Nontuberculous Mycobacterial Pulmonary Infections in Non-HIV Patients

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Julie V. Philley, MD, and David E. Griffith, MD

INTRODUCTION

Nontuberculous mycobacteria (NTM) are a diverse group of predominantly environmental organisms. A minority of the approximately 160 identified NTM species, perhaps 20% to 25%, have the potential to be human pathogens, and of those, *Mycobacterium avium* complex (MAC), *M. abscessus*, and *M. kansasii* are the most commonly isolated NTM species associated with clinically significant human disease in North America.1

The prevalence of NTM lung disease cases is rising and far exceeds the incidence of disease caused by *Mycobacterium tuberculosis* in the United States.2 This growing disparity is a reflection of multiple factors including improved tuberculosis control measures, increased awareness of NTM lung disease by clinicians, and advances in laboratory isolation and identification of NTM. As there is no mandatory reporting related to NTM disease, the incidence of NTM pulmonary infections can only be estimated, but the evidence suggesting that NTM lung disease prevalence is increasing is consistent and compelling.2,3

Caution must be exercised when comparing NTM lung disease with tuberculosis. While there are similarities in that both NTM and tuberculosis are associated with granulomatous inflammation and chronic progressive pneumonia, the differences are even more important, especially from a therapeutic perspective. Several of these differences are emphasized in the following discussion. In general, however, NTM lung disease is much more difficult to diagnose and treat than tuberculosis. This article describes pulmonary NTM with a focus on treatment of the most commonly encountered pathogens.

EPIDEMIOLOGY

NTM are ubiquitous in the environment, often isolated from soil and water, including household water sources. There is increasing concern that biofilms that form in municipal and household water supplies may be a significant harbor for NTM and the source of NTM for lung disease in some patients.4–6 Biofilms allow NTM to adhere and live on artificial surfaces, and also provide...
a protective shield against disinfectants. Biofilms have been identified as important sources of nosocomial infections and pseudo infection associated with bronchoscopes, endoscope washers, ice machines, and other instruments that use nonsterile tap or distilled water.

*M. avium*, *M. kansasii*, *M. simiae*, and *M. xenopi* are readily recovered from tap water in areas where these species are common. The incidence of NTM in the United States (predominantly MAC, *M. kansasii*, and more rarely *M. abscessus*) has been associated with specific geographical areas, which may be related to differing water supplies. Early skin test studies in adults indicate that a substantial proportion have had prior infection with NTM, notably in the southeastern United States.

While MAC species can be recovered readily from municipal plumbing sources, the direct connection to individuals with NTM lung disease has been difficult to document. For instance, a recent study showed that the household water of patients with MAC thought to contain *M. intracellulare* did not contain that species but actually contained other species of MAC, including predominantly *M. chimaera* (73%) and other MAC-X species (20%), even though the majority of patients in the study were infected with *M. intracellulare*. This study was the first to demonstrate the presence of *M. chimaera* in the household water of patients with MAC lung disease and emphasizes the importance of species differentiation among isolates of MAC. These studies suggest that the reservoir for *M. intracellulare* is the environment outside the home. Most laboratories do not differentiate species within the MAC complex, and the role for differentiation is currently unclear; it is very likely that in the future the identification of species within the MAC complex will be prognostically and therapeutically important.

Human-to-human transmission of NTM has been documented in only one setting, cystic fibrosis (CF) patients, with an apparently virulent strain of *M. abscessus* subsp *massiliense*. This association is clear enough to add further emphasis to the importance of respiratory separation of CF patients.

**RISK FACTORS FOR INFECTION**

The most common clinical manifestation of NTM infection is lung disease, but lymphatic, skin/soft tissue, and disseminated disease are encountered.

Lymphatic NTM disease is primarily a disease of children, while skin/soft tissue NTM infections are typically the result of penetrating trauma, including nosocomial infections associated with surgical procedures and foreign body implants. In the presence of immune compromise, both lymphatic and skin and soft tissue infection can be indicators of disseminated NTM disease. Disseminated NTM infections, primarily *M. avium*, occur in HIV-infected patients with CD4+ T-lymphocyte counts below 50/mL. Treatment of HIV-infected individuals is beyond the scope of this review.

Tumor necrosis factor-α (TNF-α) inhibitors also predispose to severe and/or disseminated NTM disease, which suggests that TNF-α is essential in the prevention of disease activation and progression. Winthrop et al published data from the U.S. Food and Drug Administration (FDA) MedWatch database of reports of NTM disease in patients receiving TNF-α blocker therapy. MAC was the most common NTM infection. Extrapulmonary disease was common (44%), and 9% of patients died. Other immunosuppressive regimens and biologic agents may increase risk but are less well defined. In addition to NTM infection, TNF-α blockers are associated with activation of *Aspergillus species*, histoplasmosis, coccidioidomycosis, listeriosis, and especially *M. tuberculosis*. Careful patient
evaluation for occult or underlying infection must be performed when utilizing TNF-α blockers.

Congenital immune deficiencies, such as chronic granulomatous disease, are associated with defects in production of interferon (IFN)-γ or interleukin (IL)-12, or defects in receptors or pathways controlling responses to IFN-γ.25,26 IFN-γ pathway defects include receptor and signaling mutations and are important given the role of macrophages in the innate immune response to NTM, with IL-12 and IFN-γ essential for intracellular killing of mycobacteria. These conditions are rare and represent a small minority of patients with NTM disease.

**CLINICAL PRESENTATION**

There are 2 distinct prototypical NTM lung disease presentations. The first is lung disease associated radiographically with nodules and bronchiectasis (nodular/bronchiectatic disease), which is typically seen in the right middle lobe and lingula of thin, white, nonsmoking postmenopausal women with underlying bronchiectasis (Figure 1). This type of lung disease has been labeled “Lady Windermere” syndrome, in reference to an Oscar Wilde play involving proper Victorian women who felt it inappropriate to exhibit a public cough. Women without obvious immune defects who have developed pulmonary nodular bronchiectatic NTM disease often have distinct body characteristics that may include scoliosis, low body mass index, pectus excavatum, mitral valve prolapse, and joint hypermobility.27,28 The relationship between these physical traits, the development of bronchiectasis, and NTM infection remains unclear. Nodular/bronchiectatic disease is most closely associated with MAC lung disease, but can be seen with essentially any NTM respiratory pathogen.

The second type of NTM lung disease occurs in individuals with chronic obstructive pulmonary disease (COPD), and is closely associated with cigarette smoking. This type of NTM lung disease is characterized radiographically by fibrocavitary upper lobe abnormalities (Figure 2), which are more typical of pulmonary tuberculosis; in fact, most of these patients are diagnosed after first being evaluated for tuberculosis. Cavitary lung disease associated with COPD patients presents formidable challenges because treatment generally requires some period of parenteral antibiotic therapy as well as consideration of adjunctive surgery (Figure 3). It is also clear that this form of disease has increased mortality compared with the nodular/bronchiectatic form of NTM lung disease,1 and requires an aggressive therapeutic approach. This form of NTM disease is most often seen with *M. kansasii*, *M. xenopi*, and MAC, although most NTM respiratory pathogens are capable of producing this radiographic pattern.
Diagnosis

The diagnosis of pulmonary NTM disease as defined in the most recent NTM diagnostic and treatment guidelines from the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) involves 3 parts: clinical, radiographic, and microbiologic. Patients are usually symptomatic, including some combination of cough, weight loss, fatigue, nights sweats, and/or hemoptysis. Characteristic radiographic changes as outlined previously should accompany these symptoms. Last, and most important, the diagnosis of NTM lung disease hinges on appropriate microbiologic findings. Two positive acid-fast bacilli (AFB) cultures for NTM from sputum samples (either expectorated or induced) or 1 positive culture from tissue biopsy or bronchoalveolar lavage usually suffices to make the diagnosis of NTM lung disease. It must be emphasized that meeting the criteria for diagnosing NTM lung disease does not necessarily require that treatment be initiated. Also, because of the wide range of virulence among potential NTM pathogens, even if some NTM species, especially those frequently associated with specimen contamination, appear to meet the microbiologic diagnostic criteria they should be viewed with skepticism as clinically significant pathogens.

Laboratory Methods

Sputum AFB cultures are typically used to identify pulmonary NTM pathogens. Sputum microscopy is still utilized worldwide, especially in developing countries, as the standard for diagnosing tuberculosis. Therefore, NTM patients in many
parts of the world go undiagnosed and are treated presumptively as tuberculosis patients.

Labor-intensive conventional identification methods using biochemical schemes and chemo-taxonomic methods such as high-performance liquid chromatography are rapidly being replaced by more rapid and definitive molecular gene sequencing or proteomic methods. The widely used AccuProbe culture identification tests (Hologic GenProbe, San Diego, CA) are nucleotide probes complementary to 16S ribosomal RNA (rRNA) and are used for species identification of only a few groups of NTM, including *M. avium*, *M. intracellulare*, MAC, *M. kansasii*, and *M. gordonae*. Another probe method is the INNO LiPA multiplex probe reverse hybridization assay (Innogenetics, Ghent, Belgium), which amplifies the 16-23S rRNA internal transcribed spacer region for species identification. The GenoType Mycobacterium assay (Hain Lifescience GmbH, Nehren, Germany) is similar to the INNO LiPA but targets the 23S rRNA gene. The advantages of these latter methods is that they identify multiple species of NTM on one probe and can identify many species that the AccuProbe cannot identify.

Proteomic methods using matrix-assisted laser desorption ionization mass spectrometry-time-of-flight (MALDI-TOF) are being used in large reference and clinical laboratories to identify some NTM, but have not yet been completely validated for many NTM species. As with molecular methods, proteomic methods require quality-controlled commercial or in-house databases for definitive identification of species. The development of a database is a labor intensive and time-consuming process requiring highly experienced technologists and is not possible without analyzing large numbers of isolates. Commercial web-based systems may facilitate sequence analysis but should be carefully checked against reference strain sequences because some systems have been slow to add newer species or changes in taxonomic states. The 16S rRNA gene is considered the most commonly sequenced gene for species identification.

The recent recognition of the possibility of interspecies gene combinations in gene sequences has necessitated the use of multi-gene–based identification and typing methods for many rapidly growing mycobacteria species or subspecies, including the *M. abscessus* group. For differentiation of the subspecies within *M. abscessus*, many advanced mycobacteriology labs recommend performance of *rpoB* gene sequencing supplemented with sequencing or PCR restriction fragment length analysis of the *hsp65* gene or PCR restriction enzyme analysis of another gene sequence such as the *erm* (erythromycin resistance methylase) gene.

**ANTIMICROBIAL SUSCEPTIBILITY TESTING**

The current Clinical and Laboratory Standards Institute (CLSI) guidelines for NTM susceptibility testing recommend the broth microdilution method for both rapidly and slowly growing NTM species. Importantly, recommended antimicrobial breakpoints are only applicable as long as CLSI standard methods are used. The expected association between in vitro antibiotic susceptibility and clinical response to many antibiotics does not exist for many NTM pathogens. For instance, macrolides and amikacin are the only 2 antibiotics used for MAC therapy where there is a clear association between in vitro susceptibility and clinical response. In vitro susceptibility results for other drugs such as rifampin, rifabutin, ethambutol, and streptomycin are not clinically useful and in vitro susceptibility testing for these antibiotics is not recommended by CLSI.
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SLOWLY GROWING MYCOBACTERIA

M. AVIUM COMPLEX

The history of therapy for MAC disease can be divided into 2 distinct time periods, the pre-macrolide and macrolide era. During the 1950s, drugs such as isoniazid, para-aminosalicylic acid, and streptomycin were the mainstay of treatment for NTM disease. The introduction of ethambutol and rifampin in the mid 1960s and early 1970s increased conversion rates, but the advent of macrolide therapy in the early 1990s improved sputum conversion to a mean of 56% in pooled studies from 1994 to 2002.37–40 The administration of clarithromycin and azithromycin alone promotes macrolide resistance, and thus multidrug therapy is standard of care.39 It is noteworthy that there still are no FDA-approved drugs for NTM lung disease.

The role of macrolides as the cornerstone of MAC therapy was reinforced by a recently published study evaluating 180 MAC lung disease patients with nodular bronchiectatic disease who were treated with macrolide-based regimens over an approximately 10-year period.41 In the study, 84% of patients achieved sputum AFB culture conversion with a 3-drug regimen including macrolide, ethambutol, and rifamycin. Most patients did not tolerate daily therapy with this 3-drug regimen but were able to tolerate 3 times weekly administration. Microbiological recurrence was common and most frequently was due to new MAC genotypes, which were interpreted as evidence of reinfection rather than as true microbiologic relapse. No patient developed macrolide resistance on the 3-drug macrolide-based regimen.

Current Treatment Regimens

The treatment regimen for upper lobe fibrocavitary disease is daily 3-drug antimicrobial therapy in combination with an injectable aminoglycoside.1 A typical regimen would include clarithromycin 500 mg orally twice daily or azithromycin 500 mg daily, ethambutol 15 mg/kg daily, and a rifamycin (either rifampin 600 mg orally daily or rifabutin 150 to 300 mg daily). The injectable aminoglycoside can be given as intramuscular (IM) or intravenous (IV) streptomycin 7 to 10 mg/kg or IV amikacin 7 to 10 mg/kg 3 times weekly, at least for the first 3 months.

The primary goal of therapy for both nodular bronchiectasis and cavitary forms of MAC is 12 months of negative sputum cultures while on therapy (Table 1).1 Patients are considered treatment failures if they have not had a response (microbiologic, clinical, or radiographic) after 6 months of appropriate therapy or achieved culture negativity of sputum after 12 months of therapy.

Nodular bronchiectatic MAC lung disease is typically treated with 3 times weekly dosing of clarithromycin 1000 mg or azithromycin 500 mg, ethambutol 25 mg/kg, and rifampin 600 mg (or rifabutin 150–300 mg), as recommended by the ATS/IDSA.1 Dosing adjustments may be required for low body weight and age. Severe cases, including reinfection or relapse, may require the addition of an injectable aminoglycoside. Inhaled amikacin may provide another option for therapy, but care should be taken to ensure that adequate companion drugs are available to prevent the emergence of amikacin resistance (see “Inhaled amikacin” below). A macrolide with ethambutol as a single companion drug may be adequate for minimal nodular bronchiectatic MAC disease if the patient is intolerant to a rifamycin (see “Two-drug therapy” below).

Cavitary MAC disease or severe nodular bronchiectatic disease is treated with a daily regimen that includes clarithromycin 500 to 1000 mg/day or azithromycin 250 mg/day, ethambutol 15 mg/kg
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per day, and rifampin 10 mg/kg per day (maximum 600 mg) or rifabutin 150 to 300 mg/day. Three times weekly therapy may be sufficient, but limited data are available. For patients with cavitary changes on either daily or 3 times weekly oral drugs, IV or IM amikacin or streptomycin at a dose of approximately 7 to 15 mg/kg 3 times weekly for at least the first 3 months is recommended. Prolonged treatment may be required. The role of inhaled amikacin in this setting is unknown.

Use of a quinolone and a macrolide without other companion drugs and macrolide monotherapy is not recommended due to poor response and promotion of macrolide resistance. Fluoroquino-

### Table 1. Treatment of Pulmonary Mycobacterium avium Complex Infection

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antimicrobial Treatment</th>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular bronchiectasis (macrolide susceptible)</td>
<td>Clarithromycin (15 mg/kg up to 1000 mg) in 2 divided doses, usually 500 mg twice a day or Azithromycin (500 mg)</td>
<td>3 times weekly</td>
<td>Negative cultures for 12 mo(^b)</td>
</tr>
<tr>
<td></td>
<td>Rifampin (600 mg) or Rifabutin (150–300 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethambutol (25 mg/kg)</td>
<td>3 times weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin (7–10 mg/kg IV or 500 mg inhaled)(^a) or Streptomycin (7–10 mg/kg IV or IM)(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavitary(^c) (macrolide susceptible)</td>
<td>Clarithromycin (15 mg/kg up to 1000 mg) in 2 divided doses or Azithromycin (250 mg)</td>
<td>Daily</td>
<td>Negative cultures for 12 mo(^b)</td>
</tr>
<tr>
<td></td>
<td>Rifampin (10 mg/kg; max 600 mg) or Rifabutin (150–300 mg)</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethambutol (15 mg/kg)</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin (7–10 mg/kg IV)(^a) or Streptomycin (7–10 mg/kg IM or IV)(^a)</td>
<td>3 times weekly</td>
<td></td>
</tr>
<tr>
<td>Nodular bronchiectasis or cavitary(^d) (macrolide resistant)</td>
<td>Rifampin (600 mg) or Rifabutin (150–300 mg)</td>
<td>Daily (all drugs)</td>
<td>Negative cultures for 12 mo(^b)</td>
</tr>
<tr>
<td></td>
<td>Ethambutol (15 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amikacin (7–10 mg/kg)(^a) or Streptomycin (7–10 mg/kg)(^a)</td>
<td>Once daily, 3 times weekly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhaled amikacin(^e)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IM = intramuscular; IV = intravenous.
\(^a\) For severe disease, reinfection or relapse cases. Dosage should be adjusted to achieve peak serum levels of 20–25 µg/mL.
\(^b\) On appropriate therapy.
\(^c\) If large cavity or treatment failure, consider surgical resection.
\(^d\) Consider early surgical resection.
\(^e\) Inhaled amikacin 500 mg daily may be considered as an adjunct.

lones have been used to treat MAC lung disease for many years, but there has been little evidence to support their use as first-line agents for treating MAC. The use of macrolide and fluoroquinolone without other companion drugs places the patient at risk for the development of macrolide-resistant MAC disease. Additionally, both drug classes are associated with a prolonged QT interval on an electrocardiogram, which may predispose to cardiac toxicity and excess mortality.42,43

Susceptibility Testing

When selecting pharmacotherapy for MAC pulmonary disease, in vitro susceptibility testing may not be a guide for effective in vivo response to antibiotics, as it is in the treatment of tuberculosis.1 Other NTM species that share this property with MAC include M. abscessus subsp abscessus, M. xenopi, M. malmoense, and M. simiae. Previous studies with MAC show a lack of correlation of in vitro minimum inhibitory concentration (MIC) to clinical response to other (antituberculous) antimicrobials including ethambutol, streptomycin, rifampin, and rifabutin. More recently, studies from Japan showed a lack of correlation between in vitro susceptibility for MAC and in vivo response to rifampin, ethambutol, and streptomycin.44,45

Until recently, for MAC there was only evidence to support a correlation between in vitro macrolide susceptibility and in vivo clinical response. Recent studies have shown, however, that clinical response for the antimicrobials amikacin and clarithromycin is correlated with in vitro susceptibility MICs for MAC.46 Both the CLSI and the ATS/IDSA recommend that new MAC isolates should be tested in vitro only for susceptibility to macrolides,1,36 although clinical regimens should include a rifamycin and ethambutol. New guidelines may also include amikacin susceptibility testing.46

Therapies Under Study

Inhaled amikacin. While treatment outcomes for MAC lung disease with standard macrolide-based regimens are generally favorable, more effective antimycobacterial agents are needed to attain better therapeutic responses. One possibility is inhaled amikacin added to multidrug treatment regimens for advanced or recalcitrant NTM lung disease. The efficacy of this strategy remains uncertain as there is little available published data.47,48

An initial trial including 6 patients suggested that inhaled amikacin might be quite effective. A more recent study evaluated inhaled amikacin to treat refractory M. abscessus and MAC patients, who were followed for a median of 19 months.48 Twenty-five percent of these patients had negative AFB cultures while receiving the inhaled amikacin. Patients had variable symptomatic and objective responses to the amikacin, and 35% stopped amikacin due to side effects or adverse events.

A multicenter prospective, placebo-controlled, blinded clinical trial investigating the addition of inhaled liposomal amikacin to a stable regimen for treatment of refractory MAC and M. abscessus lung disease was recently completed.49 After 3 months of the inhaled liposomal amikacin regimen, approximately 30% of MAC patients converted sputum to AFB culture negative. The median time to conversion was only 1 month of therapy. The placebo-controlled and blinded phase of the study was followed by an open-label phase which was associated with further sputum AFB culture conversion in patients who initially received placebo. Side effects or adverse events attributable to the drug were reported by 73% of patients, and 16% discontinued the medication because of them. In this small, preliminary study, it appears that the liposomal amikacin preparation has the potential to add significantly to the therapy of
otherwise treatment-refractory MAC lung disease patients.

**Moxifloxacin.** For patients failing standard therapy, the addition of moxifloxacin to multidrug regimens may improve long-term outcome. A recent study evaluated the effect of adding moxifloxacin in 41 MAC lung disease patients who did not have sputum conversion after at least 6 months of a macrolide-containing regimen. With a median moxifloxacin administration duration of more than 300 days, the overall treatment success rate was 29%, with a median time to sputum conversion of 91 days. A positive sputum AFB smear at the start of treatment with moxifloxacin-containing regimens was an independent predictor of an unfavorable microbiologic response. This modest outcome must be confirmed by others prior to the establishment of moxifloxacin as an effective agent for MAC lung disease.

**Two-drug therapy.** While 3-drug macrolide-based therapy with ethambutol and a rifamycin is currently recommended as “standard” MAC therapy, the efficacy of 2-drug therapy with macrolide and ethambutol has not been examined rigorously. A recent study compared a “standard” MAC treatment regimen including clarithromycin, ethambutol, and rifampin to a 2-drug regimen with just clarithromycin and ethambutol in 119 patients. The rate of sputum culture conversion after 12 months of therapy was 41% with the 3-drug regimen and 55% with the 2-drug regimen. Adverse events leading to discontinuation of treatment occurred in 37% in the 3-drug group and 27% in the 2-drug group. Macrolide resistance did not occur in either treatment arm. As is the case with the interpretation of similar uncontrolled NTM therapy studies, it is still unclear if the 2-drug regimen can be used in place of the standard 3-drug regimen for most MAC lung disease patients.

**Clofazimine.** Limited data suggests that for patients who do not tolerate rifamycins, clofazimine may provide an effective alternative, combined with ethambutol and a macrolide. A recent in vitro study showed significant synergy between amikacin and clofazimine for 16 clinical MAC isolates. The clinical significance of such synergy is not proven. For instance, it has been known for many years that the combination of rifampin and ethambutol results in synergistic killing of MAC in vitro, but there is no proven clinical consequence of that observation.

**Macrolide Resistance**

MAC strains become macrolide resistant via the selection of the 23S rRNA gene. Macrolide-resistant MAC lung disease is difficult to treat and has lower cure rates. The macrolide, whether azithromycin or clarithromycin, is the key antibiotic for the treatment of MAC. When resistance occurs, regimens are tailored to be as aggressive as possible given patient tolerance constraints. Regimens typically include a parenteral aminoglycoside, rifabutin, and ethambutol. Inhaled amikacin is also frequently used, although data for this drug in this setting is limited. Clofazimine, an older drug used to treat drug-resistant tuberculosis and Hansen's disease, is also prescribed, although obtaining clofazimine is difficult and its utility is largely unknown.

Prevention of resistance is paramount, and thus adequate companion drugs to accompany macrolide therapy for all regimens are necessary. Once an isolate becomes macrolide-resistant, continued macrolide therapy is not indicated, although macrolides occasionally are prescribed for their anti-inflammatory properties. The use of dual therapy with only quinolones and macrolides to treat MAC lung disease is not recommended as this approach promotes macrolide resistance. In addition,
screening for NTM is recommended for certain patients, such as those with CF, who are placed on macrolide monotherapy for reasons other than treatment of NTM. At a minimum, the clinician must have a low threshold to screen for and/or diagnose NTM lung disease in at-risk individuals. Early specialist referral for patients with this complex disease is warranted.

Role of Surgery

Adjunctive surgery for selected patients is associated with favorable treatment outcomes, although experienced mycobacterial lung disease surgeons are perhaps a critical factor for successful outcomes. As with drug-resistant tuberculosis, many aspects of surgical management for NTM patients remain nonstandardized including surgical indications, optimal patient selection, and choice of specific surgical procedures.

Impediments to Successful Therapy

Treatment outcomes for MAC lung disease regimens are in general less successful than treatment outcomes for tuberculosis. One explanation for the suboptimal clinical response to current antimicrobial agents is the relatively poor antimycobacterial activity of these agents due to “innate antibiotic resistance,” which refers to multiple mycobacterial defense mechanisms against antimicrobial agents that are not reflected by in vitro MICs. In addition, a recent study has shown that standard macrolide-based regimens for MAC therapy are associated with significant pharmacologic interactions resulting in low plasma concentrations of all drugs including macrolides. Targeted levels for pharmacodynamic indices for essentially all drugs commonly used in MAC treatment were obtained. Improvement in the pharmacodynamic parameters would almost certainly require increased dosages of the MAC medications, which would inevitably be poorly tolerated. Thus, MAC medications are relatively weak antimicrobials that due to drug-drug interactions are usually associated with suboptimal pharmacodynamic indices that cannot be improved because patients generally cannot tolerate higher doses of the medications.

Another impediment to favorable treatment outcomes for standard MAC regimens is the lack of adherence by practitioners to published treatment guidelines. In a survey of primarily pulmonary and infectious disease specialists who identified themselves as treating NTM lung disease patients, fewer than one third followed published treatment guidelines, and as many as 30% prescribed medication regimens that could promote resistance to macrolides. The reasons for the lack of adherence to the published treatment guidelines were not addressed. Although there is clearly a perception that the current published NTM treatment guidelines are inadequate for treating many patients with MAC lung disease, recent studies suggest that adherence to these guidelines at least establishes a reasonable baseline for treatment success. The perceived suboptimal treatment response is likely due to problems such as microbiologic recurrence due to MAC re-infection that are not necessarily a consequence of a poor or inadequate treatment regimen.

M. KANSAII

M. kansasii is the NTM that most closely resembles M. tuberculosis genetically, antigenically and clinically, and not coincidentally remains the most easily treatable of the NTM pulmonary pathogens. M. kansasii lung disease often presents in a similar manner to reactivation tuberculosis with upper lobe cavitary lesions. In fact, most patients with M. kansasii are initially identified as tuberculosis suspects. Unlike most other NTM, there is a good correlation
between in vitro susceptibility and in vivo response for a variety of antimicrobial agents for *M. kansasi*, including rifamycins, macrolides, and fluoroquinolones. Untreated strains of *M. kansasi* are susceptible to rifamycins (rifampin and rifabutin) with MICs ≤1 µg/mL. Isoniazid and ethambutol are not currently recommended for reporting by the CLSI as no broth MICs breakpoints are available. Because of favorable clinical responses associated with in vitro susceptibilities, currently only rifampin and clarithromycin should be reported except in rare cases of drug intolerance or in cases in which an *M. kansasi* strain has become rifampin resistant. In that circumstance, testing ancillary agents such as amikacin, ethambutol, fluoroquinolones, linezolid, trimethoprim-sulfamethoxazole, tetracyclines, and rifabutin becomes important. Surprisingly, the prognosis of even rifampin-resistant *M. kansasi* disease is good.\(^1\)

The standard regimen for treatment of pulmonary *M. kansasi* pulmonary infection is outlined in *Table 2*.\(^1\) A study by Griffith et al suggested that an intermittent regimen (3 times weekly) of rifampin, ethambutol, and macrolide is effective, less toxic, and less expensive than the standard 18-month daily dosage regimen including rifamipin, ethambutol, and isoniazid.\(^63\) With the intermittent regimen, the mean time to sputum culture conversion to negative was less than 2 months. Because of the excellent activity of the macrolides and fluoroquinolones with *M. kansasi*, it is quite likely that a shorter duration of therapy is possible.

### *M. MALMOENSE*

The British Thoracic Society (BTS) performed a prospective study of 106 patients with *M. malmoense* lung disease over a 5-year period.\(^64\) The results of 2 years of treatment with rifampin plus...
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ethambutol were equivalent to those of treatment with rifampin, ethambutol, and isoniazid, although only 53% of patients were alive at 5 years and 44 of the original 106 patients (42%) were cured of the infection. In a follow-up study, the BTS randomly assigned 167 patients with *M. malmoense* lung disease to clarithromycin, rifampin, and ethambutol, or ciprofloxacin, rifampin, and ethambutol. Overall response rates were low, but the group receiving clarithromycin had slightly better clinical response and lower mortality. In a retrospective case series from the Netherlands, Hoefsloot et al found good clinical outcome in 21 of 30 (70%) patients. The success rate was higher in patients receiving isoniazid and rifampin than for patients receiving a macrolide-based regimen. Currently, there is no consensus on an optimal treatment regimen for *M. malmoense*, but a regimen including isoniazid, rifampin, and ethambutol with or without a macrolide or fluoroquinolone is recommended.

**M. XENOPi**

*M. xenopi* lung infections have been noted to occur in patients with underlying comorbidities and co-infections, which may help explain the very high all-cause mortality associated with *M. xenopi* lung infection. One BTS trial demonstrated extremely low 5-year survival rates for *M. xenopi* lung disease patients: 24% for those treated with rifampin/ethambutol, and 10% for those treated with isoniazid/rifampin/ethambutol and either ciprofloxacin or clarithromycin. The regimen including clarithromycin performed slightly better, but mortality and treatment failure rates were still high.

In an uncontrolled retrospective study of 136 French patients with *M. xenopi* pulmonary infection, the absence of treatment was associated with a particularly poor prognosis; median survival was 10 months in untreated patients compared with 32 months in treated patients. Combination therapy with a rifamycin-containing regimen was associated with improved survival. These outcomes were not adjusted for comorbidities; therefore, the difference in survival cannot be definitively attributed to *M. xenopi* treatment. In a similar study from the Netherlands, multiple different treatment regimens were used in 49 patients with *M. xenopi* lung disease, but no specific drug combination showed consistently superior results. A recent study of *M. xenopi* infection in nude mice found that amikacin-containing regimens were the most effective. No differences were found between regimens containing clarithromycin and ofloxacin in vivo.

While still controversial and lacking conclusive evidence of superior efficacy, the current ATS/IDSA recommendation for a regimen including rifampin/ethambutol with clarithromycin and adjunctive aminoglycoside initially seems appropriately aggressive given the high mortality associated with *M. xenopi* infection. While isoniazid is also recommended, it does not appear to add significantly to the other drugs in the regimen.

**M. SZULGAI**

Although pulmonary *M. szulgai* disease is rare, respiratory *M. szulgai* isolates are generally regarded as clinically significant. This assertion has recently been questioned, which reinforces the need to evaluate all patients with NTM respiratory isolates according to ATS/IDSA guidelines. *M. szulgai* disease occurs most commonly in patients with underlying lung disease such as COPD. In 2 studies of patients treated for *M. szulgai* infection, patients responded well to multiple treatment regimens, usually including rifampin, ethambutol, and either clarithromycin or ciprofloxacin. Given the limited available data, the current ATS/IDSA recommendations...
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Treatment guidelines appear adequate for diagnosis and treatment of *M. szulgai* lung disease. *M. szulgai* is susceptible in vitro to most anti-tuberculosis drugs as well as quinolones and newer macrolides. A combination of 2 drugs has been reported to be effective.¹

**M. SIMIAE**

*M. simiae*, when isolated in clinical samples, is more often a contaminant than a true pathogen.¹ The clinical presentation is usually similar to that of other slowly growing NTM associated with nodular bronchiectatic disease. It is noteworthy that *M. simiae* can also be associated with a more rapidly progressive cavitary form of disease.

When identified as a true pathogen, *M. simiae* is extremely difficult to treat effectively and in fact, among slowly growing NTM pathogens, *M. simiae* is the most difficult. To date, there are no predictably effective drug combinations for treating *M. simiae* infection.⁷³–⁷⁵ A multi-drug regimen based on susceptibility testing is recommended for this multi-drug resistant organism; however, many *M. simiae* isolates show in vitro susceptibility to amikacin only or perhaps amikacin plus sulfa, leaving very limited therapeutic options. Some experts recommend parenteral amikacin-based regimens with a combination of 2 other agents such as sulfa, fluoroquinolone, macrolide, and linezolid regardless of the in vitro susceptibilities.¹ *M. simiae* clearly presents a great challenge with little guidance for treatment other than anecdotal experience.

**RAPIDLY GROWING MYCOBACTERIA**

**M. ABSCESSUS**

Of the NTM commonly isolated from clinical respiratory specimens, *M. abscessus* subsp *abscessus*, is one of the most feared and difficult-to-manage NTM pathogens because it is notoriously refractory to therapy (Figure 4). *M. abscessus* subsp *abscessus* is part of a group of NTM—along with *M. chelonae, M. fortuitum*, and others—termed the rapidly growing mycobacteria (RGM) on the basis of in vitro growth characteristics. *M. abscessus* was recognized as a distinct species over 20 years ago when it was separated from the *M. chelonae/abscessus* or *M. fortuitum/chelonae* complexes. However, many laboratories still report *M. abscessus* isolates as part of a complex rather than by species.

**Species Identification and Antimicrobial Resistance**

Most microbiology laboratories are unable to make RGM species and subspecies identification...
tions because they require molecular laboratory techniques not widely available. These identifications are important. For instance, *M. chelonae* and *M. fortuitum* are uncommon causes of NTM lung disease and might be viewed with appropriate skepticism as true pathogens if only a single clinical isolate is obtained. More importantly, RGM species identification helps guide therapeutic decision making.

Further confounding the RGM taxonomic complexity is the recent recognition that *M. abscessus* can be split into 3 subspecies on the basis of the activity, or lack of activity, of an inducible macrolide-resistance gene. Macrolide antimicrobial agents act by binding to the 50S ribosomal subunit and inhibiting peptide synthesis. Erythromycin resistance methylase (*erm*) genes impair binding of macrolides to ribosomes and reduce the inhibitory activity of these agents. The primary mechanism of innate RGM macrolide resistance is the presence of an inducible *erm* gene (*erm* 41). Most isolates of *M. abscessus* subsp *abscessus*, *M. fortuitum*, and several other RGM, but not *M. chelonae*, contain an active inducible *erm* gene. If an *M. abscessus* subsp *abscessus* isolate is exposed to macrolide, the *erm* gene activity is induced, with subsequent in vivo macrolide resistance, which may not be reflected by the initial in vitro macrolide MIC. The organism may appear to be macrolide susceptible in vitro but will not respond to the macrolide in vivo. Because of this in vivo macrolide resistance, an NTM isolate must be incubated with a macrolide prior to determining an MIC for the macrolide. An *M. abscessus* subsp *abscessus* isolate may have a mutation inactivating the *erm* gene, resulting in retention of in vitro and in vivo macrolide susceptibility, so that both molecular identification of the *erm* gene and phenotypic analysis of macrolide susceptibility are necessary for all clinically significant *M. abscessus* subsp *abscessus* isolates.

*M. abscessus* isolates have undergone a taxonomic split with the unofficial designation of 3 subspecies: *M. abscessus* subsp *massiliense*, *M. abscessus* subsp *bolletii*, and *M. abscessus* subsp *abscessus*. These subspecies all have an identical complete 16S rRNA gene sequence. In the United States, almost all clinical disease is due to subspecies *abscessus* and *massiliense*. *M. abscessus* subsp *massiliense* is the consensus taxonomic designation for the subspecies with a large deletion in their *erm* gene resulting in a nonfunctional *erm* gene; the designation *M. abscessus* subsp *abscessus* is applied to the subspecies for which the majority of isolates have an active *erm* gene. It must be recognized that only *M. abscessus* subspecies *abscessus* and *M. abscessus* subsp *bolletii* have official taxonomic designation. (The latter subspecies includes the former species *M. bolletii* and *M. massiliense*.)

Microbiology labs that depend on traditional microbiological techniques for species identification lack adequate technology for separating NTM species or subspecies. Organism identification facilitates informed decision making by the clinician. If the species identified is *M. abscessus* subsp *massiliense*, then the *erm* gene is inactive and macrolides should be effective in vivo. Conversely, most isolates of *M. abscessus* subsp *abscessus* have an active *erm* gene and therefore less chance of response with macrolide-containing regimens. However, *erm* gene activity can be determined by nonmolecular techniques that are within the capabilities of most microbiology laboratories that do in vitro drug susceptibility testing for NTM isolates. The isolate is incubated for a period of time (14 days) in the presence of macrolide prior to measuring the MIC of the organism for macrolide. This information is invaluable for informing initial antibiotic regimens. Unfortunately, the only
currently approved method for in vitro evaluation of \textit{erm} gene activity is this somewhat slow antimicrobial susceptibility test.

\textit{M. abscessus} subsp \textit{abscessus} has other antibiotic resistance mechanisms, including an additional \textit{erm}-like gene, multiple efflux pumps, an aminoglycoside 2'-N-acetyltransferase, and 12 homologs of aminoglycoside phosphotransferases.\textsuperscript{59} These antibiotic resistance mechanisms likely explain the frequent failure of antibiotic treatment of \textit{M. abscessus} subsp \textit{abscessus} disease. Van Ingen and colleagues hypothesized that \textit{M. abscessus} subsp \textit{abscessus} has acquired \textit{erm} genes, aminoglycoside-converting enzymes, and other armaments, not because of antibiotics but as protective mechanisms against the antimicrobial molecules secreted by microorganisms, such as \textit{Streptomyces}, that are a source of aminoglycoside and macrolide antibiotics and with which \textit{M. abscessus} subsp \textit{abscessus} shares its environmental habitats.\textsuperscript{80}

Aside from these innate resistance mechanisms, acquired macrolide resistance can occur as a result of mutation(s) in the 23S rRNA gene, which is usually the consequence of macrolide monotherapy for an \textit{M. abscessus} subsp \textit{abscessus} organism and can occur in the presence or absence of an active \textit{erm} gene.\textsuperscript{81} The possible emergence of acquired macrolide mutational resistance again underscores the importance of both molecular and phenotypic drug susceptibility analysis.

\textbf{Treatment}

The multiple innate mechanisms of antibiotic resistance, especially \textit{erm} gene activity, displayed by \textit{M. abscessus} subsp \textit{abscessus} at least partially explain in retrospect the long-recognized discordance between apparent in vitro susceptibility and poor in vivo response to the agent with putative susceptibility. In the context of the extensive innate drug resistance, the treatment of \textit{M. abscessus} subsp \textit{abscessus} lung disease remains difficult, and results are inconsistent as reflected in 2 very different recently published studies.\textsuperscript{82,83} Jarand and colleagues reported a retrospective analysis of treatment outcomes for 107 patients with \textit{M. abscessus} pulmonary disease.\textsuperscript{82} Antibiotic treatment was individualized on the basis of drug susceptibility results and patient tolerance. Sixteen different antibiotics were used in 42 different combinations for an average of 4.6 drugs per patient over the course of therapy, with a median of 6 intravenous antibiotic months. At least 1 drug, most commonly amikacin or cefoxitin, was stopped because of side effects or toxicity in the majority of patients. Twenty-four patients had surgery in addition to medical therapy. Forty-nine patients converted sputum cultures to negative, but 16 relapsed. There were significantly more surgical patients who culture-converted compared with medical patients. Seventeen (15.9\%) deaths occurred in the study population, a number similar to a study of RGM lung disease published 20 years ago.\textsuperscript{76}

Jeon and colleagues published the results of antibiotic treatment for 65 patients with \textit{M. abscessus} lung disease.\textsuperscript{83} Patients were initially hospitalized and treated with 4 weeks of parenteral amikacin and cefoxitin in combination with oral drugs, including clarithromycin, ciprofloxacin, and doxycycline. Patients tolerated the cefoxitin for an average of only 22 days. Sputum conversion and maintenance of negative sputum cultures for more than 12 months were achieved in 58\% of patients. Surgical resection was performed in 22\% of patients. Seven (88\%) of 8 patients with preoperative culture-positive sputum achieved and maintained culture negativity postoperatively. Sputum conversion with macrolide-resistant strains occurred in 27\% of patients versus 71\% with macrolide-susceptible strains (\textit{erm} gene activity was not de-
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termined). Treatment success was associated with in vitro susceptibility to clarithromycin but not with any of the other antimicrobial agents used. These sputum conversion rates are surprisingly high given the in vitro susceptibility pattern of \textit{M. abscessus} previously reported for fluoroquinolones and doxycycline and the relatively short period of parenteral therapy. One explanation for these good results is the presence of a high percentage of isolates that were really \textit{M. abscessus} subsp \textit{massiliense}, without an active \textit{erm} gene, in the study population.

Subsequent work has shown that patients with \textit{M. abscessus} subsp \textit{massiliense} infection have a much more favorable response to macrolide-based therapy, presumably due to an inactive \textit{erm} gene, than patients infected with \textit{M. abscessus} subsp \textit{abscessus}.\textsuperscript{84,85} It was reported that clarithromycin induces greater \textit{erm} gene activity, and thus higher macrolide resistance, than azithromycin.\textsuperscript{86} A more recent report refuted this observation, however, so that there is no clear clinically relevant advantage of azithromycin over clarithromycin in the treatment of \textit{M. abscessus} subsp \textit{abscessus}.\textsuperscript{87} The 2 macrolides appear to be equally effective against \textit{M. abscessus} subsp \textit{massiliense}.\textsuperscript{86} For unclear reasons, in the United States but not in Korea, there appears to be more lung disease caused by \textit{M. abscessus} subsp \textit{abscessus} than \textit{M. abscessus} subsp \textit{massiliense}.\textsuperscript{88}

Newer antimicrobial agents such as linezolid and tigecycline are active in vitro against \textit{M. abscessus} but rather disappointing, at least so far, for treating \textit{M. abscessus} subsp \textit{abscessus} lung disease in vivo.\textsuperscript{89,90} In a study of 52 patients receiving tigecycline for emergency/compassionate care for \textit{M. abscessus} infections, most patients with pulmonary or skin and soft tissue infections clinically improved.\textsuperscript{90} However, 90% of the patients reported adverse events, primarily nausea and vomiting. To date, there are only preliminary or anecdotal reports of linezolid activity for \textit{M. abscessus} subsp \textit{abscessus} lung disease. It is perhaps informative that adverse events for tuberculosis patients treated with linezolid occur with a frequency similar to that noted for tigecycline.\textsuperscript{91}

In a recent study it was found that neither linezolid or tigecycline is bactericidal against \textit{M. abscessus} subsp \textit{abscessus}.\textsuperscript{92} The authors concluded that the lack of bactericidal antibiotics provides a reasonable explanation for the poor therapeutic outcomes in \textit{M. abscessus} subsp \textit{abscessus} infection. This observation appears to be one more example of innate antibiotic resistance exhibited by this organism.

The optimal therapy for \textit{M. abscessus} subsp \textit{abscessus} lung disease remains elusive but usually requires one or more parenteral agents. As noted, there is poor correlation between in vitro susceptibility for a specific antibiotic and in vivo response to that antibiotic for \textit{M. abscessus} subsp \textit{abscessus}. \textit{M. abscessus} subsp \textit{massiliense} responds in a more predictably favorable manner to macrolide-containing regimens than \textit{M. abscessus} subsp \textit{abscessus}, and it remains unclear whether there is a significant role for macrolide in most \textit{M. abscessus} subsp \textit{abscessus} lung infections. Surgery for limited \textit{M. abscessus} subsp \textit{abcessus} lung disease, combined with antibiotic agents, also clearly offers an improved treatment outcome but is an option for only a minority of selected patients.\textsuperscript{76,84,86} Clearly, better and more effective agents for treating \textit{M. abscessus} subsp \textit{abscessus} are needed.

Currently, we typically recommend IV amikacin and tigecycline with oral linezolid for treatment of \textit{M. abscessus} lung disease. Progress with \textit{M. abcessus} subsp \textit{abscessus} disease remains frustratingly slow and incremental. Laboratory support
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Table 3. Treatment of Pulmonary Mycobacterium abscessus Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antimicrobial Treatment</th>
<th>Regimen</th>
<th>Duration</th>
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<tbody>
<tr>
<td><em>M. abscessus subsp abscessus</em>, <em>M. abscessus subsp bolletii</em> (macrolide resistant due to functional <em>erm</em> gene)</td>
<td>Amikacin (7–10 mg/kg IV or 500 mg inhaled) or Imipenem (1000 mg twice daily) or Cefoxitin (4 g twice daily) and/or Tigecycline&lt;sup&gt;b&lt;/sup&gt; (25–50 mg) and/or Linezolid (600 mg)</td>
<td>Daily (all drugs)</td>
<td>6–12 mo depending on response&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>M. abscessus subsp massiliense</em> or <em>subsp abscessus</em> (macrolide susceptible due to non-functional <em>erm</em> gene)</td>
<td>Clarithromycin (1000 mg) or Azithromycin (500 mg) or Imipenem (500 mg twice daily) or Cefoxitin (4 g twice daily) and/or Tigecycline&lt;sup&gt;b&lt;/sup&gt; (25–50 mg) and/or Linezolid (600 mg)</td>
<td>Daily (all drugs)</td>
<td>Negative cultures for 12 mo&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

IM = intramuscular; IV = intravenous.

<sup>a</sup> Dosage adjusted to achieve peak serum levels of 20–25 µg/mL.

<sup>b</sup> Dosage adjusted for tolerability factors. Antiemetics prior to dose may be of benefit.

<sup>c</sup> Symptomatic, radiographic, or microbiologic improvement balances with side effects and patient motivation.

<sup>d</sup> On appropriate therapy.


for clinicians is all too commonly suboptimal, and treatment strategies remain frustratingly ineffective. However, in the midst of this generally unsatisfactory scenario, new and important insights into the mechanisms of antibiotic resistance exhibited by *M. abscessus* subsp *abscessus* have been discovered and will undoubtedly lead to more successful treatment outcomes in the future.

**M. CHELONAE**

Many laboratories report this rapidly growing species within an *M. abscessus* complex, which is not helpful to the clinician. Unlike *M. abscessus*, *M. chelonae* does not carry an active *erm* gene and therefore macrolides may be effective in these individuals.<sup>78</sup> Isolates of *M. chelonae* are susceptible to doxycycline and ciprofloxacin 25% of the time and are always susceptible to tobramycin and clarithromycin. Imipenem, clofazimine, and linezolid are also susceptible at times. *M. chelonae* are resistant to cefoxitin.<sup>93–95</sup>

**M. FORTUITUM**

*M. fortuitum* lung disease is rare outside of the setting of esophageal and gastric motility disorders and rarely requires treatment.<sup>77</sup> Typically, most clinicians agree that until the underlying disorder is corrected, patient symptoms will not improve. Treatment should be based on in vitro susceptibility and use at least 2 agents with in vitro activity against
the clinical \textit{M. fortuitum} isolate. \textit{M. fortuitum} isolates are usually susceptible to fluoroquinolones, doxycycline and minocycline (50%), sulfonamides and trimethoprim/sulfamethoxazole, amikacin, imipenem, and tigecycline, and approximately one half of the isolates are susceptible to cefoxitin.\textsuperscript{93,94,96} Most \textit{M. fortuitum} isolates have a functional \textit{erm} gene and are macrolide resistant; therefore, macrolides are not typically recommended.\textsuperscript{97,98} Twelve months of negative cultures while on appropriate treatment is recommended, similar to other NTM species.

### NTM SPECIES USUALLY ASSOCIATED WITH SPECIMEN CONTAMINATION

It is important for clinicians to recognize NTM species that are almost never a cause of lung disease. The most important example is \textit{M. gordonae}, which is commonly isolated from respiratory specimens but almost never associated with progressive lung disease. \textit{M. gordonae} is an environmental NTM species that can grow in all but the most hostile liquid environments, including reagents used for processing and culturing AFB cultures. In some state laboratories, it is the third most common NTM recovered from clinical specimens. Other NTM species that are sometimes isolated from respiratory specimens but rarely cause lung disease include \textit{M. terrae} complex, \textit{M. smegmatis}, and \textit{M. scrofulaceum}. An especially important reason to be aware of these species, which may be significant pathogens in other contexts, is that a patient may meet diagnostic criteria with one of these species but would still be extremely unlikely to have a significant lung infection as a result. Starting therapy for a patient with 2 positive sputum AFB cultures for \textit{M. gordonae} would be inappropriate.

### NONPHARMACOLOGIC INTERVENTIONS

#### AIRWAY CLEARANCE

There is limited data regarding the use of bronchodilators, inhaled corticosteroids, and hypertonic saline for the treatment of NTM lung disease. Many specialists agree that bronchodilation followed by inhalation of hypertonic saline (3%–7%) with some type of chest physiotherapy (ie, cough techniques, flutter valves, vest) provides some patients assistance with sputum expectoration.

#### DIET AND LIFESTYLE

As mentioned, some patients acquire NTM pathogens from household plumbing.\textsuperscript{99,100} It is still unknown, however, how much of a risk NTM in municipal water and household plumbing present and whether these water sources are the major source of NTM for most patients with NTM lung disease. Additionally, the identification of species within the MAC complex in household water samples continues to evolve. Some studies have demonstrated that \textit{M. intracellulare} is not present in household plumbing.\textsuperscript{101}

It is not certain that avoidance of showers without avoidance of other potential aerosol-generating activities associated with running water in the home would eliminate the risk of household NTM transmission. Increasing the temperature of the hot water heater to 130°F or higher or changing shower heads at regular intervals might decrease risk of NTM transmission. MAC can be isolated from soil, but it is unknown whether exposure to specific soil-based sources of MAC organisms may contribute to the development of NTM lung disease. It is unclear if avoidance of soil and/or soil-based activities would minimize risk of acquiring NTM lung disease.

There is no evidence to support any role for dietary changes in the treatment of MAC lung
disease. Maintaining adequate caloric intake and body mass index and following pre-albumin levels as a marker of nutrition may be helpful. 

Exercise, including pulmonary rehabilitation, is encouraged in individuals with chronic lung disease, but this has not been studied in NTM lung disease. Aerobic activity and deep breathing activities such as yoga are generally encouraged.

**SURGERY**

Lung resection for NTM has historically been a last resort measure in patients with severe, unresponsive disease. Surgery in the pre-macrolide era was accompanied by perioperative complications. In a series of 28 patients with MAC lung disease, Nelson and colleagues described surgical intervention results in the macrolide era, following patients for a mean of 39 months postoperatively. Culture negativity was achieved in more than 90% of patients, with an overall operative mortality of 7.1%. In 2002, Shirashi et al characterized 21 patients, 2 of whom experienced a bronchopleural fistula with no overall operative mortality. In the largest retrospective review to date, Mitchell et al characterized 236 patients who underwent surgical intervention for NTM lung disease at a single institution, 80% of which were MAC isolates. The average length of hospital stay was 6.5 days, with an overall mortality rate of 2.6%. Of note, the overall mortality rate has declined from 7.1% in the 1980s to 0.6% for 162 procedures completed during the period of 2001–2006, largely due to improved techniques and the introduction of macrolide therapy the late 1990s. Surgical morbidity rate was reported at 18.5%. All patients had at least 2 months of intensive, susceptibility-driven antibiotic therapy prior to surgery, with a pre-surgical emphasis on nutritional status. Only 57% of patients were culture negative at the time of surgery. Long-term microbiologic data was not reported. In a second review at the same institution, Yu et al reviewed the cases of 134 individuals with bronchiectasis of the right middle lobe and lingula who underwent 172 operations, namely middle lobectomies and lingulectomies. There was no operative mortality. Morbidity was noted in 12 patients (7%) during the postoperative period. Culture negativity was achieved in 84% postoperatively (92/110), while 16% had not converted their sputum postoperatively, suggesting failure of medical and surgical therapy.

Most specialists agree that adjunctive surgical intervention in the hands of an experienced multidisciplinary team and center offers benefit to a selected population of NTM patients, although the most beneficial timing of operative measures in the disease course has not been clearly defined.

**SUMMARY**

Clinicians are increasingly likely to encounter patients with NTM lung disease in the United States. Awareness of the clinical settings most likely associated with NTM lung disease is important for timely diagnosis and initiation of therapy. Clinicians must also have some familiarity with the NTM species most commonly associated with progressive lung disease and, equally important, those NTM species that are not. While there are some general similarities between NTM lung disease and tuberculosis, those similarities are limited, especially in the context of therapy. The general discordance between in vitro susceptibility testing for specific antimicrobial agents and the in vivo efficacy of those agents is particularly frustrating but must be confronted to achieve treatment success. Clinicians who do not regularly see NTM lung disease patients are encouraged to seek expert consultation for management of these very challenging patients.
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