Nontuberculous Mycobacterial Disease in Transplant Recipients

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Introduction

Nontuberculous mycobacteria (NTM) include over 170 species and subspecies many of which have been reported to cause disease in transplant recipients. The frequency of NTM disease among transplant recipients varies from center to center ranging from 1.4% to 22.4% [1–4] among lung transplant recipients; however, actual NTM disease occurs in less than 5% of patients [1, 2, 4]. Posttransplant infection can occur through several ways including reactivation of prior infection, donor-derived infection, contamination at the time of transplant, or posttransplant environmental contamination. The most common site of infection is the lung although these nearly ubiquitous mycobacteria can produce disease at any site in immunocompromised individuals, so a high index of suspicious is necessary in order to make an early diagnosis and initiate appropriate therapy promptly [5]. Treatment of NTM is complicated because of the multiple drugs required for treatment, drug-related toxicity, potential for drug-drug interactions, and long duration of therapy. Untreated NTM can produce significant morbidity and mortality with outcomes varying by mycobacterial species, drug resistance patterns, and type of transplant. This chapter will review the diagnosis and treatment of NTM disease among transplant candidates and recipients.

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Epidemiology

The prevalence of NTM disease in the general population is increasing in many areas [6–10]. However, lack of mandated reporting and difficulty in distinguishing clinically significant disease from colonization or indolent infection make the prevalence of NTM disease hard to determine. The prevalence of NTM disease in transplant recipients is equally difficult to establish although case series and retrospective cohort studies have provided estimates of the prevalence of disease in this high-risk population.

The proportion of mycobacterial infections due to NTM varies depending on the prevalence of tuberculosis (TB). Among 7342 solid organ transplant (SOT) and 1266 hematopoietic stem cell transplant (HSCT) recipients at a center in South Korea where TB is prevalent, there were 152 patients identified with a mycobacterial infection of whom 22 (15%) had NTM isolated [11]. The overall incidence of TB was 257.4 per 100,000 patient-years compared to 42.7 per 100,000 patient-years for NTM. In areas with lower rates of TB, the proportion of mycobacterial infections due to NTM is typically 80–90% [3, 12, 13].

The type of transplant is an important factor determining the risk of NTM disease with higher rates of NTM disease reported among HSCT than SOT recipients in some studies [14]. For example, in a study from South Korea, the incidence of NTM in HSCT recipients was 258.7 per 100,000 patient-years, significantly higher than that seen in SOT recipients (27.1 per 100,000 patient-years) [11].

Solid Organ Transplants

The overall incidence of NTM disease among SOT recipients varies by the type of transplant with the highest rate among lung (0.46–8.0%) [2–4, 13, 15] and heart (0.24–2.8%) [16, 17] transplant recipients followed by kidney (0.16–0.38%) [18–24] and liver transplants (0.04–0.1%) [15, 25].

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Lung Transplants

Lung transplant recipients have the highest rate of developing NTM infection after undergoing transplantation [26]. Much of the data concerning the epidemiology of NTM disease in lung transplants comes from large retrospective series, primarily from low TB prevalence areas. In general, between 3.8% and 22% of lung transplant recipients undergoing surveillance bronchoscopies have NTM isolated from bronchoalveolar lavage samples [2–4, 13]. However, most of these patients were not thought to have invasive NTM disease; only 10–14% of such patients were considered to have NTM disease [4, 27].

One of the first studies to describe the frequency of NTM in lung transplant recipients was published in 1999 and described a 12-year experience at a single center in Australia [13]. Of 261 transplants, there were 23 mycobacterial infections detected (8%) and all but two of whom had NTM isolated. The most common site of NTM disease was the lung (83%) and the most common causative organism was *M. avium* complex (MAC). Median time from transplant to diagnosis of NTM infection was 450 days and ranged between 50 and 3272 days [13]. A case series from the United States reported 34 patients with NTM disease over 7.5 years from all solid organ transplants. Nineteen occurred in lung transplants, 6 single and 13 bilateral allograft transplants [15]. The median time of occurrence was 8 months following transplantation procedure. In another series from the United States, 15 (22.4%) of 237 lung transplant recipients over a 15-year period developed NTM disease corresponding to an incidence of NTM isolation of 9 per 100 person-years and incidence rate of NTM disease of 1.1 per 100 person-years [4]. The most common NTM isolated was MAC (70%) followed by *Mycobacterium abscessus* (9%).

M. abscessus has become an increasingly common and challenging NTM infection in transplant recipients. An international survey of 31 of 62 transplant centers that responded reported that 17 of 5200 (0.33%) transplant recipients were identified to have *M. abscessus* after transplantation with two patients known to have pretransplant "colonization" [28]. Disease developed in the allograph in 12 patients, in the skin/soft tissue in 3 patients, and in both in 2 patients. Median time to diagnosis was 18.5 months, ranged between 1 and 111 months.

NTM can be isolated from 6% to 13% of patients with CF, and up to 20% of CF patients awaiting transplantation become infected [1, 29]. In several studies invasive NTM infections have been reported to occur in 0.5–3.4% of CF patients after undergoing lung transplantation [1, 28, 30]. In a review of both CF ($n = 60$) and non-CF ($n = 60$) lung transplants, mycobacteria were isolated from 7.2% and 9.1% of recipients, respectively [31]. *M. abscessus* is a particularly challenging pathogen to treat in patients with CF. Among 13 patients with pretransplant cultures positive for *M. abscessus*, all of whom met ATS criteria for disease, 3 developed posttransplant complications, and all 3 responded to treatment [32]. Survival posttransplant was 77% 1 year after transplantation, 64% at 3 years, and 50% at 5 years with no deaths related to *M. abscessus*. Additionally, there was no significant difference in survival when compared with other transplanted patients.

Other SOT

The frequency of NTM disease in other types of SOT is less common than with lung transplants. Among renal transplants, the incidence of NTM has been reported between 0.16% and 0.38% [12, 14, 15, 18–24, 33]. Of 3921 renal transplants between 1984 and 2002, 18 were identified as having mycobacterial infections after undergoing allograft transplantation, only 3 of which were due to TB. Thirteen of the patients were alive and well at a mean follow-up of 9.2 years since the infection diagnosis [12]. In Spain, between 1980 and 2000, there were 27 renal transplant patients (2.1%) with mycobacterial infections, 20 had TB, 5 had *M. kansasii*, and 2 patients had *M. fortuitum* infection [34].

The incidence of NTM infection among heart transplant recipients ranges between 0.24% and 2.8% [16, 35]. Novick and colleagues reported a 17-year experience at Stanford and noted that only 14 of 502 heart transplant recipients developed NTM infections over a mean of 3.5 years of follow-up [16]. The rate was higher among those receiving azathioprine and prednisone than cyclosporine alone. Additional heart transplant patients with pulmonary and extrapulmonary disease have been reported with various NTM species including *M. abscessus*, *M. xenopi*, and *M. scrofulaceum*. The estimates for NTM disease in liver transplants have been reported to be quite low at 0.1% [15, 25] although a recent study from Korea reported an incidence of 14.7 per 100,000 patient-years [11].

HSCT

The incidence of NTM infection among HSCT recipients has ranged from 0.4% to 4.9%; however, the reported incidence in allogenic stem cell graft recipients has been as high as 3–9.7% [36–41]. Among 6259 HSCT recipients at the University of Washington over a 20-year period, 40 were identified as having NTM infection (0.64%) of which 28 were considered to have invasive mycobacterial disease (0.44%) [37]. The median time to diagnosis was 251 days following transplantation. All three patients with definitive pulmonary disease were treated successfully.

A retrospective study from the University of Toronto reported that 4% of their 1097 allogenic HSCT patients had NTM isolated with 2.7% having NTM disease [42]. The median time to diagnosis was 343 days. All had pulmonary

NTM disease with 93% experiencing pulmonary-only involvement. In general, the rate of NTM disease in HSCT recipients has been higher than that in SOT recipients but not in all studies. A recent study from Korea reported an incidence of NTM in HSCT recipients at 258.7 per 100,000 patient-years, higher than that seen in SOT recipients (27.1 per 100,000 patient-years) [11].

Risk Factors for NTM Disease

Risk factors for development of NTM disease vary from study to study but recipients of lung transplant are at highest risk for NTM disease compared with other SOT recipients [15]. In a case-control study of 34 post-lung transplant recipients matched to 102 control patients, lung transplant was strongly associated with NTM disease (56% vs. 10%; OR 11.49) [15]. Among HSCT recipients a number of risk factors for NTM disease have been reported including a higher risk with allografts versus autografts, myeloablative versus nonmyeloablative transplants, matched unrelated donor over sibling allografts, underlying GVHD, use of steroids to treat GVHD, leukemia relapse, and the existence of bronchiolitis obliterans [36]. A recent study from Toronto reported that severe chronic graft-versus-host disease and CMV viremia were factors associated with an increased risk of NTM [42].

Immunologic Susceptibility to NTM Disease

Immunity to mycobacterial infection requires an effective interplay between the myeloid and lymphoid cells through the interleukin 12-interferon-gamma pathway [43]. A complicated cascade of events is set into effect following exposure to mycobacterial antigens, and organism-specific antigen primed T cells at the infection site orchestrate events leading to cell death of these intracellular pathogens. The critical effector cell for controlling NTM is the macrophage, which ingests mycobacteria, and once engulfed by the macrophage, the bacteria's fate is determined by the cell's state of immune activation, which is determined by interactions between cells in the TH1 pathway and their associated cytokines, particularly the IL-12/IFN-gamma axis [44]. Mononuclear phagocytes produce interleukin-12 which stimulates T cells and natural killer cells through the interleukin-12 receptor [43]. Signal transducer and activator of transcription (STAT)4 is activated leading to induction of interferon-gamma production which binds to its receptor causing activation and differentiation of macrophages [45, 46]. IFN gamma via cytokine receptor activates Janus kinase (JAK1 and JAK2) tyrosine-phosphorylation and stimulation of STAT1, which mediates activation of interferon-stimulated genes. In vitro experiments have shown that addition of IFN-γ promotes killing of microbes by upregulating T_H1 responses through neutrophils, monocytes, and macrophages [47]. IFN-γ activation of macrophages via T_H1 lymphocyte activation induces macrophages to overcome inhibition of mycobacteria containing phagolysosome maturation [48]. IFN-γ has also been noted to prime macrophages for enhanced microbial killing and activation of inflammatory response via Toll-like receptor (TRL) pathway [49, 50]. Furthermore, as a response to TLR signaling, IFN-γ alters epigenetic governance of macrophages, inducing and priming enhancers to increase transcriptional output [51].

The activated macrophages are then able to kill relatively avirulent intracellular organisms like NTM. Numerous other cytokines such as IL-18, IL-23, and IL-29, receptors like vitamin D receptor, and unidentified cofactors may also be important in garnering hosts' effective containment and elimination of immune-inflammatory response against NTM. Novel influences on macrophage lysosomal activity due to IL-12, IL-27, and STAT-3 were demonstrated by Jung et al. [52]. These adjunct cytokine and transcription signals promote enhanced trafficking of mycobacteria to lysosomes in human macrophages. This may have important implications in future approaches for effective containment of mycobacterial infection.

HIV-associated acquired immunodeficiency has demonstrated the critical role of CD4-positive T-helper lymphocytes (CD4+ cells) in maintaining host resistance to MAC and other NTM. CD4 cell decline is also associated with a cascade of dysfunction within the cell-mediated immune, or TH1 pathway, including alterations in cytokine levels and hosts' immune responsiveness [53, 54].

Interleukin-12 (IL-12) [55], IFN-γ, and tumor necrosis factor alpha are important for sustained macrophage activation and regulation of effective intracellular microbicidal activity. Reactive nitrogen and oxygen species are a family of toxic antimicrobial molecules derived from nitric oxide and superoxide, respectively. They assist in intracellular mycobacterial killing; IFN-γ is the principal cytokine in promoting nitrosative stress and bacterial cell death [56]. Recently, the important influence of restricted IFN-γ-mediated activation of pulmonary macrophages by the local suppressor of cytokine signaling (SOCS)1 was reported [57]. Additionally, this group showed that factors secreted by alveolar epithelial cells enhanced the microbicidal capacities of macrophages by mechanisms independent of reactive nitrogen species transcribed under the influence of IFN-γ; the clinical significance for such processes in physiologic clearance of environmental NTM that are routinely exposed to the human respiratory tract needs further investigation [57].

Transplant recipients are treated with immunosuppressive drugs in order to prevent and treat solid organ allograft rejection. In recipients of stem cell allograft, intragenic immune suppression is the mainstay of therapy for graft sustenance and treatment of acute or chronic graft-versus-host disease.

Immunosuppression is achieved through depleting lymphocytes, diverting lymphocyte traffic, or blocking their response pathways described above [58]. Besides the therapeutic effect of these drugs, there is also the undesirable effect of increasing the risk of infection from numerous pathogens including NTM.

Microbiology

NTM consists of over 170 species and subspecies that are found throughout the environment including from soil and water, both natural and treated. NTM are traditionally divided into two groups based on their rate of growth on subculture; rapid growers show visible growth by 7 days and slow growers after 7 days (Table 30.1). Many of these organisms have been reported to cause disease in transplant recipients. Most infections are caused by more virulent organisms such as *M. avium* complex, *M. kansasii*, and *M. abscessus*. Isolation of low-virulence mycobacteria is not uncommon, and in immunologically intact, nonsusceptible individuals, they frequently represent either laboratory/environmental contaminant or nondisease-associated colonization. However, in the setting of allogeneic transplantation, all organisms must be considered as potential pathogens until proven otherwise.

The most clinically important slowly growing NTM include *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii* although numerous other slow growers have been reported to cause disease in transplant recipients (Table 30.1). MAC currently consists of at least ten species; the most common to cause infection in humans are *M. avium*, *M. intracellulare*, and *M. chimaera* [59]. MAC isolates are usually susceptible to the macrolides like azithromycin and clarithromycin and clofazimine with variable susceptibility to rifamycins, ethambutol, amikacin, and streptomycin. *Mycobacterium kansasii* is a slowly growing organism that is considered one of the most virulent NTM. *M. kansasii* is usually susceptible in vitro to the first-line anti-tuberculosis agents except pyrazinamide as well as to the macrolides and fluoroquinolones [60–62].

Rapidly growing mycobacteria are particularly common among HSCT recipients and include *Mycobacterium fortuitum*, *Mycobacterium chelonae,* and members of the *Mycobacterium abscessus* complex. Rapid growers are more resistant to current antimicrobials than most slow growers and some species contain an erythromycin ribosomal methylase gene (*erm*) that can lead to inducible macrolide resistance [63]. *M. abscessus* is further subdivided into three subspecies (ssp) including ssp. *abscessus*, ssp. *massiliense*, and the least common ssp. *bolletii* [64, 65]. Approximately 80% of isolates of *M. abscessus* ssp. *abscessus* carry a functional *erm*(41*)* gene that results in inducible macrolide resistance in the presence of a macrolide; this resistance is not reflected by the initial 3-day in vitro MIC reported by some laboratories [63]. *M. abscessus* ssp. *massiliense* does not undergo inducible macrolide resistance as the *erm*(41) gene is nonfunctional and, hence, the disease is easier to treat [66–68]. Depending on the organism, the following antimicrobials show variable in vitro susceptibility: macrolides, aminoglycosides, clofazimine, fluoroquinolones, tigecycline, cefoxitin, and imipenem/meropenem [69].

Table 30.1 Nontuberculous mycobacteria reported to have caused disease in transplant recipients

Slowly Growing mycobacteria	Rapidly growing mycobacteria
Mycobacterium asciaticum	*Mycobacterium abscessus*
M. avium	*M. bolletii*
M. celatum	*M. chelonae*
M. genevense	*M. fortuitum*
M. haemophilum	*M. margeritense*
M. intracellulare	*M. massiliense*
M. gastri	*M. mucogenicum*
M. gordonae	*M. neoaurum*
M. kansasii	*M. smegmatis*
M. malmoense	
M. marinum	
M. scrofulaceum	
M. szulgai	
M. terrae	
M. thermoresistable	
M. triplex	
M. xenopi	

Clinical Presentation

The clinical presentation of NTM disease in transplant patients varies depending on the type of transplant, degree of immunosuppression, patient comorbidities, and species of NTM involved [70]. Patients may present with pleuropulmonary, skin and soft tissue, bone and joint, catheter-related, as well as disseminated disease [5]. Among HSCT recipients, catheter-related infections are one of the most common infections followed by skin and soft tissue infections [36–41, 71, 72]. In lung transplant recipients, pleuropulmonary infections are most common ranging from 54% to 82% followed by skin and soft tissue infections [14, 73]. Cough and sputum production are common and more common in transplant recipients with NTM than TB. Skin, soft tissue, and disseminated infections are the most common types of NTM infections in heart and kidney transplants.

Time to presentation varies between types of transplants and tends to be longer for NTM than TB. A recent study from South Korea reported a median time to diagnosis of 24.2 months for NTM and 8.5 months for TB. For HSCT recipients the median time to presentation is 5 months and over 10 months for SOT [70]. Among SOT patients, the median time to diagnosis has ranged from 15 to 30 months for heart, 20 to 24 months for kidney, 15 months for lung, and 10 months for liver transplants [5, 33, 70].

Pulmonary Disease

Pleuropulmonary disease is the most common presentation in lung transplant recipients but occurs in other transplants as well [74]. In fact, pleuropulmonary infections account for about one-third of NTM infections in recipients of HSCT with MAC being the most common causative organism. Cough, with or without sputum production, is the most prominent symptom although weight loss, fatigue, hemoptysis, night sweats, dyspnea, and chills also occur [75]. Chronic lung disease is a well-recognized predisposing factor in immunosuppressed patients, including transplant recipients. The radiographic features suggestive of pulmonary NTM include small nodules, tree-in-bud opacities, and/or small cavitary lesions with bronchiectasis [2]. Infections due to *M. kansasii* frequently involve the upper-lung lobes, and thin-wall cavities are seen commonly. Other pleuropulmonary manifestations include empyema as well as chest wall and surgical wound infections [76].

Skin, Soft Tissue, and Musculoskeletal Infections

While most NTM disease affects the lung in lung transplant recipients, skin and soft tissue infections are also a major concern post surgically [4, 13, 25, 33, 77, 78]. In one series, 4 of the 53 lung transplant patients had soft tissue infections (3 with *M. abscessus* and 1 with *M. chelonae*) and 1 died from progressive disseminated disease [4]. Typical findings include painful to minimally painful erythematous to violaceous subcutaneous nodules usually on the extremities or near the site of surgical wounds [4, 77]. Lesions will often ulcerate and may follow lymphatic distribution resembling sporotrichosis. The most common species to cause skin and soft tissue involvement are the rapidly growing mycobacteria and *Mycobacterium marinum* [33, 79].

M. fortuitum produces skin and soft tissue infection in immunologically competent patients; most infections occur due to accidental inoculation. In transplant recipients, surgical sites and scars may become sites of infection. Most infections due to *M. chelonae* are seen in patients with underlying predisposing conditions such as chronic corticosteroid use, rheumatoid arthritis, lupus, and cancer [80, 81], while *M. abscessus* has notably caused surgical infections surrounding transplant sites [25, 77, 82]. Health-related infections occur sporadically and have been seen in patients after deep intramuscular injection, sternal wound infection following cardiac surgery, and after a variety of reconstructive and plastic surgical procedures including augmentation mammoplasty and chest wall reconstruction after tumor resection [83].

Musculoskeletal infections may present as septic arthritis, tenosynovitis, or osteomyelitis. These infections may involve noncontiguous sites due to disseminated disease. In one review of NTM in SOT recipients, 67% presented with soft tissue and musculoskeletal involvement with over 50% involving noncontiguous sites [25].

Catheter-Related Infections

Catheter-related infections have become the most common healthcare-related infections due to RGM with most infections occurring in patients with long-term indwelling intravascular catheters. In immunosuppressed patients, *M. chelonae* and *M. abscessus* are among the most common NTM isolates [84]. RGM species are increasingly reported in immunosuppressed patients with catheter-related infection and include uncommon NTM like *M. smegmatis* [85], *Mycobacterium neoaurum* [86], *Mycobacterium aurum* [87], *Mycobacterium lacticola* [88], and *Mycobacterium brumae* [89]. Catheter-related infections are the most commonly encountered infectious complication in HSCT recipients accounting for approximately one-third of all NTM infections in this setting and most are due to rapidly growing NTM. Median time to presentation is approximately 2 months [37]. It is important to emphasize that RGM are frequently isolated in hospital and laboratory water supplies, and numerous pseudo-outbreaks involving contaminated blood culture materials and fiberoptic bronchoscope sterilizing machine contamination have been described [90, 91].

Disseminated Disease

Disseminated disease has been reported with all types of SOT but is most common in kidney and heart transplant recipients [14, 25, 77, 92]. In some series, approximately half of patients with pulmonary disease have evidence of dissemination [14, 33]. Disseminated disease can involve almost any body site including skin, soft tissues, musculoskeletal sites, lymph nodes, blood, bone marrow, and lung. Patients may present with fever of unknown origin often with subcutaneous nodules. The rapidly growing mycobacteria are the most common species to disseminate followed by *M. kansasii* and *M. haemophilum*.

Diagnosis

Clinical Diagnosis

The diagnosis of pulmonary disease is based on the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) criteria (Table 30.2), which involve the assessment of clinical, radiographic, and microbiological factors [69]. Given the variable clinical presentation noted in transplant recipients with NTM disease, the clinician should have a high index of suspicion and send appropriate clinical specimens for culture and histopathologic examination.

Table 30.2 Clinical and microbiologic criteria for diagnosing nontuberculous mycobacterial lung disease [69]

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

Typical chest computed tomography findings of NTM pulmonary disease include the presence of bronchiectasis and centrilobular nodules with a tree-in-bud appearance [5, 70]. In the transplant setting, bronchiolitis obliterans and rejection may produce similar findings although the presence of nodules is more suggestive of NTM disease [93].

Laboratory Diagnosis

Laboratory diagnosis of NTM disease is based on isolation of these organisms from culture of clinical specimens. Both solid and broth media are recommended for growth of mycobacteria [69]. Slow-growing mycobacteria (SGM) take between 3 and 8 weeks to grow, whereas in the case of rapidly growing mycobacteria (RGM) growth often becomes evident within 7 days on subculture. Some organisms such as *M. genavense* can take up to 12 weeks of incubation to detect growth. For most NTM species, the optimal temperature for growth is 28 to 37 °C, although some species require either higher or lower temperatures for optimal growth. Specimens obtained from cutaneous sites should be incubated at 35 and 28–32 °C. In addition, some fastidious species such as *M. haemophilum* require addition of hemin or ferric ammonium citrate for growth.

The clinical usefulness of antimicrobial drug susceptibility testing remains unclear because of the lack of correlation between the in vitro activity of some antimycobacterial drugs and clinical outcomes. A broth-based culture method with both microdilution and macrodilution methods is considered acceptable for testing against MAC[69]. Initial isolates and treatment failures should be tested against clarithromycin because of the good correlation between identification of macrolide resistance and poor treatment outcomes. Recent studies also suggest correlation between amikacin and treatment outcomes with an MIC >64 ug/ml associated with lack of microbiologic response [94]. Isolates of *M. kansasii* should be tested for susceptibility to rifampin and if resistant, additional drugs should be tested such as macrolides and fluoroquinolones [69]. For rapidly growing mycobacteria, broth microdilution minimal inhibitory concentration determination is recommended [69].

Molecular methods such as gene sequencing and line probe assays are becoming increasingly available for rapid speciation and even identification of genetic mutations that confer drug resistance. A line probe assay is commercially available (Hain, Germany) that can detect several common NTM species and identify mutations which cause macrolide and aminoglycoside resistance [95]. While whole genome sequencing is the gold standard, the test remains expensive and not widely available.

Treatment

Treatment of NTM disease requires a multidrug regimen in order to achieve cure and prevent the emergence of resistance. In addition, surgical excision/debridement may be required in extrapulmonary disease and in some cases lessening of the immunosuppressive regimen is required [74]. The optimal combination of drugs (Table 30.3) and duration of therapy are not known for any NTM species. Given the high recurrence rate seen in non-immunosuppressed patients, the current ATS/IDSA recommendation to treat pulmonary NTM disease for 12 months of negative cultures should be considered the minimal duration [69]. Cutaneous and disseminated disease should be treated for a minimum of 6 months although longer durations may be required depending on the infecting species, site of disease, resistance pattern, and response to therapy [70]. Treatment of catheter-related infections includes prompt removal of infected devices and combination antimicrobial therapy for a minimum of 6–12 weeks [70]. Prolonged therapy greater than 12 weeks may be necessary depending on the infecting organism and clinical response to treatment. Lessening of immunosuppression increases the risk of solid organ graft rejection, stem cell graft compromise or graft loss, and potential worsening of graft-versus-host disease. Unlike patients with HIV/AIDS, immune reconstitution syndrome has not been a concern in transplant population.

As in non-immunosuppressed patients, isolation of an NTM from a clinical specimen does not necessarily indicate

Table 30.3 Commonly used drugs for nontuberculous mycobacterial infections

Drug	Route of administration	Dosage	Adverse reactions
Amikacin	Intravenous	10–15 mg/kg once daily or 15–25 mg/kg three times weekly	Nephrotoxicity, auditory-vestibular toxicity
Azithromycin	Oral	250–500 mg daily	Nausea, vomiting, diarrhea, auditory-vestibular toxicity Prolonged QT
Cefoxitin	Intravenous	50 mg/kg/dose 2–3 times daily	Fever, rash, cytopenias
Clarithromycin	Oral	500 mg twice daily	Hepatitis, taste disturbance, inhibits metabolism of rifabutin
Clofazimine	Oral	100 mg once daily	Discoloration of skin, enteropathy, nausea, vomiting, prolonged QT
Ethambutol	Oral	15 mg/kg/dose once daily	Optic neuritis, peripheral neuropathy
Imipenem	Intravenous	500–1000 mg 2–3 times daily	Nausea, vomiting, diarrhea, hepatitis, fever, rash
Isoniazid	Oral	5 mg/kg/dose once daily	Hepatitis, peripheral neuropathy
Linezolid	Oral, intravenous	600 mg once or twice daily	Cytopenias, peripheral neuropathy, optic neuritis
Minocycline	Oral	100 mg twice daily	Photosensitivity, nausea, vomiting, diarrhea, vertigo, tooth discoloration
Moxifloxacin	Oral	400 mg daily	Nausea, vomiting, diarrhea, insomnia, agitation, tendonitis, photosensitivity, prolonged QT
Rifabutin	Oral	300 mg daily	Cytopenias, orange discoloration of fluids, hepatitis, nausea, vomiting, diarrhea, hypersensitivity/flu-like syndrome, increased metabolism of many drugs, uveitis for rifabutin
Rifampin	Oral	600 mg daily	Cytopenias, orange discoloration of fluids, hepatitis, nausea, vomiting, diarrhea, hypersensitivity/flu-like syndrome, increased metabolism of many drugs
Tigecycline	Intravenous	50 mg once or twice daily	Nausea, vomiting, diarrhea, pancreatitis, hypoproteinemia, hepatitis
Trimethoprim-sulfamethoxazole	Oral	10–20 mg/kg/dose twice daily	Nausea, vomiting, diarrhea, cytopenia, fever, rash

that treatment is required. Studies in lung transplant recipients have reported that 75% or more of patients who have NTM isolated from the respiratory tract are "colonized" [2, 4, 26]. Repeated isolation of a more virulent species is more suggestive of NTM-related disease although in extrapulmonary disease it may not be possible to obtain additional samples for culture.

Despite the difficulties faced when treating NTM disease, most patients who have developed NTM disease after undergoing transplantation have survived and been cured with less than 5% of deaths related to the NTM disease. However, in many cases, treatment is prolonged and requires surgical debridement, and adverse reactions including hearing loss in those receiving aminoglycosides are common [33]. Consultation with an expert in the treatment of NTM disease is advised.

Slowly Growing NTM

Mycobacterium avium Complex

The ATS/IDSA recommend treatment with three to four drugs depending on the radiographic extent of disease (Table 30.4) [69]. For immunocompetent patients with nodular lung disease and bronchiectasis, three times weekly dosing of clarithromycin (1000 mg) or azithromycin (500 mg), ethambutol (25 mg/kg), and rifampin (600 mg) are recommended. However, for fibrocavitary or severe nodular/bronchiectatic disease, or in the transplant setting, medications should be administered daily instead of three times weekly with adjustment in doses where necessary (clarithromycin 500–1000 mg/day or azithromycin 250–500 mg/day, ethambutol 15 mg/kg per day, and rifampin 10 mg/kg per day (maximum 600 mg) or rifabutin 150–300 mg/day). For patients with cavitary changes or other severe forms of infection, amikacin or streptomycin given intravenously or intramuscularly at a dose of approximately 15–25 mg/kg three times weekly is recommended for the first 2–3 months [69]. Because of drug interactions (described below), rifabutin and azithromycin are preferred over rifampin and clarithromycin, respectively.

In the transplant setting, there are no specific recommendations for the duration of therapy. For pulmonary disease, the patient should be treated for at least 12 months of negative cultures although longer durations may be needed in transplant recipients. Patients are considered treatment failures if

Table 30.4 Treatment regimens for nontuberculous mycobacterial infections in transplant recipients

Organism	Example regimens	Dose	Alternative
M. avium complex *(noncavitary)*	Azithromycin Rifabutin Ethambutol	250–500 mg daily 300 mg daily 15 mg/kg daily	Moxifloxacin 400 mg daily Clofazimine 100 mg daily
M. avium complex *(cavitary)*	Azithromycin Rifabutin Ethambutol Amikacin	250–500 mg daily 300 mg daily 15 mg/kg/day per day 10–15 mg/kg once daily or 15–25 mg/kg three times weekly	Moxifloxacin 400 mg daily Clofazimine 100 mg daily
M. haemophilum	Azithromycin Rifabutin Moxifloxacin	250–500 mg daily 300 mg daily 400 mg daily	Ethambutol 15 mg/kg daily Clofazimine 100 mg daily
M. kansasii	Isoniazid Rifabutin Ethambutol	300 mg daily 300 mg daily 15 mg/kg per day	Azithromycin 250–500 mg daily Moxifloxacin 400 mg once daily Clofazimine 100 mg daily
M. marinum	Azithromycin Ethambutol	250–500 mg daily 15 mg/kg per day	Rifabutin 300 mg daily Moxifloxacin 400 mg daily Trimethoprim-sulfamethoxazole DS twice daily Doxycycline 100 mg twice daily Minocycline 100 mg daily
M. abscessus spp. *abscessus or bolletii*	Azithromycin Imipenem Amikacin Clofazimine	250–500 mg daily 500–1000 mg 2–3 times daily 10–15 mg/kg once daily or 15–25 mg/kg three times weekly 100 mg daily	Cefoxitin 12 gm in divided doses 3–4 times daily Tigecycline 50 mg 1–2 times daily Linezolid 600 mg 1–2 times daily
M. abscessus spp. massiliense	Azithromycin Imipenem Amikacin	250–500 mg daily 500–1000 mg 2–3 times daily 10–15 mg/kg once daily or 15–25 mg/kg three times weekly	Cefoxitin 12 gm in divided doses 3–4 times daily Clofazimine 100 mg daily Tigecycline 50 mg 1–2 times daily Linezolid 600 mg 1–2 times daily
M. chelonae	Azithromycin Imipenem Amikacin	250–500 mg daily 500–1000 mg 2–3 times daily 10–15 mg/kg once daily or 15–25 mg/kg three times weekly	Clofazimine 100 mg daily Tigecycline 50 mg 1–2 times daily Linezolid 600 mg 1–2 times daily
M. fortuitum	Imipenem Moxifloxacin Trimethoprim-sulfamethoxazole DS	500–1000 mg 2–3 times daily 400 mg daily 1 table twice daily	Cefoxitin 12 gm in divided doses 3–4 times daily Tigecycline 50 mg 1–2 times daily Doxycycline 100 mg twice daily Minocycline 100 mg twice daily Linezolid 600 mg 1–2 times daily

they have not responded after 6 months of appropriate therapy or achieved culture negativity of sputum after 12 months of therapy. Common factors in such patients include medication nonadherence, the use of inadequate regimens (e.g., clarithromycin with a fluoroquinolone only), and emergence of macrolide-resistant MAC isolates. Use of a macrolide alone or in combination with a fluoroquinolone is not recommended due to poor response and the frequent emergence of resistance [96, 97].

Mycobacterium kansasii

The ATS/IDSA guidelines recommend a daily three-drug regimen of isoniazid, rifampin, and ethambutol (Table 30.4) [69]. Although the role of isoniazid in this regimen is not clear (the MICs are 100x higher than with MTB), excellent results have been obtained in clinical studies using this regimen [60, 61]. Clarithromycin is highly active against *M. kansasii*, and clarithromycin-containing regimens have been associated with good treatment outcomes [98–100]. Rifabutin and azithromycin are preferred over rifampin and clarithromycin, respectively, because of drug interactions with some immunosuppressive medications.

The recommended duration of treatment is 12 months of negative cultures, although good results with 12 months of therapy have been reported [61]. As with MAC, a longer duration may be appropriate in the transplant setting but this has not been studied. Other drugs usually given in three-drug combinations are effective for the retreatment of disease that has become resistant to rifampin; they include macrolides, fluoroquinolones, trimethoprim/sulfamethoxazole, streptomycin, and amikacin [69]. At least in non-transplant populations, relapse after treatment with rifampin-containing regimens is uncommon.

Other Slow-Growing Mycobacteria

A number of other slowly growing mycobacteria have been reported to cause NTM disease in transplant recipients (Table 30.1). A detailed discussion of the treatment of these less common NTM is beyond the scope of this chapter. However, a few comments regarding treatment of *M. haemophilum* and *M. marinum* follow. *M. haemophilum* has been almost exclusively seen in patients with severe immune dysfunction either due to HIV-associated AIDS or in recipients of hematopoietic stem cell transplantation [101]. Disseminated infections are reported and predilection for tendon sheaths, bone, and joints is similar to infections seen with RGM. Drug susceptibility testing is not standardized and the correlation between susceptibility test results and clinical outcomes is uncertain. Current recommendations are to treat with a fluoroquinolone, macrolide, and rifamycin which has led to successful treatment (Table 30.4) [69, 102].

M. marinum is a slowly growing mycobacteria found in aquatic environments. Infection usually occurs when traumatized skin is exposed to water containing the organism. At least seven cases of *M. marinum* have been reported in transplant recipients including both SOT and HSCT patients [79, 103, 104]. Most have presented with erythematous tender cutaneous nodules on the extremities after exposure to fish tanks. Treatment regimens have included combinations of macrolides, rifamycins, fluoroquinolones, and cycline derivatives with cure in most patients including a patient with disseminated disease. The ATS currently recommends treatment of cutaneous disease with two active agents for approximately 1–2 months after resolution of the nodules (Table 30.4) [69]. However, most transplant recipients have been treated successfully for 3–9 months with one relapse after 6 months of ciprofloxacin and ethambutol.

Rapidly Growing NTM

M. abscessus Complex

Combination therapy including intravenous agents is necessary for clinically significant disease. Drug combinations including oral azithromycin, clofazimine, or linezolid/tedizolid plus intravenous cefoxitin, imipenem, tigecycline, or amikacin can be successful; however, refractory *M. abscessus* infections are common and remain difficult to treat (Table 30.4) [69]. Patients are begun on three or four of the above antibiotics during an initial multidrug intensive phase including intravenous antibiotics that are usually transitioned to a multidrug regimen of oral and possibly inhaled antibiotics. Long-term sputum conversion is difficult to achieve in patients with *M. abscessus ssp abscessus* lung disease with a functional *erm*(41) gene [68, 105, 106]. Sputum conversion rates among nonimmunocompromised patients with pulmonary disease due to *M. abscessus* ssp *abscessus* have been approximately 25% [66–68]. However, in patients infected with subspecies *M. massiliense* that lacks a functional *erm*(41) gene, culture conversion rates have reached over 80%. Among 16 patients with *M. abscessus* following lung transplantation that were treated, 11 (73%) had a radiographic or microbiologic response to treatment and 10 were considered cured [28]. Death was attributed to *M. abscessus* in two patients. Of note, the strains were not subspeciated so some patients may have been infected with the easier-to-treat *M. massiliense*.

M. chelonae

Mycobacterium chelonae causes skin and soft tissue disease similar to that of *M. abscessus* [69]. Unlike *M. abscessus* and *M. fortuitum*, *M chelonae* does not carry an *erm* gene and therefore effective therapy with a macrolide-based regimen may be more obtainable in these individuals [63]. *M. chelonae* is typically susceptible to macrolides, clofazimine, and tobramycin and resistant to cefoxitin with variable activity to fluoroquinolones, doxycycline, linezolid, and imipenem [81, 107]. Treatment usually involves a combination of three of the antibiotics above (Table 30.4).

M. fortuitum

Mycobacterium fortuitum is a rapid grower similar to *M. abscessus* and *M. chelonae*. It is a rare cause of lung disease, sometimes identified in patients with achalasia and other gastroesophageal reflux disorders [69, 108]. *M. fortuitum* isolates are usually susceptible to fluoroquinolones, doxycycline and minocycline, sulfonamides and trimethoprim/sulfamethoxazole, amikacin, imipenem, and tigecycline, and approximately one-half of the isolates are susceptible to cefoxitin [81, 107, 109]. Like *M. abscessus*, most *M. fortuitum* isolates have a functional *erm* gene so macrolides should not be counted on to treat this infection. Multidrug therapy with agents shown to be susceptible in vitro should be given for 12 months or until clinical resolution of the disease (Table 30.4).

Drug Interactions

Significant drug-drug interactions may occur between antimycobacterial drugs and immunosuppressive drugs used to prevent rejection (Table 30.5). Rifampin is a potent inducer of the CYPA3A4 pathway and thus can decrease the serum concentrations of calcineurin inhibitors and mTOR inhibitors such as sirolimus [70, 77]. Use of rifampin has been associated with acute rejection rates as high as 35% [110, 111]. Rifabutin, which is a less potent inhibitor of cytochrome p450, is the preferred rifamycin in these settings. Clarithromycin is an inhibitor of the CYP3A4 pathway and p-glycoprotein and thus raises the concentration of calcineurin and m-TOR inhibitors. In order to avoid this drug interaction, azithromycin is recommended over clarithromycin.

Table 30.5 Drug interactions between antimycobacterial and antirejection drugs[a]

Antibiotic class/ antibiotics	Cyclosporine	Sirolimus/everolimus	Tacrolimus
Azalide/macrolide			
Azithromycin	Possible mild increase in cyclosporine levels	No significant interaction	Possible mild increase in tacrolimus levels
Clarithromycin	Increase in cyclosporine levels	Increase in sirolimus/everolimus levels	Increase in tacrolimus levels
Fluoroquinolones			
Ciprofloxacin	No significant interaction	No significant interaction	No significant interaction
Levofloxacin	Possible mild increase in serum concentration	No significant interaction	No significant interaction
Moxifloxacin	No significant interaction	No significant interaction	No significant interaction
Rifamycins			
Rifampin	Decrease in cyclosporine levels	Decrease in sirolimus/everolimus levels	Decrease in tacrolimus levels
Rifabutin	Mild decrease in cyclosporine levels	Mild decrease in sirolimus/ everolimus levels	Mild decrease in tacrolimus levels

[a]Serum drug concentrations should be measured and doses adjusted as needed to effectively treat the NTM infection and avoid rejection or drug-related toxicity

Because of the many potential drug interactions, therapeutic drug monitoring should be strongly considered in order to maintain adequate serum drug concentrations and avoid unwanted toxicity [33].

When rifamycin is not used, an alternative drug should be selected. Studies in nontransplant populations have reported similar microbiologic outcomes in patients receiving a three-drug regimen including clofazimine instead of rifampin [112], and there is some evidence of activity in patients with refractory disease [113, 114]. A small study in five SOT patients reported good tolerance to clofazimine [115] although one pediatric bone marrow transplant patient has been reported to have developed an enteropathy [116].

Monitoring for Adverse Reactions and Treatment Response

Multidrug treatment regimens used for NTM infections are frequently associated with drug-related adverse events so monitoring of patients for toxicity is essential. The most common adverse reactions associated with antimycobacterial agents are included in Table 30.3. Transplant patients are often on other drugs that could have overlapping toxicities with antimycobacterial drugs; thus, close monitoring for adverse reactions is even more critical in this population. All patients who are being treated for NTM disease should have periodic assessment of complete blood counts, liver function tests, and creatinine. For patients receiving ethambutol or linezolid, a baseline assessment of visual acuity and color discrimination testing are recommended with periodic reassessments during the course of therapy. In addition, a baseline audiogram is needed for patients on an aminoglycoside and should be repeated during the course of treatment.

Response to treatment should be documented through periodic clinical, radiographic, and microbiologic evaluations. For pulmonary disease, treatment duration is based on the time of culture conversion so monthly cultures should be obtained to document the time of conversion. For patients with extrapulmonary disease, clinical and radiographic evaluation are most critical as resampling of extrapulmonary sites may not be possible or practical.

Survival

The impact of NTM infections on survival has varied between studies although in most the direct impact has been minimal. In a cohort of 237 lung transplant recipients from a center in the United States, NTM infection was not associated with an increased mortality [4]. In a retrospective cohort study to evaluate the impact of NTM on survival, 33 patients with NTM infection post-SOT were evaluated [92]. Surprisingly, there was not an increased mortality in patients with *M. abscessus* disease compared with other NTM disease. However, development of NTM infection during the first year after transplantation was strongly associated with decreased survival, independent of organ type. NTM infection was considered a contributing cause of death in only three of the nine patients whose death certificates were available for review. A recent study from a large Midwestern center reported that among 3338 SOT recipients, 50 (1.5%) had NTM infection, 43 of whom were lung transplant recipients. However, NTM infection was not associated with mortality in infected lung transplant recipients versus those not infected although NTM disease was associated with increased mortality compared with colonization in lung transplant recipients [26]. There was no difference in survival between NTM-infected

and NTM-uninfected lung transplant recipients: the former were more likely to develop bronchiolitis obliterans (80 vs. 52%, $p = 0.02$) although this finding was not noted in multivariate analysis. One study reported that NTM colonization and NTM pulmonary disease increased the risk of death after lung transplantation although NTM pulmonary disease was not considered the direct cause of disease [2]. The increased risk of death persisted even after adjusting for single-lung transplantation and presence of bronchiolitis obliterans.

Isolation of NTM Before Transplantation

Isolation of NTM during pretransplant period is not uncommon in patients undergoing lung transplant given their underlying lung disease, and pretransplant isolation of NTM has been associated with a greater risk of NTM disease after undergoing transplantation [1]. The International Society for Heart and Lung Transplantation (ISHLT) states that "chronic infection with highly virulent and/or resistant microbes that are poorly controlled pretransplant" is an absolute contraindication for transplantation [117]. However, "colonization or infection with highly resistant or highly virulent bacteria, fungi, and certain strains of mycobacteria…" is considered a relative contraindication. Furthermore, infection with multidrug resistant *M. abscessus* is considered a relative contraindication if the infection is "sufficiently treated" preoperatively and there is a reasonable expectation for adequate control postoperatively. Unfortunately, none of these recommendations provide clear guidance to providers or patients as it is difficult to distinguish "colonization" from indolent infection and active disease and sufficiently treated are not defined.

NTM are commonly isolated in patients with CF but the risk of NTM infections posttransplantation is not well defined. The Cystic Fibrosis Foundation (CFF), European Cystic Fibrosis Society (ECFS), and the ISHLT recommend that individuals with CF who are being considered for lung transplantation be evaluated for NTM pulmonary disease and the presence of current or previous history of respiratory tract samples with NTM should not preclude consideration for transplantation [117, 118]. Those who are found to have NTM lung disease should be started on treatment prior to transplant listing, and once they have achieved sequential negative cultures, they should be considered eligible for transplantation. This includes patients who have completed therapy. ISHLT states that progressive pulmonary or extrapulmonary disease secondary to NTM despite optimal therapy or an inability to tolerate optimal therapy is a contraindication for transplant listing; however, the CFF and ECFS state that even if the NTM cannot be cleared from the respiratory tract, this is not an absolute contraindication for transplant in patients with CF [118, 119]. Isolation of NTM prior to HSCT is also not a contraindication to transplant as patients have been successfully transplanted [14].

Prevention

Recent outbreaks of NTM infections in transplant patients and patients who have undergone cardiac surgery have highlighted the potential for nosocomial acquisition of NTM [120, 121]. Most nosocomial infections can be traced back to contamination with tap water containing NTM, so avoidance of tap water during and after transplantation surgery is critical. Person-to-person transmission of *Mycobacterium abscessus* ssp. *massiliense* may have occurred among patients with CF as described in two CF clinics in the United States and United Kingdom [122, 123], and a recent study suggested global transmission of two clones of *M. abscessus* and one of *M. massiliense* among CF patients [124]. To date, person-to-person transmission of NTM has not been described in other settings. Because of the possibility of transmission among CF patients, current CF foundation infection control and prevention guidelines should be adhered to [125].

Effective chemoprophylactic treatment including azithromycin, clarithromycin, and rifabutin has been demonstrated through randomized clinical trials to prevent disseminated MAC in advanced AIDS patients [126, 127]. Not surprisingly, some physicians have called for posttransplant prophylaxis with azithromycin for CF patients "colonized" with rapidly growing mycobacteria [77]. However, there is no evidence to support this practice and it is unlikely to be effective given the presence of an *erm*(41) gene in most *M. abscessus* complex strains. Multidrug treatment regimens to decrease the bacterial load as much as possible are likely to be more effective at preventing development of NTM disease in the posttransplant setting.

Summary

Nontuberculous mycobacteria (NTM) are common in the environment, being most often associated with soil and water sources. NTM isolation does not always portray clinically significant disease, albeit, in patients with severe immune dysfunction following allogeneic transplantation, these near-ubiquitous environmental bacteria may lead to serious and potentially life-threatening systemic disease. The true prevalence of NTM among transplant recipients is largely unknown. Correct laboratory identification of NTM species, adequate genetic analysis, and susceptibility testing are essential for identification of mycobacteria and are necessary in assembling effective antimicrobial treatment regimens. Reference laboratory evaluation may be required depending

on local laboratory capabilities. Antibiotic regimens are chosen according to NTM species, site of infection, and drug susceptibility profile, which can vary greatly according to the NTM species isolated. The treatment of NTM involves multiple antibiotics given for a prolonged period of time and is often accompanied by side effects and drug-drug interactions, especially in transplant patients on antirejection drugs and other agents given for suppressing hosts' immune response for prevention or treatment of graft-versus-host disease. Treatment by experienced NTM physicians is often necessary. It is essential for transplant providers to maintain a low index of suspicion in order to promptly and correctly diagnose NTM infections in the susceptible transplant population and provide host- and pathogen-specific treatment options.

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