American Journal of Transplantation 2013; 13: 77–82
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doi: 10.1111/ajt.12101

Special Article

Nontuberculous Mycobacterial Infections in Solid Organ Transplantation

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Key words: Mycobacteria, mycobacterium avium complex, nontuberculous mycobacteria, pulmonary infection, transplant

Introduction

With the availability of advanced microbiologic techniques for the detection and identification of nontuberculosis mycobacteria (NTM) over the last 10 years, the number of NTM species has swelled to over 125 (1). Over half of these have the potential to cause human disease, but fewer than two dozen account for most reported cases. Due to impaired cell-mediated immunity, transplant recipients are susceptible to infection with these organisms. There are no prospective studies or registries of these infections, so our understanding of these infections in solid organ transplant (SOT) recipients comes from case reports and a few case series (2–7). While relatively rare compared to other posttransplant infections, these infections are important due to the difficulty in establishing the diagnosis, the need for multidrug, long-term treatment and the interaction between treatment regimens and the drugs used to prevent rejection. This guideline will focus on the common NTM causing infection following transplantation including *Mycobacterium avium-intracellulare* complex (MAC), *M. kansasii*, *M. marinum, M. haemophilum* and the rapid growing mycobacteria (RGM): *M. fortuitum, M. chelonae* and *M. abscessus*. The most frequently encountered species causing pulmonary disease include *M. avium* complex, *M. kansasii, M. xenopi* and *M. abscessus* (6).

Epidemiology

Most NTM are ubiquitous free living saprophytic organisms which have been recovered from a wide variety of environmental sources including soil, water, dust, aerosols, plant material, animals and birds (8). They are often resistant to disinfection and thus can be recovered from drinking water distribution systems including those in hospitals. Most infections are felt to arise following exposure in the environment although nosocomial infections of water contaminated medical devices have been described (8). Until recently there was no compelling evidence of either person to person or animal to person transmission; however, a recent report describes an outbreak of *M. abscessus* ssp *massiliense* infection in a lung transplant and cystic fibrosis center where person to person transmission may have occurred (9). These organisms can be recovered worldwide but most reports of infection are from the developed world (10).

Since NTM infections are not reportable, incidence data in the transplant population can only be estimated. Limited data suggest an incidence rate for NTM infections to be between 0.16% and 0.38% among kidney transplant recipients, 0.24% and 2.8% among heart transplant recipients and 0.46–8.0% in lung transplant recipients (4–6). In a series of 253 patients with a median of 25 months follow-up after lung transplant, 22% had NTM isolated from at least one culture, but only 2.5% required treatment (4). Among liver transplant recipients the rate appears to be at least 0.04% but this is based on even more limited data (2). It is unclear why the incidence of NTM in liver transplant recipients appears to be lower than other SOT groups.

The timing of infection after transplantation can vary from early to very late. In a series of 82 transplant patients with NTM infection, onset of infection was a mean of 48 months after transplant but with a range of 10 days to 269 months (5).

In the nontransplant patient population, four categories of increased risk for NTM infection have been identified. First, among HIV infected persons, a CD4+ T cell count of less than 50/μL is associated with increased risk of disseminated NTM infection. Among non-HIV infected patients, genetic syndromes affecting the interlukin-12/interferon-γ pathways, treatment with antitumor necrosis factor-α agents and structural lung disease from chronic obstructive pulmonary disease (COPD), cystic fibrosis and bronchiectasis all confer increased risk (10,11). In the current era of induction with antilymphocyte agents and 2–3 agents for immunosuppression, a formal risk analysis for infection has not been performed, but disruption of mucocutaneous barriers, structural abnormalities and the net state of immunosuppression are likely contributing factors. In a recent

study of 36 lung transplant recipients diagnosed with NTM infection, both NTM colonization and disease were associated with a significantly increased risk of death (12). A risk factor analysis for NTM infection after lung transplantation found cystic fibrosis, NTM infection before transplantation and the use of rabbit antithymocyte globulin as significant risk factors (13).

Clinical manifestations

Most clinical manifestations of NTM infection fall into one of six categories: pulmonary disease, skin and soft tissue infection, musculoskeletal infection, disseminated disease, catheter associated disease and lymphadenitis, with pulmonary and cutaneous involvement being the most common. (2,5). The spectrum of pulmonary disease includes a solitary nodule, pulmonary infiltrates, abscesses and cavitary nodules with symptoms varying according to the syndrome and may include chronic cough, sputum production, dyspnea and, less commonly, hemoptysis (6,10). Fever may or may not be present (3).

Apart from pulmonary infection in lung recipients, skin and soft tissue infection is the most common (5). Typical findings include painful to minimally painful erythematous to violaceous subcutaneous nodules most commonly on the extremities or in the region of the surgical wound occurring singly or in clusters (4). Lesions will commonly ulcerate and can also have a lymphangitic distribution resembling sporotrichosis (10). Tenosynovitis, osteoarticular disease and osteomyelitis have all been reported (2). The most common species causing skin and soft tissue and musculoskeletal infections are the RGM, *M. fortuitum, M. abscessus* and *M. chelonae* (6). *M. marinum* can produce a lymphangitic eruption resembling sporotrichosis identical to that seen in nontransplant patients after water exposure particularly fish tank water (7).

Disseminated disease with NTM infection has been reported in all SOT types but is most common among kidney recipients (2,5). Nearly half of patients with pulmonary disease will have evidence of dissemination (2,6). Sites of dissemination can include skin, lymph nodes, bone marrow, visceral organs including the allograft and musculoskeletal sites (6). *M. abscessus, M. chelonae* and *M. kansasii* have been the species most frequently associated with dissemination (6). Gastrointestinal tract infection, catheter associated infection and lymphadenitis have been reported infrequently in SOT recipients (2,5,6).

Diagnosis

Establishing the diagnosis of NTM infection can be quite difficult and giving it careful consideration in the differential diagnosis is the critical first step. Although recovery of an NTM from a sterile source such as blood or skin biopsy provides straightforward evidence of invasive disease, in contrast, differentiation of colonization from disease in the respiratory tract can be a formidable challenge.

Table 1: American Thoracic Society/Infectious Diseases Society of America Criteria for diagnosing NTM lung disease

Clinical (both required)
Pulmonary symptoms, nodular or cavitary opacities on chest radiograph or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules (A, 1), AND
Appropriate exclusion of other diagnoses (A, 1)
Microbiologic
Positive culture results from at least two separate expectorated sputum samples (A, II). If the results from 1 are nondiagnostic, consider repeat sputum AFB smears and cultures (C, III), OR
Positive culture result from at least one bronchial wash or lavage (C, III), OR
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 sample or bronchial washing that is culture positive for NTM (A, II).

Adapted from Ref. (10).

Data presented by Knoll and colleagues suggest that in the respiratory tract, colonization is more frequently encountered than invasive disease by a factor of ten (4). The American Thoracic Society/Infection Diseases Society of America have published have published clinical and microbiological criteria for diagnosing NTM lung disease (10) (Table 1). Although developed for patients with generally normal immune function, these criteria provide a useful reference point for diagnosing pulmonary infection in SOT recipients. Nevertheless, applying these criteria too rigorously may lead to under diagnosis of invasive disease in SOT patients. For example, *M. gordonae* is a common laboratory isolate and generally regarded as a nonpathogen; however, among immunocompromised patients including SOT recipients, there are reports of both pulmonary and extrapulmonary invasive disease with this organism (14). There are no specific criteria for diagnosis of extrapulmonary disease and an assessment of the clinical, histopathological and microbiologicalfindings must be performed to establish a diagnosis.

When NTM infection is suspected, clinical specimens from involved sites such as abscess fluid, synovial fluid, cerebrospinal fluid and bronchoalveolar lavage fluid should be submitted to the mycobacteriology laboratory for mycobacterial culture and staining and biopsy specimens submitted for culture, staining and histopathology. The RGM, NTM that typically grow within about 7 days, can be isolated from routine bacterial cultures, but most cultures are usually not incubated long enough for other NTM to grow. Most NTM will grow on standard mycobacteria media at standard temperatures but several species require special processing in the mycobacteriology laboratory to reliably recover them from clinical specimens (10,15). For example, *M. marinum* and several other NTM grow at temperatures lower than standard incubation temperatures, thus if these

organisms are suspected on clinical grounds, the specimens should be incubated at both 28–30°C and standard temperature (9,14). Other NTM such as *M. hemophilum* and *M. genavense* require special supplementation of the media for growth to occur. Finally, the incubation period for NTM can vary from as short as a few days for the RGM, while others such as *M. genavense* should be incubated for at least 8–12 weeks (10,15). Unless these specialized laboratory techniques for detection of growth are routinely performed by the mycobacteriology laboratory, laboratory personnel should be notified to insure optimal efforts for recovery are being utilized. It is critically important that NTM be identified to the species level and recently the importance of identifying the related species of the *M. abscessus* complex has been recognized (16). Commercially available DNA probes, PCR-based methods and high-performance liquid chromatography are used to rapidly identify some NTM species once growth on media has occurred (10). Unlike the turnaround time for a microbiology report with identification and susceptibilities of a few days for aerobic bacteria, a final report with susceptibilities may take 4 months or longer for some NTM. Although the commercially available interferon gamma release assays (IGRA) have no role in the diagnosis of NTM infection, it is worth noting the antigens used in these assays are present in *M. marinum, M. kansasii* and *M. szulgai,* hence, the potential exists for cross-reaction with these three NTM and possibly other unrecognized unsequenced NTM (17).

Treatment

The treatment of NTM depends on multiple factors including the organism isolated, the extent of the patient's disease, the type of SOT received, overall immunosuppression and the patient's tolerance to medications prescribed. Antimicrobial treatment usually requires a multidrug regimen and therapy must be continued for months to years based on national guidelines and case series, as given the rarity of these infections no controlled trials are available to guide length of therapy or the agents recommended (10). Two drug therapy is generally standard, but three agents may be indicated when the illness is life threatening, the burden of organisms is high or the patient has a RGM and susceptibility or identification to species level is not yet available. Treatment recommendations for NTM encountered infrequently are anecdotal. Cultures should be performed during therapy to judge response, predict the duration of therapy and monitor for resistance to antimycobacterial agents. Consideration should be given to tapering of the immunosuppression regimen, but immune reconstitution syndrome may occur, as it has been reported in SOT patients after therapy for other granulomatous diseases including tuberculosis (18).

Antimicrobial treatment options vary according to species, so the first step is to accurately identify the species or the species group (MAC, includes *M. avium* and *M. intracellularae*) (10). The value of using *in vitro* susceptibility testing to guide treatment decisions is variable depending on the species of NTM. Multiple drug susceptibility testing is generally useful only for RGM. In other cases susceptibility testing can be misleading, and is recommended only for specific "drug-bug" combinations (for example, clarithromycin for MAC and rifampin for *M. kansasii* both of which have established criteria for reporting as susceptible or resistant) (19). For most of the slow growing mycobacteria the susceptibility of the organism can be predicted based on the identification (19). For RGM, empiric initial treatment should be guided by species, but once susceptibility testing to specific agents is available, therapy may need to be modified. For other species, even if criteria are established for a few specific agents, clinical correlation is not available (19) (Tables 2 and 3). For therapy of the slow growing NTM in patients not treated previously, no clear correlation exists between treatment efficacy outcome and susceptibility in patients treated with more than a single agent (10,20). One possible reason for this is that *in vitro* testing is done with single antimicrobials and when certain agents are used in combination they are efficacious despite the results of the testing. For example, ethambutol increases the mycobacterial cell wall permeability (19,21) and there is *in vitro* synergy with rifampin. Combination therapy with at least two or more a antimicrobials is standard in most NTM infections in transplant patients. However, in patients with prior treatment, susceptibility testing may be used as a guide despite the lack of available evidence (III).

A major problem with the treatment of NTM is interactions between immunosuppressive agents and the rifamycins and macrolides (see chapter 32). Rifampin will markedly decrease the levels of the calcineurin inhibitors and sirolimus and its use may result in rejection due to the difficulty in obtaining adequate immunosuppression. For this reason rifabutin is preferred over rifampin in SOT patients and azithromycin over clarithromycin even though the ATS/IDSA guidelines statement suggests rifampin and clarithromycin as preferred agents for MAC treatment. In addition, interactions between the antimycobacterial agents occur. Rifampin is a potent inducer of CYP3A4 enzymes and clarithromycin is an inhibitor. Rifabutin is a less potent inducer of CYP3A4 and therefore has less effect on the metabolism of cyclosporine, tacrolimus, and sirolimus. Clarithromycin, partially, but not completely, offsets the effect of the rifamycins on the calcineurin inhibitors. Another problem is the intolerance of the patient to the medications. Many of these agents cause gastrointestinal toxicity and patients with disseminated disease to the GI tract or intrabdominal lymph nodes are often the most difficult to treat with oral agents. All of these agents may have toxicities, Examples include aminoglycoside related nephrotoxicity and ototoxicity, isoniazid related hepatotoxicity, ethambutol related visual toxicity and quinolone related tendon rupture. Clinicians should consult the ATS.IDSA guidelines for guidance. Many agents are available in an IV form (Table 4).

Table 2: Recommended treatment agents and use of susceptibility testing for slow growing and fastidious NTM in SOT patients on cyclosporine, tacrolimus or sirolimus based on guidelines for all patients from ATS/IDSA and expert opinion

Pathogen (level of evidence non-SOT patients)	Recommended regimen (see reference for details and Table 4 for dosing regimens)	Second line or additional agents[1]	Routine susceptibility testing for initial treatment	Special considerations	Length of treatment
M. avium complex (A or B, II depending on severity)	Azithromycin Rifabutin Ethambutol	Clarithromycin Rifampin Amikacin or Streptomycin	Only for clarithromycin as class drug for macrolides	Never use macrolides alone. Start ethambutol at 25 mg/kg	At least 12 months after negative cultures
M. kansasii (A, II)	Rifabutin Ethambutol Isoniazid plus pyridoxine	Rifampin Clarithromycin or azithromycin Sulfamethoxazole Moxifloxacin Amikacin or streptomycin	Rifampin If rifampin resistant or the patient is failing treatment	May be reported as resistant to isoniazid but inhibited by achievable concentrations	18 months with at least 12 months of negative cultures
M. marinum (B, III)	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 (C,III)	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

[1]For patients in whom drug interactions with calcineurin inhibitors or mTOR inhibitors is not a consideration, there is more data to support the use of clarithromycin to treat MAC (10). Although there is no demonstrated superiority of one rifamycin over the other, rifampin is recommended by most experts due to fewer adverse events than with rifabutin (10).

Table 3: Generally useful treatment agents for empiric therapy and treatment after *in vitro* susceptibility testing for rapid growing NTM in SOT patients on *cyclosporine, tacrolimus or sirolimus*

Pathogen (level of evidence SOT patients)	Regimens should be based on *in vitro* susceptibility data for the patient's isolate (see reference for details and table 4 for dosing regimens)	Second line or additional agents	Special considerations
M. abscessus (C, III)	Azithromycin Plus amikacin, imipenem, or cefoxitin Or two parenteral agents	Clarithromycin Linezolid Tigecycline	Lung infection is difficult to cure May want to start 3 drug therapy until susceptibility available
M. chelonae (C, III)	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 (C, III)	Two drugs: Amikacin Ciprofloxacin or other quinolones Sulfonamides	Sulfonamides Doxycycline or minocycline Imipenem Tigecycline	All isolates contain an inducible erythromycin methylase gene; use macrolides with caution (10)

Table 4: Dosing regimens and drug interactions

Drug	Adult dose	Drug interactions		Dose adjust for renal insufficiency
		Rifamycins	Cyclosporine Tacrolimus Sirolimus	
Azithromycin	250–300 mg daily PO or IV 500 mg daily PO or IV, three times a week (MAC) 1200 mg po/week prophylaxis	Yes	Yes	No
Clarithromycin	500 mg BID PO 1000 mg PO three times a week (MAC)[1]	Yes	Yes	Yes, mild
Ethambutol	15 mg/kg/daily 25 mg/kg three times a week (MAC)	No	No	Yes, mild
Rifabutin	150–300 mg/daily or three times a week (MAC)[1]	n/a	Yes	No
Rifampin	600 mg daily or three times a week (MAC)[1] PO or IV	n/a	Yes	No
Ciprofloxacin	500 mg PO (400 mg IV) BID	Yes	Yes, mild	Yes, moderate
Levofloxacin	500–750 mg daily PO or IV	Yes	Yes, mild (CsA)	Yes, moderate
Moxifloxacin	400 mg daily PO or IV	No	No	
Amikacin	10–12 mg/kg daily or three times a week IV or IM[1]	No	Potentiate renal toxicity	Yes, major
Streptomycin	500–1000 mg daily or three times a week IV or IM[1]	No	Potentiate renal toxicity	Yes, major
Tobramycin	5 mg/kg daily or three times a week IV or IM[1]	No	Potentiate renal toxicity	Yes, major
Linezolid	600 mg BID PO or IV	No	No	None
Isoniazid	5 mg/kg/daily up to 300 mg daily PO give with pyridoxine 50 mg daily PO	No	No	Minimal
Doxycycline	100 mg BID PO or IV	No	No	None
Minocycline	100 mg daily PO	No	No	None
Tigecycline	100 mg IV × one then 50 mg IV q 12 h	No	Yes, mild	None
Cefoxitin	8–12 g daily in divided doses IV	No	No	Yes, moderate
Imipenem	500 mg q 6 h IV	No	No	Yes, moderate
Sulfamethoxazole Trimethoprim/ sulfamethoxazole	1000 mg BID to TID 800–1600 mg (sulfa component) BID PO or IV	No	Possible potentiation of renal toxicity	Yes, moderate

[1]Intermittent therapy (thrice weekly) with aminoglycosides may decrease toxicity. For other agents less frequent dosing may have inconsistent effects on immunosuppressive agents and is not usually recommended as initially therapy or for patients with cavitary lung disease. In many patients therapy will need to be individualized due to renal function, GI toxicity, site of infection and species of NTM.

Because infections may persist despite antimycobacterial therapy, surgery may be required to treat localized skin infections due to NTM. Resection of cutaneous NTM infections in SOT patients has been successful, usually in combination with drug treatment. Surgery has not been as useful in lung transplant patients as in cases of refractory lung disease due to NTM in nonimmunocompromised patients since transplant patients are more likely to have more extensive disease (4). Lung transplant patients with surgical site or pleural infection have required chronic suppressive therapy (22). Because transplant recipients often have more disseminated disease, surgical resection of affected lung is considered only when disease is predominantly localized to one lung. Treatment needs to be continued for many months to years in most patients with NTM infections. The length of treatment is shortest for cutaneous infections with *M. marinum* and longest for lung infections with almost any species of NTM. In treating MAC and *M. kansasii* the goal of therapy is 12 months of negative sputum cultures so sputum must be collected periodically during therapy (A, II) (10). This goal is similar for *M. abscessus* (C, III) but may be less attainable. Many experts regard pulmonary infection with *M. abscessus* to be nearly incurable and the goal of therapy should be control of infection rather than cure. Repeat cultures and susceptibilities are warranted in patients failing therapy or who relapse and require repeat treatment.

Prevention/prophylaxis

Rifabutin, clarithromycin and azithromycin are effective prophylactic agents for MAC in individuals with AIDS (A, I) (23,24). Prophylaxis has not been systematically studied for other NTM species. In lung transplant recipients, there is emerging evidence that NTM colonization especially with *M. abscessus* or MAC pretransplant may be associated with overt NTM disease posttransplant (12). Some centers exclude patients with NTM infection from transplantation until the patient completes at least 3 months of

therapy for NTM (12). Patients with cystic fibrosis undergoing lung transplantation and known to be colonized with RGM should be considered for posttransplant chemoprophylaxis with azithromycin to prevent surgical site infections (III). Similarly, patients infected or colonized with MAC prior to lung transplant should be considered for multidrug MAC therapy prior to lung transplantation (12) (III). For patients who have completed therapy for a documented NTM infection, some experts extrapolate from the HIV data and recommend secondary prophylaxis, but for this and for other situations, there is insufficient evidence to recommend routine prophylaxis (III).

Future directions

More information is needed to improve understanding of NTM related infections in all patients but especially after SOT. Better understanding of epidemiology and diagnosis is needed. Laboratory susceptibility testing needs to be further developed and standardized for all species and antimycobacterial agents. Prospective multicenter trials of prophylaxis in prelung transplant patients who are colonized with MAC or RGM are warranted. New agents and regimens are need for therapy of the most difficult to treat species. A registry of SOT patients with NTM disease and their treatment and disease outcomes, including the function of the transplanted organ after therapy, would help us better understand these infections over time.

Acknowledgment

This manuscript was modified from a previous guideline written by Susan Dorman and Aruna Subramanian published in *American Journal of Transplantation* 2009; 9(Suppl 4): S63–S69 and endorsed by the American Society of Transplantation/Canadian Society of Transplantation.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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