Nontuberculous Mycobacterial Pulmonary Disease

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INTRODUCTION

Nontuberculous mycobacteria (NTM) species are mycobacterial species other than those belonging to the Mycobacterium tuberculosis complex and Mycobacterium leprae. NTM infection and disease is not tuberculosis and manifests in many ways different from tuberculosis, an important distinction to keep in mind in terms of presentation, clinical features, and challenges in management. NTM are ubiquitous in the environment and have been recovered from tap and natural water sources, soil, and food products and around livestock, cattle, and wildlife species. More than 140 NTM species have been identified, but since infection caused by NTM is not reportable, the incidence of NTM infection is unknown. Surveys of U.S. laboratories have reported that approximately 60% of recovered mycobacterial species were NTM.

NTMs have been isolated from body surfaces or secretions without causing apparent disease and were often considered contaminants or colonizers with no clinical significance. However, with increased awareness and modern and more rapid microbiologic methods for detecting the presence of NTM in a clinical setting where comorbid pulmonary and nonpulmonary conditions may exist, their clinical significance has now been recognized. It has been observed that there is increased isolation and prevalence of many species of NTM in several geographic areas, such as in the southeast United States, as well as in other parts of the world. The clinical significance of this observation is unclear. It is also important to recognize that epidemiological studies based on laboratory statistics must be evaluated by correlating them with the microbiological and other criteria established by the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines to best understand their clinical relevance. Furthermore, it has been suggested that the contemporary prevalence of NTM disease in certain regions of North America may be higher than the prevalence of tuberculosis, with laboratory records showing 88% of these cases being Mycobacterium avium complex (MAC). The prevalence of NTM infection–associated hospitalizations is increasing worldwide as well. Co-infection with tuberculosis and multiple NTMs has been observed clinically and documented in patients with and without HIV.

This manual reviews the microbiologic and clinical features of NTM infection as well as its diagnosis and management, focusing on both rapidly growing mycobacteria (RGM) and the more com-
Case Patient 1

Initial Presentation and Evaluation

A 67-year-old man who is a smoker with a past history of *M. tuberculosis* infection treated in the 1970s presents to the emergency department with cough and shortness of breath. Physical examination reveals a thin man with hyperresonance on lung examination and crackles in the left apex. Chest radiograph reveals an old *M. tuberculosis* scar with fibrocystic disease and a cavitary opacity in the left upper lobe (Figure 1). Pulmonary function tests document moderate obstructive airway dysfunction. HIV test is negative. Sputum smears are positive for acid-fast bacilli. Culture determines that the organism is not *M. tuberculosis*, and repeat cultures identify moderate growth of *M. kansasii*.

- Are there any distinguishing features of NTM infection?

Approach to Diagnosis

The diagnosis of NTM disease is very complex and at times confusing. It should be based on clinical, radiologic, and mycobacterial correlation with good communication between the experts in this field. The ATS/IDSA criteria for diagnosing NTM lung disease are shown in the Table.9 These criteria best apply to MAC, *M. kansasii*, and *Mycobacterium abscessus* but are clinically applied to other NTM respiratory pathogens. Because of the nonspecific symptoms and lack of diagnostic specificity of chest imaging, the diagnosis of NTM lung disease requires microbiologic confirmation. Specimens sent to the laboratory for identification of NTM must be handled with care to prevent contamination and false-positive results. Transport media and preservatives should be avoided, and transportation of the specimens should be prompt. These measures will prevent bacterial overgrowth. Furthermore, the yield of NTM may be affected if the patient has used antibiotics, such as macrolides and fluoroquinolones, prior to obtaining the specimen.

NTM should be identified at the species level.9 The preferred staining procedure in the laboratory is the fluorochrome method. Specimens should be cultured on both liquid and solid media. Some species require special growth conditions and/or lower incubation temperatures, and other identification methods may have to be employed, such as DNA probes, polymerase chain reaction genotyping, nucleic acid sequence determination, and high-performance liquid chromatography. Species-specific skin test antigens are not commercially available and are not helpful in the diagnosis of NTM disease because of cross-reactivity of *M. tuberculosis* and some NTM. However, increased prevalence of NTM sensitization based on

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1. Figure 1. Chest radiograph demonstrating an old *Mycobacterium tuberculosis* scar with fibrocystic disease and a cavitary opacity in the left upper lobe.
purified protein derivative testing has been noted in a recent survey, which is consistent with an observed increase in the rates of NTM infections, specifically MAC, in the United States.\(^\text{10}\) It remains unclear why NTM infections and an escalation to continual clinical disease occur in certain individuals. Many risk factors, including inherited and acquired defects of host immune response, have been associated with increased susceptibility to NTM infections. Furthermore, the development of a biofilm matrix around NTM make them environmentally more resilient.\(^\text{11}\) Moreover, it is hypothesized that inoculation with the BCG vaccine and the endemicity of tuberculosis infection in certain areas of the world may be protective against infection with NTM.\(^\text{12}\)

- Does diagnosis of NTM lung disease require microbiologic confirmation? Are skin tests helpful?

As a gold standard, clinical specimens for mycobacterial cultures should be inoculated onto one or more solid media (eg, Middlebrook 7H11 media and/or Löwenstein-Jensen media, the former of which is the preferred medium for NTM) and into a liquid medium such as BACTEC 12B broth or Mycobacteria growth indicator tube (MGIT) broth. Growth of visible colonies on solid media typically requires 2 to 4 weeks, but liquid media, such as the radiometric BACTEC system used as a supplementary and not as an exclusive test, usually produce results within 10 to 14 days. Furthermore, even after initial growth, identification of specific isolates based on the growth characteristics on solid media requires additional time. Use of specific nucleic acid probes for MAC and \(M.\, kansasii\) and HPLC testing of mycolic acid patterns in acid-fast bacilli smear–positive specimens can reduce the turnaround time of specific identification of a primary culture-positive sample. Other newer techniques including 16S ribosomal DNA sequencing and polymerase chain reaction-restriction fragment length polymorphism analysis (PRA) also allow NTM to be identified and speciated more reliably and rapidly from clinical specimens. Susceptibility testing is based on the broth microdilution method;
RGM usually grow within 7 days of subculture, and the laboratory time to culture is a helpful hint, although not necessarily specific. The majority of NTM grow within 2 to 3 weeks. Recognizing the morphology of mycobacterial colony growth may also be helpful in identification. Tuberculin skin testing remains a nonspecific marker of mycobacterial infection and does not help in further elucidating infection by NTM in any particular manner.

**What is the predictive value of IGRA tests in this group?**

Interferon-gamma release assays (IGRAs) are now being used as an alternative to tuberculin skin testing to diagnose *M. tuberculosis* infection. Certain NTM also contain gene sequences that encode for ESAT-6 or CFP-10 antigens used in the IGRAs and hence give a positive IGRA test. These include *Mycobacterium marinum*, *Mycobacterium szulgai*, and *M. kansasii*.\(^{13,14}\) However, MAC organisms specifically do not produce positive results on assays that use these antigens, and thus the new IGRAs are useful in ruling out MAC infection.

**CLINICAL CONSIDERATIONS**

NTMs are classified by their culture growth and microbiological criteria into 2 groups: rapid growing (RGM), which include *Mycobacterium fortuitum*, *M. abscessus*, and *Mycobacterium chelonae*, and slow-growing (SGM), including MAC and *M. kansasii*. Based on clinical presentation, NTM can be further broadly characterized as follows:\(^{15-21}\)

1. Skin and soft tissue infection usually acquired via direct inoculation and caused by RGM such as *M. fortuitum*, *M. chelonae*, and *M. abscessus* and other NTM. RGM typically manifest in skin, soft tissue, and bone, and can cause soft tissue, surgical wound, and catheter-related infections. Although the role of RGM as pulmonary pathogens is unclear, underlying diseases associated with RGM include previously treated mycobacterial disease, coexistent MAC, cystic fibrosis, malignancies, and gastroesophageal disorders. *M. abscessus* is the third most commonly identified respiratory NTM and accounts for the majority (80%) of RGM respiratory isolates seen. Other than RGM, NTM reported to cause lung disease as well as affect the skin, bone, and joints include *Mycobacterium simiae*, *Mycobacterium xenopi*, and *Mycobacterium malmoense*. Ocular granulomatous diseases such as chorioretinitis and keratitis have been reported with both group IV mycobacteria, RGM, and group III SGM such as MAC or *M. szulgai* following trauma or refractive surgery. These can mimic fungal, herpetic, or amebic keratitis.\(^{15,21}\)

2. Progressive pulmonary disease (fibrocavitary, nodular bronchiectatic, hypersensitivity), which is caused primarily by MAC and *M. kansasii*. The radiographic findings of NTM lung disease vary and depend to some extent on the species. Findings can usually be separated into a predominantly fibrocavitary or fibronodular or nodular pattern with or without bronchiectasis. Cavitary disease in the upper lung zones, similar to pulmonary tuberculosis, is seen in approximately 90% of patients with *M. kansasii* infection and in approximately 50% of those with MAC infection (Figure 2). On chest radiography, cavities caused by NTM have relatively thinner walls with fewer satellite lesions than those caused by *M. tuberculosis*. Nodules and bronchiectasis are usually present within the same
lobe, occur most frequently in the right middle lobe and lingula, and are seen best on computed tomography (CT) scan. The nodular and/or bronchiectatic radiographic pattern is seen more commonly in MAC disease but can also be seen with other NTM pathogens, including *M. abscessus*, *M. simiae*, and *M. kansasii*.22–24 Pleural effusions are uncommon in NTM infection, and NTM detected in pleural effusions are of doubtful clinical significance.

3. Superficial lymphadenitis, especially cervical lymphadenitis, seen primarily in children and typically caused by MAC, *Mycobacterium scrofulaceum*, or in some cases *M. malmoense*.25

4. NTM infection occurring in transplant patients (ie, lung, hematopoietic stem cell) or those otherwise immunocompromised or undergoing immune modulation therapy.17,18

5. Disseminated NTM infection, usually seen in patients with AIDS and severely immunocompromised patients and typically caused by MAC and *M. kansasii*.16,17,26,27 Disseminated NTM disease is associated with very low CD4+ lymphocyte counts and is seen in approximately 5% of patients with HIV infection.19,20,26 Although disseminated NTM disease is rarely seen in immunosuppressed patients without HIV infection, it has been reported in renal or cardiac transplant patients, patients who use chronic corticosteroids, and those with leukemia. More than 90% of infections are caused by MAC, but other potential pathogens include *M. kansasii*, *M. chelonae*, *M. abscessus*, and *M. haemophilum*. Although seen less frequently with the advent of highly active antiretroviral therapy (HAART), disseminated infection can develop progressively from an apparently indolent or localized infection or a respiratory or gastrointestinal source. Symptoms of disseminated infection (specifically MAC-associated disease) are nonspecific and include fever, night sweats, abdominal tenderness, weight loss, and hepatosplenomegaly. Disseminated MAC disease occurs primarily in patients with more advanced HIV disease (CD4+ count typically <50 cells/μL). Clinically, disseminated MAC manifests as intermittent or persistent fever, constitutional symptoms with organomegaly and organ-specific abnormalities (eg, anemia, neutropenia from bone marrow involvement adenopathy, hepatosplenomegaly), and elevations of liver enzymes or lung infiltrates from pulmonary involvement.

• What is the approach to treatment of NTM pulmonary infection?

**MANAGEMENT**

Making the diagnosis of NTM lung disease does not necessitate the institution of therapy.
The decision to treat should be weighed against potential risks and benefits to the individual patient based on symptomatic, radiographic, and microbiologic criteria as well as underlying systemic or pulmonary immune status. Close observation is indicated if the decision not to treat is made. If treatment for NTM is initiated, comprehensive management includes long-term follow-up with periodic bacteriologic surveillance, watching for drug toxicity and drug-drug interactions, ensuring adherence and compliance to treatment, and managing comorbidity. Generally, pulmonary disease progresses slowly, but lung disease attributed to RGM can result in respiratory failure. Thus, RGM should be recognized as a possible cause of chronic mycobacterial lung disease, especially in immunocompromised patients, and respiratory isolates should be assessed carefully. Identification and drug susceptibility testing are essential before initiation of treatment for RGM. Treatment may include a combination of injectable aminoglycosides, imipenem, or cefoxitin and oral drugs such as a macrolide (eg, clarithromycin, azithromycin), doxycycline, fluoroquinolones, trimethoprim/sulfamethoxazole, or linezolid. If there is an identifiable skin or subcutaneous site or evidence of local disease, surgical debridement or resection of localized disease combined with multidrug clarithromycin-based therapy offers the best chance for a cure.28

- How should this patient’s *M. kansasii* pulmonary infection be treated?

*Mycobacterium kansasii* is a slow-growing photochromogen NTM based on its growth characteristics on culture and pigmentation when exposed to light. It is a common cause of NTM pulmonary disease in the United States, second only to MAC.3,9 On radiography, *M. kansasii* lung disease closely resembles typical tuberculosis (ie, cavitary infiltrates in upper lung zones).24 Older age, male sex, smoking history, and underlying lung disease (eg, chronic obstructive pulmonary disease) are common clinical features. Other risk factors include malignancy, use of immunosuppressive drugs, alcohol abuse, pneumoconiosis, and HIV infection. Affected patients tend to present in their fifth decade of life or later, with an approximate 3:1 male predominance. Certain occupational groups are at increased risk, including miners, welders, sandblasters, and painters. Some patients, however, have no risk factor other than their geographic area of residence, such as the southeast United States and parts of England and Wales.3,9,29,30 *Mycobacterium kansasii* can cause disseminated disease in immunocompromised hosts, such as patients with AIDS.31

As per Clinical and Laboratory Standards Institute guidelines, routine susceptibility testing of *M. kansasii* isolates is recommended for rifampin only, as treatment failure is generally associated with rifampin-resistant strains. Treatment of *M. kansasii* pulmonary disease is a regimen of daily isoniazid (300 mg/day), rifampin (600 mg/day), and ethambutol (15 mg/kg/day), and patients should be treated until culture-negative on therapy for 1 year.9 In patients receiving HAART, rifabutin should be substituted for rifampin at modified doses and while monitoring for drug-drug interactions. Use of fluoroquinolones, macrolides, or trimethoprim-sulfamethoxazole in rifampin-resistant or isoniazid-intolerant patients lacks clear evidence, but can be considered as alternatives.

Based on this patient’s underlying history of chronic obstructive pulmonary disease and smoking as well as the characteristics of the lesion, other coexisting conditions must be treated and malig-
nancy or fungal disease must be ruled out. The diagnostic criteria for the treatment of NTM also underscore the importance of a comprehensive systematic approach with microbiologic and clinical surveillance.9

CASE 1 CONCLUSION

CT scan is performed and results suggest an aspergilloma. The patient undergoes bronchoalveolar lavage and biopsy to rule out malignancy and the results are consistent with inflammation. The patient was initially placed on 4-drug antituberculosis therapy—rifampin, isoniazid, ethambutol, and pyrazinamide—until the specific diagnosis was established and *M. kansasii* was cultured and identified. Drug treatment was then deescalated to rifampin, isoniazid, and ethambutol because pyrazinamide is not effective against *M. kansasii*. The patient shows symptomatic improvement, but repeat chest radiographs remain relatively unchanged over a period of a year.

CASE PATIENT 2

INITIAL PRESENTATION AND EVALUATION

A 42-year-old woman who is a nonsmoker and has no past medical problems except seasonal allergic rhinitis and “colds and flu-like illness” once or twice a year is evaluated for a chronic lingering cough with occasional sputum production. The patient denies any other chronic symptoms and is otherwise very active, participating in a very rigorous regular exercise program. Physical examination reveals no specific pulmonary abnormalities, a body mass index of 22 kg/m², and mild pectus excavatum. Chest radiograph is unremarkable, but a CT scan of the chest reveals minimal nodular and cylindrical bronchiectasis in both lungs (Figure 3). No previous radiographs are available for comparison. The patient is HIV-negative. Sputum tests reveal normal flora and fungus, and an acid-fast bacilli smear is negative. Later sputum culture for mycobacteria shows a scanty growth of MAC in 1 specimen.

- What are the initial considerations in a patient who presents with MAC infection?
- Should treatment be initiated in this patient?

**MYCOBACTERIUM AVIUM COMPLEX**

Among NTM, MAC is the most common cause of pulmonary disease worldwide.1–5 MAC includes 2 species: *M. avium* and *M. intracellularare*. These organisms are genetically similar and generally not differentiated in the clinical microbiology laboratory, although there are isolated references in the literature suggesting that there are differences in prognosis in patients with *M. avium* infections as compared to those with *M. intracellularare* infections. Patients with *M. avium* infection appear to have...
similar clinical characteristics and body types, including lean build, scoliosis, pectus excavatum, and mitral valve prolapse. The mechanism by which this body morphotype predisposes to pulmonary mycobacterial infection is not defined, but ineffective mucociliary clearance is a possible explanation. Evidence suggests that some patients may be predisposed to NTM lung disease because of preexisting bronchiectasis. Some potential etiologies for bronchiectasis in this population include gastroesophageal reflux with chronic aspiration, α1 antitrypsin deficiency, and cystic fibrosis. Other risk factors associated with mortality include fibrocavitary disease on chest radiograph, older age, lower body mass index, and other comorbid conditions. Although robust data are lacking, the widespread impression is that the frequency of MAC pulmonary disease may be increasing.

**CLINICAL PRESENTATION**

Pulmonary disease caused by MAC may take on one of several clinically different forms such as asymptomatic “colonization” or persistent minimal infection, endobronchial involvement, progressive pulmonary disease with radiographic and clinical deterioration, hypersensitivity pneumonitis, or persistent, overwhelming mycobacterial growth, often in an underlying damaged lung either due to chronic obstructive lung disease or pulmonary fibrosis. The traditionally recognized presentation of MAC pulmonary disease is a male smoker in his late 40s or 50s with a chest radiograph showing apical fibrocavitary lung disease. If left untreated or in cases of resistant infection or erratic treatment, this form of disease is generally progressive and can result in extensive cavitary lung destruction and respiratory failure, especially if complicated with drug resistance. Pulmonary disease in postmenopausal, nonsmoking white women (known as Lady Windermere syndrome) may also present radiographically with nodular and interstitial infiltrates frequently involving the right middle lobe or lingula but tends to have a much slower progression than cavitary disease. Even with this more indolent form of disease, progression can occur. In these cases, high-resolution CT may demonstrate multiple small, peripheral pulmonary nodules centered on the bronchovascular tree and peripheral tubular or cylindrical bronchiectasis. The radiographic term “tree-in-bud” has been used to describe what may reflect inflammatory changes, including bronchiolitis. Patients may also have other co-pathogens isolated from culture, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and occasionally other NTM such as *M. abscessus* or *M. chelonae.*

Hypersensitivity pneumonitis, which was initially described as a consequence of exposure to hot tubs, mimics allergic hypersensitivity pneumonitis with respiratory symptoms and culture/tissue identification of MAC or sometimes other NTM. It is unclear whether hypersensitivity pneumonitis is an inflammatory process, an infection, or both, and opinion regarding the need for specific antibiotic treatment is divided. However, avoidance of exposure is prudent and recommended.

**DIAGNOSIS**

The diagnosis of MAC is most readily established by culture of blood, bone marrow, respiratory secretions/fluid, or tissue specimens from suspected sites of involvement. Due to shedding of MAC into the respiratory secretions in patients with nodular bronchiectatic disease, as compared to those with the fibrocavitary form of the disease, sputum may be intermittently positive with variable colony counts and polyclonal infections. Prior to the advent of
high-resolution CT, isolation of MAC organisms from the sputum of such patients was frequently dismissed as colonization; hence, the composite criteria of symptoms with radiographic and microbiologic correlation are essential to categorize the disease and determine the need for therapy. In the absence of evidence of any clinical, radiologic, or mycobacterial progression of disease, clinical surveillance without initiating specific anti-MAC therapy is a reasonable option.9 The Bronchiectasis Severity Index based on dyspnea score, lung function tests, colonization of pathogens, and extent of disease is a useful clinical predictive tool that identifies patients at risk of future mortality, hospitalization, and exacerbations and could be used to evaluate the need for specific treatment.43 Identifying the combination of NTM infection, especially MAC, in a patient with underlying clinical and radiographic evidence of bronchiectasis is of value in determining comprehensive treatment and management strategies.

CASE 2 CONTINUED

After approximately 2 months of observation and nonspecific symptomatic treatment, the patient’s chronic symptoms continue. She now develops intermittent hemoptysis. Repeat sputum studies reveal moderate growth of *M. avium*. A follow-up CT scan shows progression of disease with an increase in the “tree-in-bud” pattern (Figure 4).

- What treatment protocols are recommended?
- What is the importance of macrolide-based treatment regimens?

TREATMENT REGIMENS

As per the ATS/IDSA statement, macrolides are the mainstay of treatment for pulmonary MAC disease.9 Macrolides have an increased concentration in the lung, and when used for treatment of pulmonary MAC disease, there is a strong correlation between in vitro susceptibility, in vivo (clinical) response, and their immunomodulating effects.44,45 Macrolide-containing regimens have demonstrated efficacy in patients with MAC pulmonary disease;46,47 however, macrolide monotherapy should be avoided to prevent the development of resistance. Prior to the advent of these agents, treatment with multidrug regimens, usually including rifampin, ethambutol, and isoniazid, achieved initial sputum conversion rates of only 50% to 70%, with 20% to 30% relapse rates.9,35 At the outset, it is critical to establish the objective criteria of determining response in all cases as well as ensure that the patient understands the goals. Moreover, experts suggest that due to the possibility of drug intolerance, side effects, and the need for prolonged therapy, a “step ladder” ramping up approach to treatment be adopted,

Figure 4. Contrast computed tomography of the chest demonstrating progression of *Mycobacterium avium* complex with increasing “tree-in-bud” pattern in the left lung.
with gradual introduction of therapy within a short time period; this approach may improve compliance and adherence to treatment.

After determining that the patient requires therapy and whether suppressive or aggressive therapy should be initiated, the standard recommended treatment for MAC pulmonary disease includes the following:

For most patients with nodular/bronchiectatic disease, a thrice-weekly regimen of clarithromycin (1000 mg) or azithromycin (500 mg), rifampin (600 mg), and ethambutol (25 mg/kg) is recommended. For patients with fibrocavitary MAC pulmonary disease or severe nodular/bronchiectatic disease, a daily regimen of clarithromycin (500–1000 mg) or azithromycin (250 mg), rifampin (600 mg) or rifabutin (150–300 mg), and ethambutol (15 mg/kg), with consideration of 3 times/week amikacin or streptomycin early in therapy, is recommended. For patients with disseminated MAC pulmonary disease should include clarithromycin (1000 mg/day) or azithromycin (250 mg/day) and ethambutol (15 mg/kg/day) with or without rifabutin (150–350 mg/day). The duration of therapy depends upon resolution of signs and immune reconstitution.

Prophylaxis for disseminated MAC disease should be given to HIV-infected adults with a CD4+ count less than 50 cells/μL. Azithromycin 1200 mg/week or clarithromycin 1000 mg/day have proven efficacy, and rifabutin 300 mg/day is also effective but less well tolerated. Rifabutin is more active in vitro than rifampin against MAC and is used in HIV-positive patients because of drug-drug interaction between antiretroviral drugs and rifampin.

For MAC hypersensitivity pneumonitis, avoidance of exposure is the mainstay of management. In some cases, steroids are used with or without a short course of anti-MAC therapy (ie, clarithromycin/azithromycin, rifampin, ethambutol).

CASE 2 CONTINUED

The patient is treated with clarithromycin, rifampin, and ethambutol for 1 year with sputum conversion after 9 months. In the later part of her treatment, she experiences decreased visual acuity. Treatment is discontinued prematurely after 1 year due to drug toxicity and continued intolerance to drug therapy. She remains asymptomatic for 8 months and then begins to experience mild to moderate hemoptysis with increasing cough and sputum production associated with postural changes during exercise. Physical examination overall remains unchanged. Three sputum results reveal heavy growth of MAC, and a CT scan of the chest shows a cavitary lesion in the left upper lobe along with the nodular bronchiectasis (Figure 5).

- What are the management options at this stage?

Based on this patient’s continued symptoms, progression of radiologic abnormalities, and current culture growth, she requires retreatment. With
the adverse effects associated with ethambutol during the first round of therapy, the drug regimen needs to be modified. Several considerations are relevant at this stage. Relapse rates range from 20% to 30% after treatment with a macrolide-based therapy. Obtaining a culture sensitivity profile is imperative in these cases. Of note, in ideal cases treatment should not be discontinued altogether, and instead the toxic agent should be removed from the treatment regimen. In this case, the patient could have continued on a 2-drug regimen of clarithromycin and rifampin. Reinfection with multiple genotypes may also occur after successful drug therapy but is primarily seen in MAC patients with nodular bronchiectasis. Patients who have failed previous therapy, even those with macrolide-susceptible MAC isolates, are less likely to respond to subsequent therapy. Data suggest that intermittent medication dosing is not effective for patients with severe or cavitary disease or in those who have failed previous therapy. In this case, treatment should include a daily 3-drug therapy, with an injectable thrice-weekly aminoglycoside. Other agents such as fluoroquinolones and linezolid may have to be tried. Clofazimine, cycloserine, ethionamide, and mefloquine are sometimes used, but their efficacy is unproven and doubtful. Pyrazinamide and isoniazid have no activity against MAC.

TREATMENT FAILURE AND DRUG RESISTANCE

Treatment failure is considered to have occurred if patients have not had a response (microbiologic, clinical, or radiographic) after 6 months of appropriate therapy or achieved conversion of sputum to culture-negative after 12 months of appropriate therapy. Multiple factors can interfere with the successful treatment of MAC pulmonary disease, including medication nonadherence, medication side effects or intolerance, lack of response to a medication regimen, or the emergence of a macrolide-resistant or multidrug-resistant strain. Inducible macrolide resistance remains a potential factor. Treatment failure may also be drug-related, due to poor drug penetration into the damaged lung tissue, and subtherapeutic tissue levels or drug-drug interactions leading to suboptimal drug levels. Peak serum concentrations \( C_{[\text{max}]} \) have been found to be below target ranges in approximately 50% of the patients using a macrolide and ethambutol. Concurrent use of rifampin decreases the peak serum concentration of macrolides and quinolones, with acceptable target levels seen in only 18% to 57% of cases. Whether this alters the outcomes of the patient is still not clear. Factors identified as contributing to the poor response to therapy include poor compliance, cavitary disease, previous treatment for MAC pulmonary disease, and a history of chronic obstructive lung disease.

• Should therapeutic drug monitoring be done in patients being treated for MAC pulmonary disease?

Studies by Koh and colleagues and van Ingen and colleagues with pharmacokinetic and pharmacodynamics data showed that in patients on MAC treatment with both clarithromycin and rifampicin, plasma levels of clarithromycin were lower than recommended minimal inhibitory concentrations (MIC) against MAC for that drug, and that rifampicin lowered clarithromycin concentrations more than did rifabutin, with the AUC/MIC ratio being suboptimal in nearly half the cases. However, low plasma clarithromycin concentrations did not have any correlation with treatment outcomes, as the peak plasma drug concentrations and the peak plasma drug concentration/MIC ratios did not differ between patients with unfavorable treatment
outcomes and those with favorable outcomes. This is further compounded by the fact that macrolide drug levels in lung tissue are higher than in plasma and hence the significance of low plasma levels is unclear; however, it is postulated that achieving higher drug levels could in fact lead to better clinical outcomes. Pending specific well-designed prospective randomized controlled trials, routine therapeutic drug monitoring is not currently recommended.

• **Is surgery an option in this case?**

With the overall 5-year mortality for MAC pulmonary disease being approximately 28% in a retrospective analysis, especially in cavitary disease, surgery is an option in selected cases as part of adjunctive therapy along with anti-MAC therapy based on mycobacterial sensitivity. Surgery is used as either a curative approach or a “debulking” measure. When present, clearly localized disease, especially in the upper lobe, lends itself best to surgical intervention. Surgical resection of a solitary pulmonary nodule due to MAC in addition to concomitant medical treatment is recommended. Surgical intervention should be considered early in the course of the disease because it may provide a cure without the prolonged treatment and its associated problems, and this approach may lead to early sputum conversion. Surgery should also be considered in patients with macrolide-resistant or multidrug-resistant MAC or in those who cannot tolerate the side effects of therapy, provided that the disease is focal and limited. Patients with poor preoperative lung function have poorer outcomes than those with good lung function, and postoperative complications arising from treatment, especially with a right-sided pneumonectomy, tend to occur more frequently in these patients.55,36,56

**CASE 2 CONCLUSION**

The patient is restarted on therapy with clarithromycin, rifampin, and moxifloxacin and has a good clinical response.

**SUMMARY**

NTM is ubiquitous in the environment, and NTM infection has variable manifestations, especially in patients with no recognizable immune impairments. Management strategies must be individualized based on degree of involvement, goal of therapy, and risk-benefit ratio. In diffuse pulmonary disease, drug treatment remains difficult due to medication side effects and high failure rates. When a localized source of infection is identified, especially in RGM disease, surgical treatment may be needed. The importance of appropriately determining which patients require close surveillance and no specific antimicrobial therapy or specific treatment with recognition of comorbidity and relapses cannot be overemphasized.

**REFERENCES**


