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Nontuberculous Mycobacterial Infection in Hematopoietic Stem Cell and Solid Organ Transplant Recipients

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Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms. In immunocompetent hosts, they are a rare cause of disease. In immunocompromised hosts, disease due to NTM is well documented. Reports of NTM disease have increased in hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients. This increase may reflect increased numbers of transplants, intensification of immune suppressive regimens, prolonged survival of transplant recipients, and/or improved diagnostic techniques. The difficulty of diagnosis and the impact associated with infections due to NTM in HSCT and SOT recipients necessitates that, to ensure prompt diagnosis and early initiation of therapy, a high level of suspicion for NTM disease be maintained. The most common manifestations of NTM infection in SOT recipients include cutaneous and pleuropulmonary disease, and, in HSCT recipients, catheter-related infection. Skin and pulmonary lesions should be biopsied for histologic examination, special staining, and microbiologic cultures, including cultures for bacteria, *Nocardia* species, fungi, and mycobacteria. Mycobacterial infections associated with catheters may be documented by tunnel or blood (isolator) cultures. Susceptibility testing of mycobacterial isolates is an essential component of optimal care. The frequent isolation of NTM other than *Mycobacterium avium* complex (MAC) from transplant recipients limits the extrapolation of therapeutic data from human immunodeficiency virus–infected individuals to the population of transplant recipients. Issues involved in the management of NTM disease in transplant recipients are characterized by a case of disseminated infection due to *Mycobacterium avium* complex in a lung transplant recipient, with a review of the relevant literature.

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms that have generally been considered an uncommon cause of human disease. Before the AIDS epidemic, most cases presented as indolent, cavitating pulmonary infections in persons with other underlying lung diseases, such as chronic obstructive pulmonary disease (COPD) or previous tuberculosis [1, 2]. During the 1980s, pulmonary and disseminated infections due to the more common NTM (e.g., *Mycobacterium avium, Mycobacterium intracellulare,* some strains of *Mycobacterium scrofulaceum,* and some unclassified strains) emerged as complications of AIDS and were termed *M. avium* complex (MAC) infections [3, 4]. Subsequently, a syndrome of predominantly midlung zone bronchiectasis with MAC pulmonary infection was described in otherwise healthy middle-aged women [5, 6].

Mycobacterial infections after receipt of a transplant have increased in frequency and severity, reflecting both increased exposure and improved diagnostic methods. In countries where tuberculosis is endemic, infections due to *M. tuberculosis* are more frequent than are infections due to NTM [7–11]. In countries with lower incidences of tuberculosis, NTM infections predominate [12–15]. In the absence of mandatory reporting of infections, the true incidence of NTM disease in the general population and in the population of transplant recipients can

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only be estimated. In the United States, the annual rate of NTM isolation, on the basis of laboratory surveillance, is estimated to be 7.5–8.2 cases of NTM isolation per 100,000 population [16]. As these data were collected in the absence of clinical information, the actual incidence of NTM disease cannot be determined. Among recipients of hematopoietic stem cell transplants (HSCTs), the incidence of NTM infection ranges from 0.4% to 4.9% [12, 15, 17–19], which is 50–600 times greater than in the general population. Among renal transplant recipients, the incidence of NTM infection is between 0.16% and 0.38% [8, 20–25]. Slightly higher rates are reported in recipients of heart transplants (0.24%–2.8% of recipients [13, 26]) and lung transplants (0.46%–2.3% of recipients [14, 27]). The only systematic study of mycobacterial infection in liver transplant recipients reported an incidence of 0.04%, which may reflect local epidemiology, underdiagnosis, or a truly low incidence of infection [28].

We report a case of disseminated MAC infection in a lung transplant recipient, and we review the clinical manifestations and the difficulties in diagnosis and management of NTM infections in hematopoietic and solid organ transplant (SOT) recipients.

CASE REPORT

A 46-year-old woman presented with fever and abdominal pain 10 months after receiving a single left-lung transplant for treatment of lymphangioleiomyomatosis. Because of her underlying disease, she had persistent chylous ascites. Her posttransplantation course of therapy was complicated by several episodes of acute rejection that required intermittent high-dose therapy with steroids. She received cyclosporine (200 mg each morning 225 mg each evening) and prednisone (30 mg/day).

At presentation, she had a 3-week history of fever and lower abdominal pain. A CT scan of the abdomen revealed ascites, retroperitoneal lymphadenopathy, and a right-side retroperitoneal mass. Diagnostic paracentesis was performed. An acid-fast smear of ascitic fluid revealed rare (grade 1+) acid-fast bacilli; mycobacterial cultures grew MAC. Mycobacterial cultures of pleural fluid, bronchial washings, blood, and aspirates of the retroperitoneal mass consistent with necrotic lymph nodes also grew MAC. The patient began to receive therapy with rifabutin, ethambutol, levofloxacin, and azithromycin (pending in vitro susceptibility data); her prednisone dosage was reduced to 20 mg/day.

The patient's condition initially improved, with resolution of her fever and abdominal pain, and she was discharged from the hospital 4 weeks after admission. One week after discharge from the hospital, she was readmitted with increasing abdominal pain, recrudescence of her fever, and an increase in retroperitoneal adenopathy (revealed on a CT scan). Clofazamine and streptomycin were added to the patient's treatment regimen pending the results of susceptibility testing of the original blood isolate.

The patient developed dyspnea with "ground-glass" opacities in the transplanted lung consistent with graft rejection precipitated by the reduction in the prednisone dosage. She was treated with high-dose steroids, but her condition progressed to hypoxemic respiratory failure, and the patient required intubation. Empirical treatment with broad-spectrum antimicrobials, including cefepime, vancomycin, metronidazole, and caspofungin, was administered. Additional complications included cytomegalovirus (CMV) infection (detected by an antigenemia assay), which was treated with intravenous ganciclovir, and acute renal failure, which necessitated discontinuation of streptomycin therapy.

The patient recovered from respiratory and renal failure; no new infections were identified. Her blood cultures remained positive for MAC for 3 months after the initial positive culture result. The isolate was determined to be susceptible to clarithromycin and clofazamine, intermediately susceptible to ethambutol, and resistant to all other agents that were tested (ciprofloxacin, moxifloxicin, rifampin, rifabutin, kanamycin, cycloserine, ethionamide, amikacin, and streptomycin). After 6 months of therapy with a regimen of rifabutin, azithroycin, ethambutol, clofazamine, and levofloxacin, the patient's condition was clinically improved. Immunosuppressive therapy includes cyclosporine and prednisone (20 mg/day). Despite gastrointestinal upset related to therapy for MAC, the patient will continue her current therapy for an additional 3 months and will then receive long-term maintenance therapy with rifabutin, ethambutol, and azithromycin. To our knowledge, this is the first case of disseminated MAC infection in a lung transplant recipient to be reported in the literature.

METHODS

We searched MEDLINE for English language articles published since 1966 using the medical subject heading (MeSH) database headings "*Mycobacterium,*" "mycobacteria, atypical," "*Mycobacterium* infections, atypical," "*Mycobacterium avium* complex," "*Mycobacterium chelonae,*" "*Mycobacterium fortuitum,*" "*Mycobacterium kansasii,*" "*Mycobacterium marinum,*" "*Mycobacterium scrofulaceum,*" "*Mycobacterium smegmatis,*" "*Mycobacterium ulcerans*" OR "*Mycobacterium xenopi*" AND "transplantation" or "bone marrow transplantation" OR "immunocompromised host." We searched reference lists to identify additional reports of NTM infection in transplant recipients. There have been a total of 276 such cases reported, 93 in HSCT recipients, and 183 in SOT recipients.

Clinical manifestations of NTM disease in HSCT recipients. Several series have reviewed NTM infections in HSCT

recipients. The reported incidence of disease in this population ranges from 0.4% to 4.9% [12, 15, 17–19]. Ninety-three cases of NTM infection in HSCT recipients have been reported [12, 15, 17–19, 29–43]. For these patients, the median time between transplantation and presentation was 4.6 months. Their median age was 32 years, and the incidence was equal for male and female patients. Graft-versus-host disease was present in 43 (46%) of the cases.

The clinical manifestations of NTM disease in HSCT and SOT recipients are displayed in table 1. The clinical manifestations of disease in HSCT recipients differed from those in SOT recipients. The most common manifestation of NTM disease in HSCT recipients was central venous catheter–related infection (in 34 [37%] of cases), including 7 exit site–related, 8 tunnel-related, and 19 catheter-related blood stream infections. Pulmonary disease (in 28 cases), cutaneous disease (in 17 cases) and disseminated disease (in 11 cases) are commonly reported.

The most frequently isolated species in HSCT recipients are rapidly growing mycobacteria, including *M. fortuitum* (in 15 cases), *Mycobacterium abscessus* (in 11 cases), *M. chelonae* (in 12 cases), *Mycobacterium mucogenicum* (in 2 cases), *Mycobacterium fortuitum-chelonae* (in 2 cases), and *Mycobacterium neoaurum* (in 1 case), accounting for 43 (45%) of 95 isolates. MAC and/or *M. avium intracellulare* (in 26 cases) and *M. haemophilum* (in 22 cases) are also common. MAC and/or *M. avium* infection are most often associated with pulmonary or disseminated disease. The rapidly growing isolates have been predominately associated with catheter-related infections. The presence of *M. haemophilum* has been reported more frequently in HSCT recipients than in SOT recipients, usually in association with pulmonary or cutaneous disease but also in association with disseminated, osteoarticular, and catheter-related disease.

Clinical manifestations of NTM disease in SOT recipients. Nontuberculous mycobacterial disease has been reported in 94 recipients of kidney transplants [1, 8, 20–25, 33, 44–92], 22 recipients of lung transplants [14, 27, 93–98], 34 recipients of heart transplants [13, 33, 61, 99–111], and 8 recipients of liver transplants [28, 61, 112–117]. Rapidly growing mycobacteria have been associated with disease in SOT recipients less often than in HSCT recipients. Among cases of NTM disease in SOT recipients, rapidly growing isolates account for 41%, 9%, and 9% of isolates from renal, heart, and lung transplant recipients, respectively. *Mycobacterium kansasii* has only been reported to cause disease in 1 HSCT recipient, but it is the most common isolate reported in heart transplant recipients (12 [35%] of 34 isolates) and the second most common isolate in renal recipients (23 [24%] of 95).

In contrast to HSCT recipients among whom cutaneous disease has accounted for <20% of reported cases of infection, for renal and heart transplant recipients, localized or disseminated cutaneous disease is the most commonly reported manifestation of NTM (in approximately one-third of cases). Pleuropulmonary NTM disease is the manifestation most commonly reported among lung transplant recipients (in 54% of reported cases) and is common in heart transplant recipients (in 26%).

Disseminated NTM infection is also common in SOT recipients. Among renal transplant recipients, disseminated disease is the second most common presentation, after cutaneous disease; in heart and lung recipients, disseminated disease is the third most common presentation, after cutaneous and pleuropulmonary disease.

Eight cases of NTM infection in liver transplant recipients have been reported [28, 61, 112–117]. Data on the isolates and clinical presentations from these cases are included in table 1. In addition, 25 cases of NTM infection in multiorgan or unspecified organ transplant recipients have been reported [14, 45, 50, 118–121]. The characteristics of these patients are summarized in table 2.

Diagnosis of NTM disease. The diagnosis of NTM disease in transplant recipients, as in immunocompetent hosts, is often difficult. Diagnosis of *significant* pulmonary infection is difficult because of the ubiquitous nature of these organisms; isolates from sputum samples may represent colonization or laboratory contamination, rather than disease. Given the difficulties in diagnosis, the American Thoracic Society (ATS) published guidelines on the diagnosis and treatment of disease due to NTM [122]. A combination of clinical, radiographic, and bacteriologic criteria is required for diagnosis of NTM pulmonary disease. Extrapulmonary disease is diagnosed through a combination of clinical findings and bacteriologic findings (e.g., results of cultures of specimens from sterile sites) with or without adjunctive histologic confirmation. These guidelines provide a comprehensive review of issues related to the diagnosis of NTM disease [122].

Several features of the diagnosis of NTM infection in transplant recipients merit emphasis. A high level of suspicion for NTM disease is essential for rapid and accurate diagnosis. Suspect cutaneous lesions in a transplant recipient should be *biopsied* for histologic examination, with use of special stains and cultures for detection of routine bacteria as well as for *Nocardia,* fungi, and mycobacteria. In HSCT recipients, catheter-related infections are the most common manifestation of NTM disease, and diagnosis (usually of rapidly growing NTM) is generally made on the basis of results of routine blood cultures. The pathogen *M. haemophilum,* which is common in HSCT recipients, requires hemin or ferric ammonium citrate for growth; microbiology laboratories should be notified if this organism is suspected.

To optimize recovery of NTM, specimens should be cultured on both solid and liquid media, and samples obtained from

Table 1. Clinical manifestations of nontuberculous mycobacterial (NTM) disease in 251 recipients of hematopoietic stem cell transplants (HSCTs) and solid organ transplants.

Transplantation type	References	No. of patients	Sex, no. M/F	Age, median years	Median time to onset, months[a]	*Mycobacterium* species, no. of isolates	Type(s) of infection, no. of patients
HSCT	[11, 14, 16–18, 28–42]	93	39/39	32	4.2	MAC/MAI, 26; *M. haemophilum,* 22; *M. fortuiutum,* 15; *M. chelonae,* 12; *M. abscessus,* 11; *M. fortuitum-chelonae,* 2; *M. mucogenicum,* 2; *M. kansasii,* 1; *M. terrae,* 1; *M. gordonae,* 1; *M. xenopi,* 1; *M. neoaurum,* 1	Catheter-related, 34[b]; pulmonary, 28; cutaneous, 17; disseminated, 11; osteomyelitis, 3; lymphadenitis, 1
Kidney	[1, 8, 22–27, 32, 43–91]	94	46/35	42	23.5	*M. chelonae,* 21; *M. kansasii,* 21; *M. haemophilum,* 13[c]; *M. fortuiutum,* 9; MAC/MAI 5; *M. marinum,* 4; *M. abscessus-chelonae,* 4; *M. xenopi,* 4; *M. abscessus,* 3; NTM NOS, 3; *M. gordonae,* 2; Rapid-grower NOS, 2; *M. scrofulaceum,* 2; *M. gastri,* 1	Local cutaneous, 32; disseminated, 18; disseminated cutaneous, 11; osteoarticular or tenosinovitis, 10; pleuropulmonary, 10; ileitis or colitis, 3; urinary tract, 2; allograft, 1; transplant wound, 1; psoas abscess, 1
Heart	[12, 32, 60, 98–110]	34	28/4	46	30	*M. kansasii,* 12; MAC/MAI, 8; *M. haemophilum,* 5; *M. scrofulaceum,* 2; *M. chelonae,* 2; *M. thermoresistable,* 2; NTM NOS, 2; *M. fortuitum,* 1	Pleuropulmonary, 9; disseminated, 8; disseminated cutaneous, 6; local cutaneous, 4; osteomyelitis, 2; LVAD wound, 1; sternotomy wound, 1; prosthetic hip, 1; lymphangitis, 1; bursitis, 1
Lung	[13, 20, 92–97]	22	13/8	49	14.8	MAC/MAI, 7; *M. abscessus,* 6; *M. haemophilum,* 4; *M. fortuitum,* 1; *M. marinum,* 1; *M. kansasii,* 1; *M. asciaticum,* 1; *M. chelonae,* 1	Pleuropulmonary, 12; local cutaneous, 6; disseminated, 2; thoracotomy wound/empyema, 1; thoracotomy wound or disseminated cutaneous, 1
Liver	[21, 60, 111–116]	8	2/6	42.5	10	MAC/MAI, 3; *M. abscessus,* 1; *M. chelonae,* 1; *M. chelonae-abscessus,* 1; *M. mucogenicum,* 1; *M. triplex,* 1; *M. xenopi,* 1	Disseminated, 4; pulmonary, 2; septic arthritis, 1; cutaneous, 1

NOTE. LVAD, left ventricular assist device; MAC/MAI, *Mycobacterium avium* complex and/or *Mycobacterium avium* infection; NOS, not otherwise specified.

[a] Time from transplantation to presentation with NTM disease.

[b] Catheter-related infections included 7 exit site–related infection, 8 tunnel–related infections, and 19 blood stream infections.

[c] Six of 13 were speciated retrospectively.

Table 2. Clinical manifestations of nontuberculous mycobacterial (NTM) disease in recipients of multiorgan transplants and unspecified solid organ transplants.

Transplantation type [reference(s)]	Patient age, years	Sex	Time to onset, months[a]	*Mycobacterium* species isolated	Type(s) of infection (no. of patients)
Heart-lung					
[13]	29	F	5.1	*M. avium*	Pulmonary (1)
[13]	55	F	109.1	*M. abscessus*	Pulmonary (1)
[13]	38	M	52.7	*M. avium*	Pulmonary (1)
[13]	24	F	12	*M. avium* complex	Pulmonary (1)
[117]	24	F	9	*M. chelonae*	Pulmonary (1)
"Organ transplant"[b] [44, 49, 118]	…	…	…	*M. chelonae*	Disseminated cutaneous (13); catheter-related (3); post-surgical (1); cutaneous (1)
Heart and subsequent kidney [119]	…	M	132; 3[c]	*M. avium*	Prosthetic hip (1)
Kidney-pancreas [120]	45	F	96	*M. marinum*	Disseminated cutaneous (1)

[a] Time from transplantation to presentation with NTM disease.
[b] Data are given for a total of 18 patients.
[c] Months after heart and kidney transplantations, respectively.

cutaneous sites should be cultured at 35°C *and* 28–32°C. Controversy exists as to the clinical utility of comprehensive drug-susceptibility testing of NTM isolates; however, susceptibility testing is helpful in the management of therapy in transplant recipients, in whom drug interactions and toxicities are common. This includes testing MAC for susceptibility to clarithromycin in those patients who have experienced the failure of macrolide therapy or prophylaxis, testing *M. kansasii* for susceptibility to rifampin, and testing rapidly growing isolates for susceptibility to amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline, and sulfonamides.

Disseminated disease in SOT recipients may be more difficult to diagnose, as in our patient. Rapidly growing isolates are less common among SOT recipients than among HSCT recipients. Mycobacterial isolator blood cultures should be performed for patients with unexplained systemic illnesses. For all transplant recipients, but particularly heart transplant and lung transplant recipients, an aggressive approach to the diagnosis of unexplained or nonresolving pleuropulmonary lesions should be used, to exclude the possibility of mycobacterial or other opportunistic infections. This includes sampling of pleural fluid and/or early biopsy of lung lesions.

The ATS clinical, radiographic, and bacteriologic criteria for NTM disease are similar for immunocompromised and immunocompetent individuals. The include the following: signs and symptoms compatible with the exclusion or adequate treatment of other disease; abnormal radiographic findings demonstrating persistent or progressive pulmonary infiltrates, cavitation, multiple small nodules, or multifocal bronchiectasis; and bacteriologic evidence of NTM in respiratory specimens [122]. These criteria emphasize the importance of radiologic techniques (e.g., CT scanning) in documentation of disease, direction of invasive sampling techniques, and documentation of response to therapy. The specific bacteriologic criteria and the differences between the criteria for systemically immunosuppressed hosts, such as transplant recipients, and for other HIV-negative hosts are outlined in table 3.

Management of NTM disease. A complete review of the management of all NTM syndromes and their specific microbiologic etiologies are beyond the scope of this review (see the ATS guidelines [122]). Some essential recommendations will be emphasized.

As NTM are ubiquitous environmental organisms, no recommendations exist regarding avoidance of exposure, with the exception of recommendations pertaining to *M. marinum*. Infection due to *M. marinum* is associated with fish tank and salt water exposure; transplant recipients should wear gloves to clean tanks, if necessary.

In general, treatment of NTM disease requires the use of combinations of active antimicrobial agents for prolonged periods to achieve cure while avoiding contributing to the emergence of antimicrobial resistance. The choice of agents depends on the specific isolate, given the variability of in vitro susceptibility patterns. The duration of therapy depends on the isolate, on the site of infection, and, most importantly, on the clinical, microbiologic, and radiologic responses to therapy.

Whenever possible, initial therapy should include a reduction in the intensity of immunosuppressive therapy. Other contributing factors, such as concomitant viral infections (in particular, CMV infection), should be treated. The choice of antimicrobial

Table 3. Bacteriologic criteria for diagnosis of nontuberculous mycobacterial (NTM) pulmonary disease.

Normal hosts or patients with local immunosuppression[a]	Patients with systemic immunosuppression[b]
At least 3 sputum or bronchial wash samples within 1 year	At least 3 sputum or bronchial wash samples within 1 year
3 cultures positive for NTM with negative AFB smears **or**	3 cultures positive for NTM with negative AFB smears **or**
2 cultures positive for NTM and 1 positive AFB smear	2 cultures positive for NTM and 1 positive AFB smear
OR	**OR**
1 bronchial wash sample and no sputum samples	1 bronchial wash sample and no sputum samples
Culture positive for NTM with grade 2+, 3+, or 4+ growth **or**	Culture positive for NTM with grade 1+ growth **or**
Culture positive for NTM and AFB smear grade 2+, 3+, or 4+	Culture positive for NTM and AFB smear grade 2+, 3+, or 4+
OR	**OR**
Tissue biopsy	Tissue biopsy
Any growth on a culture of a bronchopulmonary tissue biopsy sample	Any growth on a culture of a bronchopulmonary tissue biopsy sample
Granuloma and/or AFB detected in a lung biopsy specimen and ⩾1 culture of a sputum or bronchial wash sample positive for NTM	Granuloma and/or AFB detected in a lung biopsy specimen and ⩾1 culture of a sputum or bronchial wash sample positive for NTM
Any growth on culture of a sample from a usually sterile extrapulmonary site	Any growth on culture of a sample from a usually sterile extrapulmonary site

NOTE. AFB, actid-fast bacilli. Adapted from [122].

[a] For example, alcoholism, bronchiectasis, cyanotic heart disease, cystic fibrosis, prior mycobacterial disease, pulmonary fibrosis, or smoking, and/or chronic obstructive pulmonary disease.

[b] For example, leukemia, lymphoma, receipt of a solid organ transplant, HIV infection, or other systemic immunosuppression.

therapy for transplant recipients is similar to that for patients without systemic immune suppression. However, in addition to well-documented toxicities and interactions of drugs used to treat NTM infection, interactions between medications for NTM infection and immunosuppressive agents (and other medications) are frequent.

The interactions between antimycobacterials and calcineurin inhibitors (CNIs) or sirolimus are significant. Azithromycin therapy may be preferred to clarithromycin therapy, as it is a less potent cytochrome P450 (CYP450) inhibitor. Rifampin, and to a lesser degree rifabutin, induces CYP450 enzymes with reduced CNI levels, which may precipitate rejection of a transplant. Occasionally, modification of the immunosuppressive regimen to minimize drug interactions is considered. In all patients, monitoring of drug levels and clinical toxicities is essential. Anticipated interactions between the antimycobacterial and immunosuppressive agents are outlined in table 4.

Traditional antimycobacterial agents such as rifampin or rifabutin, ethambutol, and streptomycin are often effective in treating disease due to MAC, *M. kansasii,* and *M. haemophilum* [123–126]. However, toxicities, including ototoxicity and nephrotoxicity, are accentuated in this population. In treating *M. kansasii* infections, isoniazid therapy is often effective [124, 125]. Newer macrolides (e.g., clarithromycin and azithromycin) are the backbone of therapy for MAC [127–131], but they have significant interactions with CNIs and sirolimus. Rapidly growing mycobacteria such as *M. chelonae, M. abscessus,* and *M. fortuitum* are generally resistant to antituberculous agents; these are frequently susceptible to traditional antibacterial agents, including amikacin, ciprofloxacin, sulfonamides, cefoxitin, imipenem, clarithromycin, and doxycycline [132–135]. Newer agents (e.g., tigecycline) are under investigation [136].

Although recommendations exist for the duration of therapy for specific diseases due to NTM (e.g., 12–18 months for treating pulmonary disease, depending on the isolate), this should be considered a guide to *the minimum duration of therapy* in transplant recipients. There are no data on which to base specific recommendations for the duration of therapy in transplant recipients with NTM disease. In practice, prolongation of therapy is often needed to achieve microbiologic cures (which are often not achieved) or radiologic improvement; the response to treatment is often delayed. In particular, if the intensity of immune suppression cannot be reduced or if a high burden of disease exists (e.g., in cases of disseminated disease or smear-positive pulmonary disease), prolonged therapy or lifelong suppression may be needed.

In addition to medical therapy, adjunctive interventions should be considered. If disease is related to foreign bodies, such as central venous catheters, these should be removed. Surgical resection or debridement of infected collections or devitalized tissue should be achieved early to allow improved penetration of drugs, to decrease the burden of disease, and to minimize the risk of developing resistance.

Secondary prophylaxis has been effective in preventing relapse in HIV-infected patients treated for disseminated MAC infection [137–141]. The common isolation of NTM other than

Table 4. Interactions between immunosuppressive agents and medications used to treat infection due to nontuberculous mycobacteria (NTM).

Medication(s) for NTM infection	Immunosuppresive agent	Anticipated reaction
Rifamycins (e.g., rifampin, rifabutin)	CNIs (e.g., cyclosporin, tacrolimus)	Decreased level of CNIs
	Sirolimus	Loss of sirolimus efficacy
	Steroids	Decreased steroid effectiveness
Macrolides (e.g., clarithromycin, azithromycin)	CNIs (e.g., cyclosporin, tacrolimus)	Increased CNI level and risk of toxicity
Ethambutol	NS	NA
Aminoglycosides (e.g., streptomycin, amikacin)	CNIs (e.g., cyclosporin, tacrolimus)	Possible additive or synergistic risk of renal impairment
Clofazamine	NS	NA
Fluoroquinolones	NS	NA
Isoniazid	NS	NA
Doxycicline	NS	NA
Cefoxitin	NS	NA
Imipenem	Cyclosporin	May result in neurotoxicity (manifested, e.g., as mental confusion, agitation, and/or tremor)

NOTE. CNIs, calcineurin inhibitors; NA, not applicable; NS, no significant interaction.

MAC in transplant recipients and the absence of clinical trial data limit the extrapolation of prophylaxis data from HIV-infected individuals to transplant recipients.

Of reported cases of NTM disease in transplant recipients, relapses were managed with an additional course of prolonged medical therapy with or without surgical intervention. In only 1 case (that of a renal transplant recipient with septic arthritis due to MAC) was long-term prophylaxis initiated. In general, life-long prophylaxis after therapy *might* be preferred for tissue-invasive infections (i.e., infections other than catheter-related bacteremia or well-localized infection), given the inability to stop immune suppression in SOT recipients and some HSCT recipients. However, mortality attributable to NTM infection is modest, and toxicities may be insurmountable. If selected, prophylactic therapy should be based on antimicrobial susceptibilities of mycobacterial isolates. Unfortunately, the use of clarithromycin, azithromycin, rifampin, or rifabutin as single agents for secondary prophylaxis, although reasonable, may be ineffective in patients with persistent immune suppression and may induce antimicrobial resistance. Thus, secondary prophylaxis regimens for NTM infection in patients who receive transplants should be developed with experts in treating such infections in complex patients, and the development of such regimens should involve consideration of disease severity, the ability to decrease immunosuppression, the perceived risk of relapse, and the risk of inducing resistance.

Prognosis of NTM disease. The outcome of NTM disease in transplant recipients is highly variable. This is due to a number of factors, including the type of transplant, the ability to decrease immunosuppression, the site and extent of NTM infection, the specific NTM isolate, and the availability of effective antimycobacterial therapies.

In the 93 cases of NTM infection in HSCT recipients that were identified in the literature, the outcomes of 58 (62%) of 93 cases were reported to be "resolved" or "cured" with medical therapy. In most cases of catheter-related infection, the catheter was removed in conjunction with medical therapy. In 7 (7.5%) of 93 patients, death was attributable to NTM disease. Three patients died as a result of pulmonary disease associated with *M. hemophilum* [19, 34–36, 42], 1 as a result of pulmonary disease due to *M. xenopi* [19], 2 as a result of catheter-related blood stream infections due to *M. fortuitum* [12, 19], and 1 as a result of disseminated MAC [41]. In 1 patient with disseminated MAC and 1 patient with *M. fortuitum* catheter-related infection, death occurred prior to diagnosis.

Among recipients of renal allografts, 41 (44%) of 94 were cured or had complete resolution of NTM infection with initial therapy. Disease relapsed in 16 (17%) of the patients, and 14 (15%) of the patients had persistent disease that required modification of medical therapy and/or surgical intervention. In 3 (3.2%) of the cases, death was attributed to NTM infection. Death occurred in 2 patients with disseminated disease, 1 of whom had infection due to MAC [62], and 1 of whom had infection due to *M. fortuitum* [22]. In 1 case, death occurred due to pulmonary infection with *M. kansasii* [91]. One additional patient died early in the course of disseminated *M. kansasii* infection with concomitant disseminated CMV disease [55].

Among heart transplant recipients, 11 (32%) of 34 patients had resolution of infection with medical therapy. Nine (26%) of 34 patients died of other causes but had evidence of NTM infection at time of death. Of 22 lung transplant recipients with reported cases of NTM infection, 7 (32%) had infections that cleared with therapy, and 8 (36%) experienced an improvement in their condition while receiving therapy. In 2 patients, disease relapsed after discontinuation of treatment, and 5 (23%) of the patients had minimal or no response to therapy. One of these was a 20-year-old man who died with disseminated *M. abscessus* infection soon after receiving a transplant and who had had sputum cultures that were positive for *M. abscessus* before receiving the transplant [95].

Among renal transplant and heart transplant recipients, in particular, there were several episodes of transplant rejection and/or graft loss that occurred in patients with NTM disease. This reflects the greater risk for infection in patients who require higher levels of immunosuppression and the increasing risk of graft rejection with decreasing immunosuppression.

NTM colonization or infection prior to transplantation. Some transplantation candidates, notably those who are candidates for receipt of an HSCT or lung transplant, may be colonized or infected with NTM. Currently, the leading indications for receipt of a lung transplant are COPD, cystic fibrosis, and pulmonary fibrosis [142]. Forty percent of NTM isolates are from patients with COPD [2]; NTM isolates are recovered from 6.6%–20% of patients with cystic fibrosis [143–147]. Previously, the isolation of NTM from the sputum of patients with chronic pulmonary disease, particularly those with cystic fibrosis, was believed to represent colonization; more recently, it has been suggested that this finding may represent true disease [148, 149].

At present, optimal management for patients infected or colonized with NTM before receiving a lung transplant is unclear. If NTM contribute to disease before receipt of a transplant, preemptive therapy is indicated. This must be considered in the context of the risk for the emergence of resistance and the potential future need for antimycobacterial therapy. In patients colonized with NTM or those with minimal disease, the approach to management is less clear. Several approaches have been reported, including therapy before receipt of a transplant, peritransplantation prophylaxis, and no administration of specific therapy in the absence of symptoms.

One patient with sputum cultures that were repeatedly positive for *M. chelonae* and *M. fortuitum* underwent lung transplantation without receiving therapy for NTM, and mycobacterial cultures of specimens obtained from the patient after receiving a transplant remained negative [150]. Another patient, who was colonized with and received treatment for MAC infection before undergoing heart and lung transplantation, subsequently developed histologically documented invasive MAC disease in the transplanted lung [148]. We have observed invasive *M. abscessus* infection of the sternum in a patient who was colonized before he underwent lung transplantation; treatment of this condition required extensive debridement in addition to antimicrobial therapy. In a series of 219 lung transplant recipients reported by Kesten et al. [27], NTM were identified in the explanted lungs of 4 patients. Three of the 4 patients were treated with 3–12 months of antimycobacterial therapy, and none developed disease.

Several reports document uncomplicated HSCT following successful therapy to treat disseminated or pulmonary NTM infection [12, 15, 17, 19, 151]. Many patients initiated antimycobacterial therapy before receiving a transplant and continued therapy through transplantation. There were no reports of adverse drug reactions or recurrent NTM disease in these patients. Our own experience is similar and includes the successful control of pulmonary disease in an HSCT recipient and the treatment of a case of MAC spinal osteomyelitis in a patient who was receiving therapy for graft-versus-host disease. Although data are limited, HSCT can be successful in patients with adequately treated NTM disease.

CONCLUSION

The incidence of disease caused by NTM in transplant recipients appears to be increasing. This is probably related to improvements in patient survival, as well as to enhanced diagnostic capabilities. Although NTM infection remains a relatively uncommon complication of HSCT or SOT, the risk of mycobacterial disease is many-fold greater in these transplant recipients than it is in the general population. The spectrum of mycobacterial infections associated with transplantation differs from that associated with AIDS, and infection is more often tissue-invasive. Therapy to treat NTM disease in patients who have received a transplant is complicated by the possibility of drug interactions between antimycobacterial and immunosuppressive agents, and, also, by the possibility of allograft rejection or worsening graft-versus-host disease as the result of reduction in immunosuppression during NTM therapy. As in our patient, these factors may contribute to the morbidity or mortality of NTM infections in these highly susceptible hosts.

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