatment after transplant.²³ If active disease has been ruled out, LTBI is not a contraindication for transplant. Still, if the candidate has not received a complete course of either first-line or alternative therapy,

Table 1 Important drug–drug interactions between select antimycobacterials and immunosuppressants used after lung transplant

Antimycobacterial	IS	Interactions ^{48,77–82,115,116}
Aminoglycosides Amikacin Tobramycin	CsA, Tac	Increased risk of nephrotoxicity
Fluoroquinolones Ciprofloxacin Levofloxacin Moxifloxacin	CsA, Tac, Eve, Sir	Increase IS levels (ciprofloxacin > levofloxacin > moxifloxacin), QTc prolongation
	Corticosteroids	Increased risk of tendinopathy
Linezolid	MMF, MPA, AZA, Eve, Sir	Increased risk of cytopenia (especially thrombocytopenia)
Macrolides Azithromycin Clarithromycin	CsA, Tac, Eve, Sir	Increase IS levels (clarithromycin > azithromycin)
Rifamycins Rifampin Rifabutin	CsA, Tac, corticosteroids, MMF, MPA, Eve, Sir	Decrease IS levels (rifampin >> rifabutin)
Trimethoprim- sulfamethoxazole	MMF, MPA, AZA, Eve, Sir	Increased risk of cytopenia (especially thrombocytopenia)
	CsA, Tac	Increased risk of nephrotoxicity

Abbreviations: AZA, azathioprine; CsA, cyclosporine; Eve, everolimus; IS, immunosuppressant; MMF, mycophenolate mofetil; MPA, mycophenolic acid; Sir, sirolimus; Tac, tacrolimus.

they should be treated following transplant with a regimen that does not include rifamycins. As isoniazid monotherapy is longer in duration and associated with increased risk of hepatotoxicity, therapy with rifampin completed before transplant may be preferred when possible to optimize the likelihood of treatment completion.

Lung transplantation is almost exclusively the result of deceased donation, with rare cases of living lobar donation. Therefore, the donor's past history and risk factors for TB are often unknown or misremembered. A consensus document has been published to address the appropriate workup and utilization of organs from at-risk donors.³ Donors with radiographic abnormalities, known exposures to TB or residents of endemic areas, should be assessed for LTBI. However, there is insufficient time to perform TST, and the use of IGRA has not been validated in deceased donors and has been shown to yield significant rates of indeterminate results.²⁴ Because there have been reports of transmission of inadequately treated LTBI from lung donors, which can result in reactivation and dissemination in the recipient,^{25–28} the offer of lungs from high-risk donors must be carefully reviewed, including a consideration of chemoprophylaxis in the recipient.

Active Tuberculosis—When to Transplant and Posttransplant Outcomes

Active TB in a transplant candidate is considered an absolute contraindication for transplant, given the risk for dissemination and poor graft and patient outcomes.^{17,23,29} However, the timing at which a patient with active TB can safely undergo transplantation has not been clearly defined. A recent review of five SOT recipients with an unknown diagnosis of active TB at the time of transplant (two liver, one heart, one lung, one kidney) demonstrated overall

favorable outcomes despite two patients experiencing acute rejection episodes 1 month after transplantation.³⁰ The lung transplant patient died 6 months after transplant from acute rejection; however, the implication of active TB in the patient's demise is uncertain.

A high index of suspicion is needed for a prompt diagnosis of TB following SOT. Following transplant, patients may present with atypical, nonspecific presentations and are at higher risk for disseminated infection.^{23,31} Even with pulmonary disease, fever and constitutional symptoms can be more apparent than dyspnea or cough,³² and in the case of lung transplant, pulmonary consolidations and cavitary lesions are not frequently seen on chest radiography.³¹

Recent reviews of TB and SOT recipients by Abad and Razonable have shed some light on this subject.^{26,31} Of more than 2,000 patients, only 1.2% were lung transplant recipients, representing a prevalence of 0.96 cases per 100 lung transplant recipients. Almost half of the infections in lung recipients were donor derived, which was the highest proportion of all organ groups. The mortality rate was highest in lung transplant recipients at 25%, compared with 23.8, 20.3, and 18.8% in heart, liver, and kidney recipients, respectively. In a retrospective review of 398 lung transplant recipients, use of azathioprine and everolimus was independently associated with developing TB after lung transplant.³³ We believe that the association of TB with everolimus was likely confounded by the fact that everolimus was more commonly used in patients with comorbidities, such as renal failure, allograft rejection, and malignancies.

The standard first-line regimen for the treatment of susceptible active TB is an intensive phase with isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months, followed by at least an additional 4 months of rifampin and

isoniazid.^{19,34,35} The prolonged use of some of these agents following lung transplant is challenging due to drug interactions and toxicities (► **Table 1**). Successful treatment with rifampin-based therapy after lung transplant has been reported, but requires very careful monitoring of calcineurin inhibitor levels and toxicity.^{36,37} To address the concern of rifampin use after transplant, rifabutin has been substituted to treat active TB following SOT with success.^{38,39}

Nontuberculous mycobacteria

Epidemiology

The prevalence of NTM infections is likely underestimated, mainly due to asymptomatic colonization and nonuniversal requirements to report infections to public health authorities.⁴⁰ There is significant variation in the geographic distribution of species globally, and this has been previously detailed in a review by Zweijpfenning and colleagues.⁴¹ Species in the *M. avium* complex are the most common species from clinical isolates worldwide and account for more than half of all infections in North America^{40–42}; geographic variation also exists within this complex, with *M. avium* being more prevalent in Europe and the Americas, and *M. intracellulare* more dominant in Australia and South Africa.⁴²

North American data are primarily limited to publications from the United States (► **Table 2**). In a recent review of almost 6 million patients across the United States from 2009 to 2013, Spaulding et al found 0.13% of patients had a positive respiratory culture for an NTM species.⁴³ Canadian data report the annual rate of NTM isolation in the general population as 14.1 to 22.2 per 100,000.^{44–47} Rates of reported cases of NTM infections are increasing worldwide, likely due to growing awareness of NTM, improvement in current diagnostic techniques, increased use of immunosuppressive agents, and jurisdictions implementing decrease temperature of household water heaters.^{48–51}

Most NTM species are nonpathogenic in patients with intact cell-mediated immunity. In immunocompetent hosts, pulmonary infection is the most common manifestation, with a propensity for those with structural airway disease.¹¹ Infections of the skin and soft tissues in otherwise healthy adults typically require a mechanism of inoculation, such as a puncture wound^{52,53} or following surgery, particularly cosmetic surgery or surgeries related to medical tourism.^{54,55}

Patients with cystic fibrosis (CF) and bronchiectasis comprise a population with more NTM infections, in part due to some centers routinely screening sputum of these patients for NTM and guidelines recommending all patients be assessed for NTM infection before transplant listing.^{29,56} In a multicenter cross-sectional study, 13% of patients with CF in the United States had NTM isolated from sputum.⁵⁷ Subsequent studies have shown the prevalence as high as 28% in patients with CF and 10% in those with non-CF bronchiectasis.⁵⁸ Research in zebra fish models suggest that the CF transmembrane conductance regulator (CFTR) protein plays a role in the neutrophilic response against *M.*

abscessus and mutations of this gene may explain why patients with CF are at higher risk of infection compared with those with non-CF bronchiectasis.^{59,60} Individual factors associated with increased risk of pulmonary NTM infections in CF patients, particularly with *M. abscessus*, include concomitant allergic bronchopulmonary aspergillosis, airway colonization with *Pseudomonas aeruginosa* or *Burkholderia cepacia*, and chronic macrolide therapy.^{13,61} In one study, higher forced expiratory volume in 1 second (FEV1) was also associated with a higher probability of NTM recovery.⁵⁷

A dysfunctional cell-mediated immune response is a nearly universal requirement for the development of disseminated infections, which became apparent during the acquired immunodeficiency syndrome (AIDS) pandemic of the 1980s–1990s when disseminated MAC infections were seen in patients with profound CD4-positive T-cell lymphopenia.⁶² Other recognized predispositions include prolonged use of tumor necrosis factor- α (TNF- α) inhibitors, immunosuppression following solid organ and hematopoietic stem cell transplants, and genetic disruptions of the IL-12/interferon-gamma (IFN- γ) pathways.^{40,63} Although most IL-12/IFN- γ pathway defects are diagnosed in childhood, two diseases are becoming more recognized for their role in predisposing adults to extrapulmonary and disseminated NTM infections—GATA2 mutations and anti-IFN- γ autoantibody syndrome, the latter being more common in adults of Southeast Asian descent.^{64,65} The recent global outbreak of *M. chimaera* infections in patients exposed to certain heater-cooler units during open cardiovascular surgery has demonstrated that disseminated infections can occur in otherwise immunocompetent hosts.⁶⁶

The prevalence of NTM infections in SOT recipients is higher than that in the general population, with the highest rates in heart and lung transplant recipients (0.24–2.8% and 0.46–9%, respectively).^{67–69} Rates among renal and liver transplant recipients are lower but have been reported as high as 0.16 to 0.38% and 0.04%, respectively.^{67,68} Some identified variables associated with the development of infection following SOT include episodes of acute rejection, chronic kidney disease, and CF.⁷⁰

Clinical Manifestations and Treatment

Clinical manifestations of NTM infections are highly variable due to species-specific virulence factors, route of infection, and host immune status.⁷¹ Pleuropulmonary infections are the most common presentations in the general population and lung transplant recipients.⁶⁷ Two classical radiographic patterns exist—apical fibrocavitary disease (► **Fig. 1**), which is common to patients with underlying structural lung disease (such as pneumoconiosis or chronic obstructive pulmonary disease), and nodular bronchiectatic disease.⁷¹ The latter has been seen with MAC infections typically in thin, middle-aged, Caucasian women without any clear predisposing factor.^{72,73} Lung transplant recipients are at particular risk for NTM lung infections due to a combination of factors, including immune suppression; local defects in the transplanted allograft resulting in

Table 2 Geographic variation of common NTM species in North America

Region	Species distribution, %					Reference
	<i>M. avium</i> complex	<i>M. chelonae/abscessus</i>	<i>M. fortuitum</i>	<i>M. kansasii</i>	<i>M. xenopi</i>	
Canada						
Ontario	48.1–63.0	2.1–5.7 ^b	2.6–4.7 ^b	1.3–1.9	19.2–26.5	45–47,97
Western Canada (Alberta, British Columbia)	54.9–69.8	13.2–21.6	5.2–7.8	1.3–2.0	0–1.3	89,117
The United States						
New England ^b	86	4	NR	NR	NR	43
Middle Atlantic ^a	80.1–83.6	5.0–12.1	3.2–5.6	2.4–5.5	1.7–2.6	43,118,119
East South Central ^a	91	2	NR	NR	NR	43
South Atlantic ^a	48.3–78.0	9.0–17.9	6.3	1.9	NR	43,120
West South Central ^a	61	18	NR	NR	NR	43
Mountain ^a	80	4	NR	NR	NR	43
Pacific ^a	69.3–87.5	3.0–20.0	0.5–24	0.5–5.5	0–1.7	43,119,121–125
East North Central ^a	78	7	NR	NR	NR	43
West North Central ^a	64	10	NR	NR	NR	43

Abbreviations: M., *Mycobacterium*; NR, not reported; NTM, nontuberculous mycobacteria.

^aIn Marras et al,⁴⁵ *M. chelonae*, *M. abscessus*, and *M. fortuitum* were combined to 13.0%.

^bStates included in each region are defined in Spaulding et al.⁴³

abnormal ciliary function; bronchial devascularization, denervation, and lymphatic insufficiency posttransplant; propensity for pretransplant airway colonization with NTM; and the nature of the lung itself with constant environmental exposure.

Skin and soft-tissue infections are often associated with the RGM species, particularly following trauma or surgery. *M. abscessus* and *M. chelonae* may cause surgical-site infections that can be progressive and associated with high mortality.⁷⁴ Except in lung transplant recipients, where they account for only 10% of NTM infections, cutaneous disease and surgical site infections are the predominant presentations following SOT and hematopoietic stem cell transplant (►Fig. 2).^{67,75,76}

The signs and symptoms of disseminated infection are protean and nonspecific. These may include fever, night sweats, weight loss, lymphadenopathy, and diarrhea.⁴⁸

A crucial step in managing NTM infections is determining whether the presence of infection represents colonization or disease that may require therapy. Isolation of species known to be pathogenic from sterile spaces or histopathologic evidence of invasive disease supports the decision to treat. Pulmonary infections can be challenging to categorize as colonization or disease, and therefore criteria have been established and published in guidelines to aid in decision-making.^{48,77,78} The diagnosis of pulmonary disease is supported by repeated, good-quality respiratory cultures, compatible symptoms or objective pulmonary dysfunction, and abnormal imaging (►Table 3).

The choice and duration of therapy are dependent on the organism, in vitro susceptibility pattern (where validated),

site of infection, and degree of immunosuppression. Although the details of treatment regimens are case-specific, some considerations are highlighted.^{48,77,78} The cornerstone of therapy includes the use of combination antimycobacterial therapy, often including macrolides, rifamycins, ethambutol, isoniazid, fluoroquinolones, linezolid, tetracyclines, or aminoglycosides, depending on the organism. The duration of antimicrobial treatment is generally months to years, depending on the site of infection and severity. Several of these antimicrobials, particularly rifamycins, can interact with immunosuppressive therapy, and therefore close attention to immunosuppressant levels is required. Aminoglycosides can also potentiate calcineurin-associated nephrotoxicity⁷⁹ and linezolid has been associated with higher rates of cytopenias, especially thrombocytopenia, in SOT recipients.^{80,81} Tendinopathies occur at a higher rate with fluoroquinolones in SOT recipients, especially those on chronic corticosteroids (►Table 1).⁸²

Surgical debridement or resection should also be considered as an adjunct especially in cases of localized skin and soft-tissue infections.⁷⁸ In SOT recipients and others with iatrogenic immunosuppression, decreasing the degree of immunosuppression may be required to effectively eradicate complicated infections, with particular consideration for monitoring signs of allograft dysfunction or rejection.⁸³

The use of bacteriophages is being investigated as a novel therapeutic option for the management of multidrug-resistant (MDR) organisms. Bacteriophages are viruses that are selected from banks with natural occurring activity to attack

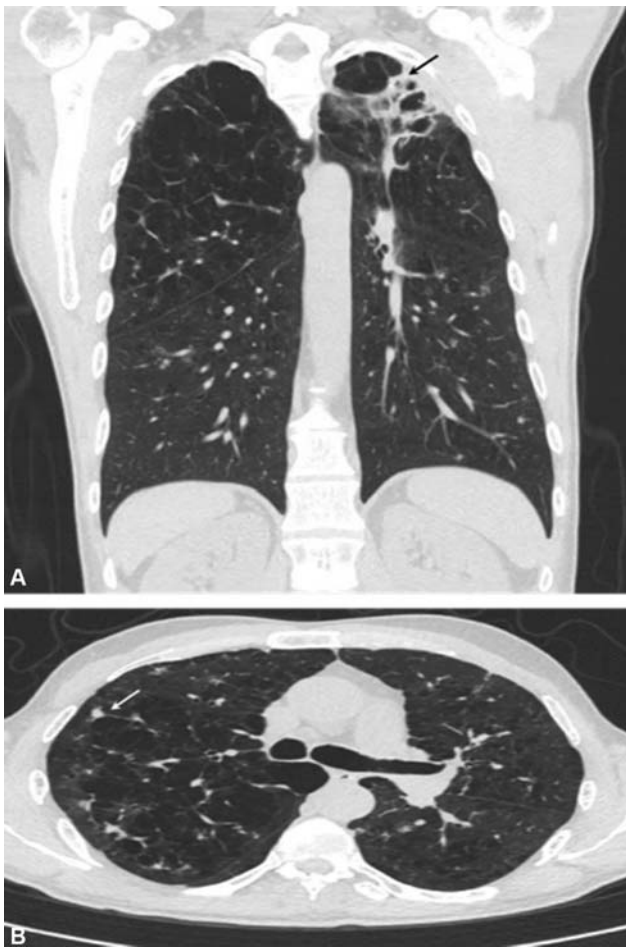


Fig. 1 High-resolution computed tomographic scan of a man with severe emphysema, bronchiectasis, and fibrocavitary *M. xenopi* pulmonary disease. There is a large left upper lobe fibrocavitary lesion (black arrow) seen on the coronal film (A). Spiculated subcentimeter nodules (white arrow) are seen in the right upper lobe seen on axial film (B).

a specific bacterial strain. In vitro studies and clinical reports show promise in SOT recipients, patients with ventricular assist devices, and nontransplant candidates.⁸⁴ To date, there have been four reported cases of their use in treating infections with MDR organisms in lung transplant recipients.^{85,86} One of these patients was a 15-year-old girl with CF and disseminated *M. abscessus* infection. After receiving over 8 years of antimycobacterials, she received a bilateral lung transplant. Following transplant, her antimicrobials were stopped due to side effects and she developed worsening pulmonary and surgical site infections. She was treated with a prolonged course of intravenous and topical bacteriophage-containing solutions in combination with resuming her antimicrobials and she experienced clinical and bacteriologic improvement over the subsequent 6 months.^{86,87} Although further research for its use in mycobacterial infections before and after transplant is needed, bacteriophage therapy seems to be a potential option for challenging NTM infections and reducing cumulative antimicrobial exposure.



Fig. 2 *M. chelonae* musculo-cutaneous infection in a solid-organ transplant. Left hand swelling and cellulitis (A) are noted with corresponding flexor tenosynovitis and associated lumbrical myositis of the third to fifth digits seen on gadolinium-enhanced magnetic resonant scan (B). The infection progressed to the ipsilateral elbow with nodule and abscess formation (C).

Pretransplant Evaluation and Posttransplant Outcomes

Although active infection with *M. tuberculosis* is considered an absolute contraindication for transplant, pursuing transplant in patients with NTM colonization and disease is a more nuanced decision.⁸⁸ Data on candidate selection and predicting outcomes are sparse, conflicting, and primarily limited to case reports or series.

Reports are varying regarding the impact of NTM infections on patient survival and graft outcomes following lung transplantation. Several cohort studies have shown that NTM infections, including both colonization and disease, are associated with as high as a twofold increase in mortality following transplant; however, no significant association was found between infection and development of CLAD in these studies.⁸⁹⁻⁹² Longworth et al specifically compared SOT recipients with NTM disease diagnosed in the first year with matched controls and showed a significant increase in 3-year mortality.⁹¹ This increased risk was similar between all NTM species.

On the other hand, several studies have found no increase in mortality associated with NTM infections following transplant. In a 15-year analysis of 237 lung transplant recipients, Knoll et al found no association with NTM infection and increased posttransplant mortality.⁹³ George et al found in their cohort of 553 lung transplant recipients that those with NTM infection did not experience increased mortality, except in a small subset of patients with active disease.⁹⁴ In another cohort of 208 lung transplant recipients, those with bronchopulmonary NTM disease posttransplant had a higher hazard of bronchiolitis obliterans syndrome (BOS), but not mortality.⁹⁵

Following lung transplant, an algorithm based on the explanted lung pathology and microbiology has been

Table 3 ATS/IDSA criteria for pulmonary NTM disease^{10,48}

Clinical (all criteria required)
<ol style="list-style-type: none"> 1. Pulmonary (chronic cough, dyspnea, or hemoptysis) or systemic symptoms 2. Nodular or cavitary lesions on chest X-ray or multifocal nodular bronchiectasis on high-resolution CT scan 3. Exclusion of other diagnoses
Microbiological (at least one criterion required)
<ol style="list-style-type: none"> 1. Positive culture results of the same species from 2 separate expectorated sputums or 2. A positive culture from at least one bronchoscopic specimen or 3. Lung biopsy with histopathologic features consistent with mycobacterial infection with a positive culture for an NTM species from the biopsy, sputum, or bronchoscopic specimen

Abbreviations: ATS, American Thoracic Society; IDSA, Infectious Disease Society of America; NTM, nontuberculous mycobacteria.

proposed by Hirama et al to help determine the antimicrobial approach of recipients with non-*M. abscessus* pulmonary NTM infection.⁹⁶ Kabbani et al compared 148 lung and heart-lung transplant recipients with granulomata in the explanted lungs to matched controls without granulomatous pathology, finding that the presence of granulomata on explant (both necrotizing and nonnecrotizing) and positive mycobacterial cultures to be positive predictors for the development of posttransplant mycobacterial colonization and disease. However, neither had significant associations with patient survival. Interestingly, in this study, pretransplant NTM disease (including *M. abscessus*) and use of preventative therapy were not statistically significant risk factors.⁹⁷ These findings support an algorithm for identifying patients early posttransplant who could benefit from more aggressive antimycobacterial therapy and highlight that pretransplant infection should not be an absolute contraindication to transplant.

***Mycobacterium abscessus* and Other Rapidly Growing Mycobacteria**

Mycobacterium abscessus is one of the most challenging pathogens due to its high degree of antimicrobial resistance, its pathogenicity including propensity for biofilm formation, its increased prevalence among patients with CF, and difficulty eradicating infection even with optimal therapy.^{13,14,98,99} For these reasons, the presence of *M. abscessus* is considered a contraindication to transplant in some centers.^{5,99,100} Life-threatening infections have occurred posttransplant in those with pretransplant colonization without invasive disease, and others with well-treated pulmonary disease have done well. Some centers require that patients infected with *M. abscessus* attain sputum smear negativity and be stable on antimycobacterial therapy before being listed for or undergoing transplantation.^{5,98,101}

Posttransplant outcomes in those with *M. abscessus* infection are mixed. In a cohort of 1,301 lung transplant recipients, Hamad et al analyzed 22 cases of *M. abscessus* infection in the first year posttransplant, concluding that pulmonary disease was associated with a significant increase in 1-year mortality, but not BOS, compared with those who were colonized.⁹⁰ In a small group of CF patients with *M. abscessus* lung disease following lung transplant, Perez et al found no difference in survival or graft outcomes compared with uninfected CF patients.¹⁰² Because of its propensity for

severe and late-onset infections, some recommend therapy for over a year followed by chronic suppressive therapy to reduce the risk of early and late recurrent *M. abscessus* infections.⁹⁸

Until 1992, *M. abscessus* was considered within the same species complex as *M. chelonae*, and to date, some laboratories still have difficulties differentiating the two species.¹⁰³ Before this distinction was made, several case reports of late-onset *M. chelonae* infections had been reported following thoracic transplant with severe or fatal outcomes.^{104,105} More recently, *M. chelonae* has been implicated in more localized cutaneous and musculoskeletal infections, which can be limb-threatening and recalcitrant.¹⁰⁶

Posttransplant outcomes in patients with species other than MAC and *M. abscessus* are primarily limited to those published in case reports.⁷⁶ *M. kansasii* airway colonization has been associated with favorable short-term outcomes following transplant.¹⁰⁷ Four cases of cutaneous infection with *M. haemophilum* have been published, all having been treated to resolution with 17 to 42 months of combination rifampin- and macrolide-based therapy.¹⁰⁸ Cases of surgical wound and localized cutaneous infections with non-*M. abscessus* species have been reported with successful outcomes following 6 to 9 months of multidrug therapy.^{106,109}

Leprosy

There have been no cases of leprosy in lung transplant recipients to date. Since the 1960s, leprosy has rarely been reported, mainly in kidney transplant recipients, with few cases in liver and heart transplant recipients. The higher reported incidence in these organ groups is likely reflective of the higher rates of kidney, liver, and heart transplantation occurring globally, while lung transplantation tends to be more geographically restricted. Date et al reported nine cases of patients with leprosy diagnosed at various time points before and after kidney transplantation.¹¹⁰ Of the patients who were followed up, all did well with resolution of cutaneous and neurologic symptoms, but several had late mortality from renal or liver dysfunction; mortality was not directly attributable to leprosy but likely was affected by long-term antileprosy therapy. In SOT, tuberculoid leprosy is less common than lepromatous leprosy, likely due to immunosuppressant drugs that impair the Th1-cell-mediated

immunity required for a tuberculoid inflammatory response.^{110,111}

There are only two reported cases of leprosy following thoracic organ transplantation, both in heart transplant recipients and both diagnosed as borderline lepromatous leprosy. One patient was a man from Louisiana with possible exposure to nine-banded armadillos (a known natural reservoir for *M. leprae*) by way of his dog.¹¹² The second was an American man originally from India who presented 5 years after transplant with concomitant diagnoses of leprosy, first-episode CMV viremia, and gastrointestinal cryptosporidiosis.¹¹³ Both patients had resolution of lesions with multidrug therapy, including dapsone and minocycline with either moxifloxacin or ethionamide. Although standard therapy for lepromatous leprosy includes clofazimine and rifampin,¹¹⁴ these were not used to avoid cardiac conduction abnormalities associated with clofazimine and drug interactions between rifampin and immunosuppressants.

Lessons learned from these non-lung transplant patients highlight strategies for management of leprosy that can be used if cases of either pauci- or multibacillary arise in a lung transplant recipient.

Conclusion

As the practice of lung transplantation continues to improve, it provides a valuable option to those suffering from chronic end-stage pulmonary diseases. The most common long-term risk of organ transplantation is that of infections associated with systemic immunosuppression. Although this risk can be mitigated, exposure to environmental and saprophytic organisms is often unavoidable. The advancements in the management of mycobacterial infections in lung transplant candidates and recipients have been the increasing recognition over the past decades, with the development of more thorough definitions and guidelines to direct therapy. We have a better yet incomplete understanding of the impact of NTM infections in lung transplant recipients. There is an ongoing need for more rigorous studies to better define durations of therapy, optimal surgical and perioperative approaches in those with NTM infection, and to enhance evidence-based transplant candidacy assessments for patients infected with NTM. As the number of transplants performed continues to climb worldwide, there is a need for multicenter collaboration to systematically study the effects of mycobacterial infections on transplant recipients and optimize management recommendations.

Conflict of Interest

None declared.

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