Pulmonary Disease Due to Nontuberculous Mycobacteria

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Nontuberculous mycobacteria (NTM) are increasingly associated with pulmonary disease. This is a worldwide phenomenon and one that is not related just to better diagnostic techniques or HIV infection. The mode of transmission of NTM is not well defined, but environmental exposure may be the major factor. While most exposed and infected individuals never acquire NTM disease, some ostensibly immunocompetent persons will. Although our understanding of the pathogenesis of NTM disease is incomplete, we believe that both host and mycobacterial factors are involved. Among the former, interferon-\(\gamma\) “trafficking” may well play a central role. When disease occurs, it is likely to present in one of three prototypical forms: a tuberculosis-like pattern often affecting older male smokers with COPD; nodular bronchiectasis classically occurring in middle-aged or older women who never smoked and present with cough; and hypersensitivity pneumonitis following environmental exposure. While *Mycobacterium avium* complex has been described with all three forms, many other NTM can produce one or another of them; variants of these prototypes also exist.

Diagnosis of NTM disease relies on microbiology and chest CT scanning, and criteria to aid diagnosis are available. Treatment of disease depends on the species involved, extent and form of disease, and overall condition of the patient. Surgery for localized disease may be useful for those species expected to be refractory to medical therapy. Observation without treatment may be appropriate for some patients with slowly progressive disease that is expected to be particularly difficult to treat.

Key words: bronchiectasis; hypersensitivity pneumonitis; *Mycobacterium avium* complex; *Mycobacterium kansasii*; nontuberculous mycobacteria; pulmonary disease; rapidly growing mycobacteria

Abbreviations: HRCT = high-resolution CT; IFN = interferon; IGRA = interferon-\(\gamma\) release assay; IL = interleukin; MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacteria; RGM = rapidly growing mycobacteria; TNF = tumor necrosis factor

Although *Mycobacterium tuberculosis* is by far the most important mycobacterial species from a public health perspective, other species are being encountered with increasing frequency and new species are being identified. Collectively, these organisms have been referred to by a variety of terms, including *anonymous* or *atypical mycobacteria, mycobacteria other than tuberculosis, and nontubercul-ous mycobacteria* (NTM). The last term is most often used today in the United States and will be used here.

While not all NTM are pathogenic for humans, many are. That said, even pathogenic NTM are usually less virulent than *M tuberculosis*, and potential pathogens may be isolated without the presence of obvious disease. Conversely, species usually considered benign “contaminants” may produce disease especially in immunocompromised hosts. Thus, a spectrum of mycobacterial virulence exists from usually pathogenic when isolated (eg, *M tuberculosis*), to often pathogenic (eg, *Mycobacterium avium* complex).
complex (MAC), to rarely but sometimes pathogenic (eg, Mycobacterium gordonae). This review will focus on NTM most commonly associated with pulmonary disease in humans.

Epidemiology and Pathogenesis

NTM are commonly occurring organisms and have been recovered in many parts of the world and from a variety of environmental reservoirs including fresh and salt water, soil, and biofilms. The mode(s) of transmission of NTM to humans has not been defined, although person-to-person transmission is thought not to occur or to be very uncommon, at least in immune-competent hosts. Isolation techniques used for limiting the spread of M tuberculosis are, therefore, not applied to NTM. Because NTM are not reportable infections/diseases, data relating to their frequency have relied on estimates extrapolating clinical cases and laboratory or skin testing surveys using antigens derived from various NTM species. These latter studies showed years ago that in some geographic areas, large proportions of the adult population are likely to be infected by NTM, suggesting an environmental reservoir of infection. However, even in such regions, clinical disease was uncommon. More recently, the isolation of NTM and diagnosis of clinical disease appear to be increasing. Several surveys of the frequency of NTM isolation from humans in the United States indicated an increase from about one third of 32,000 mycobacterial isolates between from 1979 to 1980, to almost three fourths of the isolates from 33 state laboratories by 1992. Isolates of MAC were most frequent followed by rapidly growing mycobacteria (RGM) and Mycobacterium kansasii. Moreover, there is reason to believe that many isolates are related to disease. Similar reports are available from other parts of the world, although the relative frequency of species involved varies. For example, the incidence of NTM in HIV-seronegative persons in France was recently estimated to be about 0.73 cases/100,000 population, with MAC, Mycobacterium xenopi, M kansasii, and RGM being encountered most frequently in that order. Other studies have emphasized the incidence of infection with multiple strains/species in the setting of bronchiectasis.

While improved laboratory techniques, greater awareness of NTM, and the presence of HIV infection may account for some of the apparent increase in NTM, other factors may also be important. These include more precise diagnostic standards, an expanded understanding of the presentation of NTM disease, the availability of chest CT scanning, and increasing numbers of persons at risk for NTM including immunocompromised hosts, and older adults. The extended survival of special at-risk groups like persons with COPD and cystic fibrosis may also contribute.

Although still incomplete, our understanding of NTM pathogenesis is expanding and both host and mycobacterial factors are involved. Host defenses against mycobacteria are complex and involve both nonspecific and antigen-specific factors. Among the former are epithelial integrity, gastric pH, and cytokines/chemokines such as interleukin (IL)-8, IL-12, RANTES (regulated on activation, normal T-cell expressed and secreted), and natural resistance-associated macrophage protein 1. Macrophage/monocyte programmed cell death (ie, apoptosis), possibly regulated by IL-10 and tumor necrosis factor (TNF)-α, may also be important. The roles of complement and neutrophils, although unclear, have also received attention. Natural killer lymphocytes, probably through secretion of interferon (IFN)-γ, TNF, and granulocyte-macrophage colony-stimulating factor are likely critical. Over a period of weeks following infection, specific immunity mediated by CD4+T-lymphocytes and involving production of IL-2, IFN-γ, and TNF-γ develops.

In addition to these myriad host responses, mycobacteria have evolved complex mechanisms of attachment, cellular uptake, and survival within hosts. Complicating matters are apparent species differences in these mechanisms. Some host defects such as deficiency of CD4+lymphocytes in the setting of HIV infection and IFN-γ receptor defects or reduced IFN-γ production have been related to cases of NTM as have attributes of mycobacteria such as the resistance of RGM to topical antiseptics. For the most part, however, no clear explanation is usually available to indicate why some infected people become ill or why they have a particular presentation of NTM disease. A recent study related polymorphisms within the IFN-γ/receptor gene complex to risk of pulmonary tuberculosis. Presumably similar mechanisms could also affect NTM risk.

Clinical Presentation

Based largely on experience with several species, particularly MAC, in immunocompetent persons, NTM disease in the chest most commonly presents in one of three “prototypical” forms: a tuberculosis-like pattern classically involving the upper lobes of older men with substantial smoking histories and COPD; nodular bronchiectasis, often occurring in slender older women nonsmokers including some with skeletal deformities and typically presenting with cough24,25; and hypersensitivity pneumonitis.
after use of hot tubs and medicinal baths. While \textit{M. kansasii}, \textit{M. xenopi}, \textit{Mycobacterium malmoense}, and the RGM have been most associated with the first form and MAC with all three forms, presumably many other species may be capable of producing any or all of these patterns. Moreover, variants of these presentations have also been described. For example, fibrocavitary disease may also be associated with some element of consolidation, and NTM hypersensitivity disease has been well documented following other exposures, such as household water, indoor swimming pools, and metalworking fluids.

In immunocompromised patients, an expanded spectrum of species and presentations may be encountered.

HIV deserves special mention. Although NTM are commonly isolated from respiratory secretions of HIV-infected persons, NTM are a relatively uncommon cause of lung disease and are more likely to cause extrapulmonary or disseminated disease. An exception to this generalization may be \textit{M. kansasii}, which causes lung disease without dissemination in HIV-coinfected persons, typically with low CD4 counts.

Finally, it is important to recognize that NTM lung disease may coexist with, facilitate, or be facilitated by comorbidities. Thus, COPD, cystic fibrosis, gastroesophageal reflux disease and vomiting, and chest wall disorders have all been associated with NTM, which may occur in younger persons when associated with such conditions. More recently, NTM including \textit{M. xenopi}, \textit{M. kansasii}, and \textit{M. malmoense} have been related to a combination of bronchiectasis and Aspergillus lung disease including invasive disease and aspergilloma. The rate of Aspergillus-related disease was greater in patients having both NTM and bronchiectasis than among patients with bronchiectasis alone; the presence of Aspergillus appeared to adversely affect prognosis.

The signs and symptoms of NTM lung disease are generally nonspecific and reflect the form of disease and comorbidities rather than the species of NTM involved. Chronic cough/sputum and fatigue are very common. Fever and sweats are less frequent (\textless 50\% of patients) than with tuberculosis except in the hypersensitivity form. Likewise, dyspnea is more likely related to comorbid conditions except with the hypersensitivity pattern where it may be prominent. Malaise, hemoptysis, weight loss, and wasting are uncommon and usually reflect advanced disease.

**Diagnosis**

Whereas upper lobe, cavitary tuberculosis-like NTM disease generally presents little diagnostic difficulty other than excluding tuberculosis, nodular bronchiectatic disease is more subtle. Indeed, NTM have often been considered as colonizing areas of slowly progressive disease. Histologic evidence of NTM tissue invasion and reaction, however, suggest “benign” colonization is less likely than previously thought. Because skin test antigens specific for NTM species are not readily available and often cross-react with tuberculin, skin testing has little utility for identifying the presence of NTM infection. New IFN-\gamma release assays (IGRAs) utilizing antigens highly specific for \textit{M. tuberculosis} can help distinguish tuberculosis infection from skin test sensitization due to NTM. One recent study of an IGRA system has suggested that the IGRA may be useful in distinguishing active tuberculosis from NTM, but the precise role of the IGRA for this purpose remains to be defined.

Imaging, especially CT, plays a critical role in diagnosing pulmonary NTM disease. Jeong and colleagues studied 22 patients with proven NTM disease and compared high-resolution chest CT (HRCT) scan images with histopathology of lung biopsy. They concluded that regardless of NTM species, the most common HRCT findings were small bilateral nodules, branching centrilobular nodules (ie, tree-in-bud pattern; Fig 1), and cylindrical bronchiectasis reflecting bronchiolar/peribronchiolar inflammation and bronchiolectasis and supporting the concept that microbiologic isolation of NTM in association with such HRCT findings is related to...
tissue invasion. Moreover, other studies have shown progression, typically slow, of these changes with longitudinal study. Koh et al suggested that approximately one third of patients with bilateral bronchiectasis and bronchiolitis by HRCT have NTM disease; extensive abnormalities, cavitation or consolidation, and female gender were particularly associated with NTM. The combination of bronchiectasis and multiple small nodules especially involving the right middle lobe and/or lingula and occurring in nonsmoking middle-aged or elderly women has been termed the Lady Windermere syndrome. Usually associated with MAC, this entity represents one part of the spectrum of NTM disease.

Other patterns of radiographic abnormality may be encountered. NTM-associated hypersensitivity pneumonitis may present with bilateral diffuse ground-glass infiltrates, nodules, reticulation, or mosaic attenuation consistent with patchy air trapping. A nonspecific alveolitis has also been described. Isolated pulmonary nodules or mass lesions have been described, although their prevalence is unknown. In patients with HIV and NTM coinfection, chest imaging is often normal but may show relatively nonspecific focal or diffuse airspace consolidation or adenopathy; cavitation is unusual. New or worsening infiltrates, adenopathy, and/or pleural effusion may be seen with so-called immune reconstitution syndrome after beginning highly active antiretroviral therapy for HIV. The tuberculosis-like prototype often involves the upper lobes but with thinner walled cavities, more pleural reaction, and less surrounding infiltrate than classic pulmonary tuberculosis. It is particularly associated with \textit{M avium} and \textit{M kansasii} and the RGM. Pleural effusions are less common than with tuberculosis.

Although imaging may suggest NTM disease, microbiologic studies are an essential complement for diagnosis. NTM, like \textit{M tuberculosis}, are acid-fast and can be detected by conventional or fluorochrome microscopy. In a study of 6,500 respiratory specimens, various species of NTM were as likely as \textit{M tuberculosis} to yield positive fluorochrome stains of sputum or bronchial wash specimens, with a positivity rate approaching 60% for NTM. Not all studies, however, have found such a high rate of positive microscopy. Reasons for this likely reflect differences in the extent of disease and the concentration of organisms present in the specimens studied.

Sputum acid-fast bacilli smears may be helpful in suggesting NTM but are less sensitive and specific than culture. RGM, in particular, are easily decolored and may be missed with conventional staining. Culture of NTM is the cornerstone of diagnosis.

Culture isolation and speciation may be accomplished using solid or liquid media. Solid media systems are required for precise identification of many species of NTM, allow for easy quantitation of mycobacteria, can be supplemented for purposes of isolating fastidious species of NTM, and are used for some drug-susceptibility testing. However, growth in these systems can be very slow depending on the particular species being isolated and the concentration of organisms present. Liquid-based culture media such as Bactec and mycobacteria growth indicator tube (Becton Dickinson; Sparks, MD) and others are significantly faster. The use of both solid and liquid media is, therefore, recommended for all NTM cultures.

Gene probing using recombinant RNA amplification technology (AccuProbe; GeneProbe; San Diego, CA) can facilitate distinguishing between \textit{M tuberculosis} and several common NTM including \textit{M kansasii}, MAC, and \textit{M gordoniae} (a common contaminant), and polymerase chain reaction amplification and probing of DNA (AmpliCord test; Roche Molecular Systems; Branchburg, NJ) can identify \textit{M tuberculosis}, \textit{M avium} and \textit{Mycobacterium intracellulare}). High-performance liquid chromatography, analysis of the hypervariable region of the gene encoding 16S recombinant RNA, and other techniques are also used by some laboratories for mycobacterial speciation.

Because many species of mycobacteria can be isolated from the environment and persons with NTM isolates often did not have clear evidence of a progressive pulmonary process when assessed by "acute" disease criteria applicable to tuberculosis, it was long held that many isolates represented benign colonization. However, correlative studies of histology and imaging noted above and the observation that high colony counts of NTM (ie, >100) and/or multiple (two or more) isolates of NTM with any number of colonies were frequently associated with clinical disease over time have led to more appropriate diagnostic criteria (Table 1). Although semiquantitative acid-fast bacilli smear and culture results were previously used as NTM diagnostic criteria, the current common use of broth (liquid) systems have resulted in less quantitative reporting and are not used in the current criteria.

**TREATMENT**

Some years ago, a practical classification presented by Bailey discussed grouping mycobacteria as either easy or hard to treat; \textit{M kansasii} typified the former group, and MAC described the latter. Intervening years and, particularly, the availability of newer macrolides/azilides have changed the situa-
Table 1—Diagnostic Criteria for NTM Pulmonary Disease

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<th>Clinical</th>
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<td>Signs and symptoms consistent with NTM disease*: if prior pulmonary disease is present, deterioration should be documented; and Other conditions, particularly tuberculosis and cancer, should be excluded or treated; and</td>
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<tr>
<td>Imaging†</td>
</tr>
<tr>
<td>Chest radiography with infiltrates, nodular, or cavitary opacities; or HRCT showing: multiple small (noncalcified) nodules and multifocal bronchiectasis with/without cavitation.</td>
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<tr>
<td>Bacteriology (meeting any criterion below within 1 yr)</td>
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*Patients suspected of having NTM lung disease but not meeting criteria should be followed up until the diagnosis is conclusively confirmed or excluded. Used and adapted by permission of the American Thoracic Society.††Cough, fatigue, weight loss. Fever and hemoptysis are less common and suggest advance/extensive disease. Dyspnea may reflect comorbid conditions or advanced NTM.†Mid/lower lung zones are most common site of involvement in patients with noncavitary disease.‡Three early morning sputum specimens obtained on different days is preferred before more invasive testing is pursued.§Bronchoscopic specimens are believed to be more sensitive and less likely to be environmentally contaminated than expectorated sputum (if bronchoscopic specimens are protected from tap water).

The organism involved, the extent of disease, and the patient’s general condition should be taken into account when determining treatment. NTM involving extensive areas of lung, affecting poor surgical candidates, or considered drug responsive should be treated medically. Localized disease, especially with difficult to treat NTM, may benefit from surgical resection usually with adjunctive antibiotic coverage of the NTM. Observation without treatment may be appropriate for some patients with slowly progressive disease that is expected to be particularly difficult to treat. Fifth, hypersensitivity lung disease due to NTM should be treated by avoidance of the NTM and possibly with corticosteroids; the need for treatment of the involved NTM is unclear, although some recommend a short course (3 to 6 months) of treatment. M kansasii and Mycobacterium szulgai are organisms generally responsive to treatment. Regimens including rifampin and ethambutol have been used with good success for M kansasii, although the contribution of isoniazid has been uncertain. Typically, these three drugs have been administered in doses used for tuberculosis, with ethambutol being administered at the higher end of the dose range (ie, 25 mg/kg) for the initial 2 months of therapy, and then at 15 mg/kg for the remainder of treatment (Table 3). Treatment for least 12 months after achieving negative sputum results is recommended. Such a regimen is highly effective with both low failure and relapse rates when the organism is rifampin susceptible. Initial sputum conversion conversion, however, may be somewhat slower than when treating tuberculosis. An aminoglycoside, particularly streptomycin, is often added to this regimen at a dose of 0.5 to 1.0 g IV three times per week for the first 2 to 3 months of therapy of severe/extensive disease. The observation that clarithromycin has substantial in vitro activity against M kansasii led to its use in retreatment cases, in patients who are resistant, especially to rifampin, and in patients intolerant of the traditional regimen. Similarly, limited experience using fluoroquinolones and sulfamethoxazole, especially in HIV-coinfected persons receiving highly active antiretroviral therapy, which may interact with rifamycins, suggests these agents may also be effective. Reduction of the duration of the therapy has also been attempted. A British study using daily rifampin and ethambutol (15 mg/kg) for 9 months achieved almost 100% sputum conversion but had a high relapse rate of 10% at 5 years after treatment. A three-times-weekly regimen of clarithromycin (500 to 1,000 mg per dose), rifampin (600 mg), and ethambutol (25 mg/kg per dose) was tested in 18 patients treated for a mean of 13 months and showed highly...
favorable results after a mean follow-up of 46 months.65 These results require confirmation. M szulgai can generally be treated with three or four drugs to which it is sensitive in vitro.

In contrast to M kansasii, MAC, Mycobacterium simiae, M xenopi, M malmoense, and others may be more difficult to treat especially when disease is extensive. The macrolides clarithromycin and azithromycin have become the cornerstones of therapy for MAC. Currently, it may be assumed that previously untreated strains are macrolide susceptible. Using rifampin, ethambutol, and isoniazid regimens without a macrolide, 5-year cure and mortality rates were approximately 30% and 36%, respectively, for a mix of cavitary and bronchiectatic disease.66 Using clarithromycin, ethambutol, and rifamycins (rifampin or rifabutin) supplemented by streptomycin 5 d/wk for the first several months, Wallace and coworkers67 treated 50 pulmo-

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<th>Table 2—Initial Medical Treatment of Common NTM Pulmonary Disease*</th>
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<td><strong>Species</strong></td>
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<tr>
<td>Slow-growing NTM</td>
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<tr>
<td><em>M kansasii</em></td>
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<tr>
<td><em>Mycobacterium szulgai</em></td>
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<tr>
<td>MAC</td>
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<tr>
<td><em>M malmoense</em></td>
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<td><em>M xenopi</em></td>
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<td>RGM</td>
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<tr>
<td><em>M abscessus</em></td>
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<tr>
<td><em>M chelonae</em></td>
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<td><em>M fortuitum</em></td>
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*Macrolide = clarithromycin/azithromycin; quinolone = moxifloxacin preferred; NB = *nota bene* (note well).

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<th>Table 3—Dosing of Commonly Use Drugs for NTM</th>
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<td><strong>Drug</strong></td>
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<td>Aminoglycoside</td>
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<td>Streptomycin</td>
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<td>Amikacin</td>
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<td>Ethambutol</td>
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<td>Isoniazid</td>
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<td>Macrolide</td>
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<tr>
<td>Clarithromycin</td>
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<tr>
<td>Azithromycin</td>
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<tr>
<td>Rifamycins</td>
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<td>Rifampin</td>
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<td>Rifabutin</td>
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nary MAC patients until culture negative for 1 year. Among 23 patients with negative culture findings ≥ 12 months during therapy (average total, 17.8 months), there were no relapses after a mean of 19.1 months of follow-up. Subsequent studies have shown sputum conversion rates ranging from mid-60s to 100% and long-term success rates from < 50 to 82%. One study has also suggested little value of using an aminoglycoside in early treatment. Most reports also note substantial drug intolerance, particularly GI intolerance, which may be overcome by gradually starting therapy over several weeks. This wide range of results likely reflects differences between studies in the proportion of new vs retreatment cases, susceptibility to macrolides, and extent/type of disease. Clinical parameters associated with good outcomes included sensitivity to the macrolide (or no prior therapy) and sputum smear negativity at start of treatment suggesting lower disease burden. Azithromycin, either daily at a dose of 250 to 300 mg/d or three times weekly (500 to 600 mg per dose) may yield results somewhat inferior to daily clarithromycin containing regimens but is better tolerated. Recent data suggest that while response rates for three-times-weekly macrolide-based regimens are effective for some patients, those with cavitary disease, previously treated MAC, or COPD may do less well with intermittent than daily treatment. Extrapolation of these results to M xenopi (and other species) is uncertain because cure rates for that species may diminish with sustained follow-up. Although many other agents and combinations have been used to treat MAC, most have not been rigorously studied for this indication. In particular, little data concerning fluoroquinolones are available. Current treatment for new pulmonary MAC should utilize clarithromycin or azithromycin, rifamycin, and ethambutol. An aminoglycoside should be added for the initial 2 to 3 months in patients with extensive, cavitary, or heavily smear-positive disease. Treatment should be continued for at least 12 months after sputum culture conversion. Intermittent therapy is preferred for limited disease but should not be used for persons with extensive and/or cavitary disease.

RGM species relevant to lung disease include M fortuitum, M abscessus, and M chelonae. These organisms are not responsive to "standard" antituberculosis agents, and those drugs should not be used for RGM. When treatment is deemed necessary, it should be guided by drug-susceptibility testing. Testing should be done against amikacin (and tobramycin for M chelonae), clarithromycin, quinolones (especially moxifloxacin), sulfamethoxazole, doxycycline, and imipenem. Linezolid and tigecycline may also be active. M fortuitum and M chelonae should be treated with two or more drugs, selected by in vitro susceptibilities. Treatment for ≥ 12 months of negative sputum is recommended, although somewhat longer durations may be preferable. Treatment of underlying conditions, especially esophageal or swallowing disorders, that may predispose to NTM may also facilitate clearance of these organisms.

Among the RGM, M abscessus is likely to be the most difficult to treat medically. Because disease caused by M abscessus is often slowly progressive over years, and because older adults are typically involved, observation may be appropriate in some instances. Therapy with macrolide and parenteral amikacin/cefotixin (or imipenem) for at least 2 to 4 months (longer if cavitary disease is present) has been recommended to reduce symptoms. Macro- lide monotherapy frequently produces resistance, but intermittent brief periods of treatment with a macrolide alone or with one or more parenteral agent has been suggested for symptom suppression. If M abscessus disease is localized and the patient is otherwise a good surgical candidate, resection of the disease should be seriously considered following a period of antimicrobial therapy and by a surgeon experienced in managing such cases.

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Erratum

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