Pharmacotherapy for nontuberculous mycobacterial pulmonary disease

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Purpose. To provide an updated review of the diagnosis and pharmacotherapy of nontuberculous mycobacteria pulmonary disease (NTM-PD) and summarize guideline recommendations for an interdisciplinary treatment approach.

Summary. A systemic approach was taken in which all articles in English in MEDLINE and PubMed were reviewed. The US National Library of Medicine's DailyMed database was used to assess drug package inserts. Analysis of NTM treatment guidelines is summarized in the article with a focus on medications, dosing, interactions, and medication monitoring.

Conclusion. It is critical to manage patients with NTM with a multidisciplinary team approach. Treatment is prolonged and expensive, and the potential for drug toxicity, adverse effects, and drug interactions requires monitoring. Clinical pharmacists play a role in the management of NTM.

Keywords: inhaled amikacin, *Mycobacterium abscessus*, *Mycobacterium avium*, *Mycobacterium xenopi*, NTM, nontuberculous mycobacterial pulmonary disease

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Over 190 species and subspecies of nontuberculous mycobacteria (NTM) have been identified. They are often categorized into slow growers, including the *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium marinum*, and rapid growers, such as *Mycobacterium chelonae*, *Mycobacterium fortuitum*, and *Mycobacterium abscessus*. NTM are ubiquitous organisms, often found in soil and water (including in municipal water sources). Most are saprophytes; however, approximately one-third of NTM have been linked to human diseases. These opportunistic pathogens can cause both pulmonary and extrapulmonary infections.[1] MAC is the most common isolate and cause of pulmonary NTM disease (80% of cases) in the United States. MAC leads to pulmonary disease in immunocompetent hosts while causing disseminated infection in immunocompromised hosts, including patients with AIDS. This review describes only pulmonary manifestations of MAC and other NTM.[2] NTM are not contagious and typically only cause infection in patients with underlying lung disease or a compromised immune system.[3]

NTM pulmonary disease (NTM-PD) has become increasingly recognized, with a consistently rising prevalence in the United States.[4] The 2 forms of NTM lung disease are nodular bronchiectasis and cavitary disease. Nodular bronchiectasis causes inflammation to the airway and a diminished ability to clear secretions, which can lead to infection. Cavitary disease is the more progressive form, causing scarring and fibrosis that can lead to respiratory failure. Given the insidious onset and presentation, the multitude of organisms, and the complex treatment regimens in NTM-PD, both diagnosis and treatment can be challenging for patients as well as providers. A guideline-based, multidisciplinary approach to diagnosis and treatment can help to achieve optimal outcomes. The 2007 joint American Thoracic Society (ATS) and Infectious

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Diseases Society of America (IDSA) NTM guideline[5] was updated in 2020.[1] Here we review the guidelines related to NTM-PD, with a focus on common pathogens and pharmacotherapy for NTM-PD.

Epidemiology

NTM is not a reportable condition in most states. This makes the true number of cases difficult to ascertain.[6] Current estimates suggest that more than 80,000 individuals in the United States have NTM.[2,7] About 12,000 to 18,000 new cases are diagnosed each year; based on Medicare population data between 1997 and 2007, the incidence of NTM increased at a yearly rate of 8.2%.[2,7] Recent data from a US managed care claims database collected between 2008 and 2015 found an increased annual incidence of NTM across the county, with a higher propensity for incidence among women and individuals in older age groups.[8]

Risk factors

Structural lung diseases, including chronic obstructive pulmonary disease (COPD),[9] bronchiectasis, cystic fibrosis, prior tuberculosis infection, and immunosuppressant therapy,[10] as well as esophageal motility disorders[11,12], are among the most common predisposing factors for NTM-PD.[13] Bronchiectasis and NTM infections, most commonly with MAC, often co-occur. There is evidence that bronchiectasis can occur before NTM infection in patients, but also that NTM can cause bronchiectasis.[14] This association is more common among certain patient populations, mainly in postmenopausal women with scoliosis or mitral valve prolapse. Females appear to be at increased risk for NTM infection; however, in persons less than 60 years of age, incidence is higher among men.[15]

Many individuals may be colonized with NTM, with clinical signs of infection occurring up to 10 years later.[16] The number of NTM-positive sputum cultures has been rising. Increased surveillance and improved detection techniques likely account for some of this rise; other factors such as changes in weather patterns, lower temperature settings on home water heaters, antimicrobial use, and chronic medications also have a role.[17] A case-control study demonstrated that patients who had used an inhaled corticosteroid (ICS) within the prior year had a significantly increased risk of NTM.[18] Use of ICS is higher in patients with chronic airway diseases, such as COPD, and bronchiectasis, which are identified risk factors for NTM-PD. Environmental factors are also important in biofilm formation, which gives NTM pathogens an advantage through more antimicrobial resistance and difficulty in eradication.

KEY POINTS

- Nontuberculous mycobacteria pulmonary disease (NTM-PD) is increasingly recognized, with a rising prevalence in the United States. Current estimates suggest that more than 80,000 Americans have NTM.
- Structural lung diseases, including chronic obstructive pulmonary disease, bronchiectasis, cystic fibrosis, prior tuberculosis infection, immunosuppressant therapy, and esophageal motility disorders, are common predisposing factors for NTM-PD.
- Treatment for NTM infections is long term and expensive and includes a multidrug regimen that is limited by increasing resistance, toxicity, and adverse effects. Patients need to be monitored closely for medication compliance.

Diagnosis

The diagnostic criteria for NTM include clinical symptoms, radiologic findings, and isolation of NTM from respiratory specimens. Patients with NTM usually present with nonspecific clinical symptoms such as chronic cough, fever/chills, night sweats, weight loss, shortness of breath, and hemoptysis.[5] Isolation of bacteria with histologic features of NTM from at least 2 expectorated sputum cultures or a culture from 1 bronchial wash/lavage or lung biopsy specimen is needed for diagnosis.[5] NTM in the sputum does not always require treatment and should prompt further investigation. IDSA guidelines are specific in mentioning that clinical correlation is important in diagnosis to help determine whether a respiratory sample is a pathogen or a contaminant.[15]

To make a diagnosis, a morning sputum sample should be collected, preferably on 3 different occasions, for acid-fast bacilli (AFB) analysis. AFB staining does not differentiate between *Mycobacterium tuberculosis* and NTM. If it is not possible to obtain sputum samples, a bronchoscopy with or without biopsy can be considered. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry has been used more frequently for identification of many clinically relevant slow-growing and rapidly growing species of NTM. It is a rapid method with a shorter turnaround time than sequencing. The disadvantage to the mass spectrometry technique is that it requires a larger burden of organisms than is available from a typical culture.[19] Currently, available DNA probes (labeled with acridium ester) detect MAC and *M. kansasii* and can be used on isolates from liquid or solid media. These probes are rapid (2 hours), specific (100%), and sensitive (85%-100%)[14] after growth from media.

Treatment

Treatment for NTM infections is often long term and expensive and includes a multidrug regimen that is limited by increasing resistance, toxicity, and adverse effects. Of interest to the pharmacy community, there is a paucity of literature on optimal pharmacokinetic/pharmacodynamic (PK/PD) relationships for NTM. Identification of drug PK/PD targets

from hollow-fiber models instead of outcome data limits efficacy based on drug exposure.[20-22] Because drug efficacy targets are lacking, harm mitigation strategies are emphasized so that patients can tolerate NTM regimens for as long as possible.

Patients will need to be closely monitored for medication compliance. Most treatments are not approved by the Food and Drug Administration (FDA) and have not been studied under controlled clinical trial conditions. Currently, there are only 2 products approved by FDA to treat NTM: inhaled liposomal amikacin for refractory MAC and macrolides for disseminated MAC in HIV.[23] Susceptibility testing with macrolides and amikacin is done for MAC and *M. abscessus*, while susceptibility testing with rifampin is done for *M. kansasii*.[1] There is a lack of data or recommendations on susceptibility testing for *Mycobacterium xenopi*. For macrolides, a 14-day incubation with analysis of the *erm* gene[24] should be performed to evaluate the potential for inducible macrolide resistance.[1] Baseline susceptibility testing is recommended by Clinical and Laboratory Standards Institute guidelines for NTM isolates from patients with confirmed disease.[1] A summary of medications used to treat NTM-PD is found in Table 1.

Species-specific pharmacology and guideline updates

M. avium. Macrolides have been the mainstay of MAC therapy and prophylaxis.[1] Routine susceptibility testing for only clarithromycin is recommended at baseline, if therapy fails or the patient relapses after 6 months of macrolide-containing therapy, and for patients with disseminated MAC who remain culture positive after 3 months of macrolide therapy.[5] Untreated MAC isolates for which clarithromycin minimum inhibitory concentrations (MICs) are less than 4 μg/mL are considered susceptible. In contrast, relapse strains after treatment that have a clarithromycin MIC of 32 μg/mL or greater are not considered susceptible. Newer recommendations suggest azithromycin-based regimens for fewer drug-drug interactions, better tolerance, easier dosing, and lower acquisition cost.[25]

Nodular and bronchiectatic pulmonary MAC are treated with clarithromycin 1,000 mg or azithromycin 500 mg, rifampin 600 mg or rifabutin 150-300 mg, and ethambutol 25 mg/kg dosed 3 times weekly.[25,26] Patients with fibrocavitary MAC or severe disease usually require a daily regimen of clarithromycin 500-1,000 mg or azithromycin 250 mg, rifampin 600 mg or rifabutin 150-300 mg, and ethambutol 15 mg/kg with amikacin administered intravenously (IV) 3 times a week.[27] In a study by Peloquin et al,[28] older age and large cumulative amikacin doses rather than dosing frequency and size of the dose, were shown to be associated with high risk of ototoxicity. In older patients and those with renal impairment, consider starting these patients on 8-10 mg/kg daily with a gradual increase in the dose to reach therapeutic levels.[29] Treatment should continue for at least a year after culture conversion.[1]

For macrolide-resistant pulmonary MAC, therapy with ethambutol (15 mg/kg) and rifampin (450-600 mg daily) or rifabutin (150-300 mg daily) together with IV amikacin (15-25 mg/kg 3 times weekly) (ideal duration is ≥6 months) and/or clofazimine (100 mg daily) and/or nebulized or liposomal amikacin (after completion of IV amikacin) has been recommended.[30] Consider addition of bedaquiline 400 mg daily for 2 weeks with 200 mg daily thereafter as a substitute for rifampin. Bedaquiline must not be administered together with rifampin.[31] Inhaled amikacin is an option to overcome aminoglycoside toxicity; however, this should only be added for patients for whom therapy has failed after 6 or more months.[32,33]

M. kansasii. Treatment regimens for *M. kansasii* consist of rifampin (600 mg daily), ethambutol (15 mg/kg daily), and either isoniazid or a macrolide for 12 months after a negative culture.[1,5] Two small retrospective trials showed equivalent efficacy of clarithromycin and isoniazid.[34-36] Isolates that are susceptible to rifampin are susceptible to rifabutin, and these drugs can be used interchangeably. Resistance to isoniazid and ethambutol is possible; however, if a strain is resistant, it is most likely resistant to rifampin as well.[5] Fluoroquinolones are not recommended as first-line therapy but can be considered as second-line agents (moxifloxacin) for treatment of rifampin-resistant strains.[1] In patients with disease that is not severe or bronchiectatic, therapy 3 times weekly is appropriate. However, with isoniazid-based regimens or with nodular disease, daily treatment is recommended.[1] Recommended treatment duration is at least 12 months.[37-39]

M. abscessus. *M. abscessus* is difficult to treat given resistance to β-lactams[40]; therefore, multidrug regimens (3 or more drugs) should be used. In strains without a resistance mutation, a macrolide-containing regimen is recommended.[1,24,41] Drug regimens are divided into an intensive phase and a continuation phase. For macrolide-susceptible isolates, the intensive phase consists of imipenem 1,000 mg IV twice daily (or cefoxitin 8-12 g IV daily divided into 2 or 3 doses) with azithromycin 250-500 mg orally once daily and amikacin 15 mg/kg daily (peak goal of 20-30 μg/mL and trough goal of 5-10 μg/mL). A loading dose of tigecycline 100 mg followed by 50 mg IV every 12 hours is another option for isolates with a MIC below 1.[42-44] Clofazimine[45,46] and linezolid[47] have also been studied in treatment of *M. abscessus*. Optimal duration has not been defined, but the most common recommendation is 12 months after a negative culture.

M. xenopi. Mortality rate is high with *M. xenopi*,[48,49] requiring aggressive treatment. Recent updates suggest using a daily 3-drug regimen with rifampin, ethambutol, and either a macrolide or a fluoroquinolone (moxifloxacin).[50] Recommended treatment duration is for at least 12 months after culture conversion.[1] In patients with cavitary or severe bronchiectatic

Table 1. Medications Used in Management of Nontuberculous Mycobacteria Pulmonary Disease[1]

Agent	Daily Dosing	Three Times Weekly Dosing	Hepatic Impairment	Renal Impairment	Adverse Effects
Oral					
Azithromycin	250-500 mg/day	500 mg/day	No dose adjustment	No dose adjustment	GI, reversible hearing loss, hepatotoxicity, prolonged QTc
Clarithromycin	500 mg twice daily	500 mg twice daily	No dose adjustment	CL_{cr} <30mL/min: reduce dose by 50%	GI, hearing loss, hepatotoxicity, prolonged QTc
Clofazimine	100-200 mg/day	NA	Caution in severe hepatic impairment	Caution in severe renal impairment	Skin color change, hepatotoxicity, GI, prolonged QTc
Ethambutol	15 mg/kg/day	25 mg/kg/day	No dose adjustment	CL_{cr} <30mL/min: 20-25 mg/kg per dose 3 times weekly	Vision changes, peripheral neuritis
Isoniazid	5 mg/kg up to 300 mg per day	NA	Caution	No dose adjustment	Increased liver enzymes, peripheral neuropathy
Linezolid	600 mg 1 or 2 times daily	NA	No dose adjustment	No dose adjustment	Diarrhea, leukopenia, thrombocytopenia, rash, headache
Moxifloxacin	400 mg/day	NA	No dose adjustment	No dose adjustment	Hypoglycemia, nausea, tendon rupture, prolonged QTc
Rifabutin	150-300 mg/day (150 mg with clarithromycin)	300 mg/day	Caution, not studied	CL_{cr}<30 mL/min: reduce dose by 50%	Hepatotoxicity, orange discoloration of secretions, cytopenia, uveitis
Rifampicin (rifampin)	10 mg/kg (450 or 600 mg) per day	600 mg/day	Caution, not studied	No dose adjustment	Hepatotoxicity, orange discoloration of secretions, cytopenia, increased LFTs
Parenteral					
Amikacin IV	10-15 mg/kg/day 3 times weekly, adjusted with drug levels	15-25 mg/kg/day, adjusted with drug levels	No dose adjustment	Reduce dose or increase dose interval	Auditory toxicity, nephrotoxicity, neurotoxicity
Cefoxitin IV	2-4 g 2 or 3 times daily (max 12 g/day)	NA	No dose adjustment	Reduce dose or increase dose interval	GI, rash, increased LFTs
Imipenem IV	500-1,000 mg, 2 or 3 times per day	NA	No dose adjustment	Reduce dose or increase dose interval	Increased LFTs, itch, rash, nephrotoxicity, seizures
Streptomycin IV or IM	10-15 mg/kg/day, adjusted with drug levels	15-25 mg/kg/day, adjusted with drug levels	No dose adjustment	Reduce dose or increase dose interval	Auditory toxicity, muscle weakness, nephrotoxicity

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Table 1. Medications Used in Management of Nontuberculous Mycobacteria Pulmonary Disease[1]

Agent	Daily Dosing	Three Times Weekly Dosing	Hepatic Impairment	Renal Impairment	Adverse Effects
Tigecycline IV	25-50 mg 1 or 2 times daily	NA	25 mg 1 or 2 times daily in severe hepatic impairment	No dose adjustment	GI, headache, increased liver enzymes
Inhalation					
Amikacin liposome inhalation suspension	590 mg per day	NA	No dose adjustment	No dose adjustment	Bronchospasm, cough, hemoptysis, ototoxicity, upper airway irritation, diarrhea, nausea
Amikacin IV	250-500 mg per day	NA	No dose adjustment	No dose adjustment	Bronchospasm, cough, hemoptysis, ototoxicity, upper airway irritation, diarrhea, nausea

Abbreviations: CL_{cr}, creatinine clearance; GI, gastrointestinal, IM, intramuscular; IV, intravenous; LFTs, liver function tests; NA, not applicable; QTc, QT interval.

disease, IV amikacin has been shown to improve microbiological cure in animal studies.[51,52] Treatment recommendations are primarily based on expert opinion given limited data and the high mortality with *M. xenopi* infection.[53]

Newer drug therapy

Inhaled liposomal amikacin is composed of amikacin encapsulated in 0.3-mm-diameter, charge-neutral, highly biocompatible liposomes that deliver amikacin. When engulfed by macrophages, liposomes deliver a high concentration of amikacin in the lungs.[54] Systemic absorption of liposomal amikacin is lower than for parenteral amikacin, resulting in less systemic toxicity.[55] Based on the phase 3 CONVERT trial[32], FDA approved amikacin liposomal inhalation suspension in 2018 for treatment of refractory MAC in combination with guideline-based therapy in patients who have limited or no alternative treatment options. Another multicenter, randomized, double-blind study demonstrated that liposomal amikacin, when used in combination with a multidrug regimen, produced improvements in sputum conversion and 6-minute walking distance vs placebo in treatment of refractory MAC lung disease.[31] The most common adverse reactions (incidence of ≥10% with higher incidence than in controls) in patients with refractory MAC lung disease were dysphonia, cough, bronchospasm, hemoptysis, musculoskeletal pain, upper airway irritation, ototoxicity, fatigue/asthenia, exacerbation of underlying pulmonary disease, diarrhea, nausea, and headache.[56] The label includes a box warning for risk of increased respiratory adverse reactions, including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease, that have led to hospitalizations in some cases.[56]

Inhaled amikacin for refractory pulmonary NTM disease has been used with some success for *M. abscessus*. One study assessed patients who received inhaled amikacin in addition to a failed regimen.[57] In this study with

20 patients, 15 were culture positive for *M. abscessus* and 5 were positive for MAC, and patients had received a median of 60 months of antimycobacterial treatment. Patients were followed for a median of 19 months after completion of therapy. Eight (40%) patients had at least one negative culture, and 5 (25%) had persistently negative cultures. In this study, addition of inhaled liposomal amikacin was associated with microbiologic and/or symptomatic improvement; however, adverse effects related to treatment were a concern, as amikacin therapy was stopped in 7 patients, including in 2 patients each for ototoxicity and hemoptysis.

The recommended dose for inhaled liposomal amikacin in adults is one vial (590 mg/8.4 mL) inhaled once daily using the Lamira nebulizer system (Pari, Starnberg, Germany). The vials are refrigerated (at 36-46 °F) but can be stored at room temperature for up to 4 weeks. The vials should be shaken before use and should be at room temperature. The vial contents are poured into the medication reservoir of the nebulizer.[56]

Newer antibiotic combinations such as imipenem/cilastatin/relebactam and meropenem/vaborbactam have shown activity against *M. abscessus*. This species produces a drug-resistant β-lactamase but seems to be inhibited by several β-lactamase inhibitors.[40] Based on this, studies were conducted to evaluate whether relebactam and vaborbactam would have the same effect. These 2 β-lactamase inhibitors are used in combination with carbapenems. Imipenem is currently recommended as part of treatment for *M. abscessus*, so combination with a β-lactamase inhibitor should be a better option. Meropenem alone also has activity, but this activity is thought to be less than that of imipenem. However, with the addition of vaborbactam, meropenem has increased activity. Avibactam/ceftazidime has poor activity against *M. abscessus*, making carbapenem and β-lactamase inhibitor combinations more favorable. Drug combinations for synergistic activity have recently been shown to have efficacy, including the combination of doripenem and cefdinir. Ceftazidime or ceftaroline with imipenem has also shown efficacy. Cephalosporins alone have not been shown to have reliable activity.[40]

Clofazimine[58] is available in the United States with an investigational new drug application. This oral antibiotic agent has shown in vitro activity against rapidly growing mycobacteria and most gram-positive bacteria.[59] Having both antimicrobial and anti-inflammatory activity, it has been used in treatment of MAC and *M. abscessus*.[60-62] Clofazimine is dosed at 100-200 mg orally daily with meals. The most common adverse effect is tanning or dryness of the skin.[1]

Treatment costs

The financial impact of NTM disease is considerable, especially among older patients, where medication costs can make up 76% of NTM expenditures.[63] In 2010, the estimated cost of NTM in the United States was $1,802,000.[6] Analysis of hospitalized patients with a principal diagnosis of pulmonary mycobacterial disease from 2001 to 2012 found 20,049 discharges with an average length of stay of 9.2 days. The total aggregate cost was $903,767,292 for these discharges.[64] It is important to point out that costs can differ based on the specific organism being treated. For example, the treatment cost for *M. abscessus* is higher than for other species. With regard to economic outcomes, following guideline-based treatment for MAC has been shown to result in lower hospitalization risk than when patients are prescribed non–guideline-based treatment or go untreated.[65]

Prognosis

For NTM, cure is usually defined as a decrease rather than total cessation of symptoms.[66] A recent study from a cohort in Oregon showed mortality rates of up to 35% at 5 years, mainly due to other comorbidities.[67] The recently defined scoring system BACES (body mass index, age, cavitary erythrocyte sedimentation rate, and sex) was developed to predict mortality among patients with NTM.[68]

Role of antibiotic stewardship in NTM

Along with disease improvement, patients should also be monitored for drug toxicity, adverse effects, and drug-drug interactions (Table 1). Patients should be counseled on gastrointestinal upset, as well as drug interactions, especially with clarithromycin and rifampin.[69,70] Drug regimens and/or doses may need to be adjusted based on concurrent medications or disease states such as renal insufficiency. Patients should be monitored during therapy for hepatotoxicity from rifampin, macrolides, imipenem, and tigecycline with liver function tests.[70-73] Complete blood count monitoring during therapy for leukopenia and thrombocytopenia for rifampin, imipenem, tigecycline, and linezolid is important.[70,72-74] Renal function and ototoxicity should also be monitored during therapy, especially with aminoglycosides, as in addition to plasma therapeutic drug monitoring.[1,56] Risk for ototoxicity with macrolides has been reported.[71] Ethambutol[75] and linezolid[74] can cause optic neuritis and peripheral neuropathy. Patients need to be educated about all the above-mentioned adverse effects before initiation of therapy with these medications.

There are no documented studies showing benefits of starting injectable amikacin early (at 2-4 months) in treatment of nonrefractory MAC. In addition, there are no comparative studies to recommend one rifamycin over the other. Rifabutin[76] has more adverse effects but fewer cytochrome P-450 interactions vs rifampin, especially when used in a clarithromycin-based regimen, although there are no studies that show such interactions could lead to clinical failure. Rifabutin with clarithromycin can lead to increased adverse effects such as uveitis and leukopenia.[5]

Conclusion

NTM cases have been reported worldwide as well as in the United States,

where rates are increasing, especially in older and immunocompromised patients. Management should include a multidisciplinary approach. Treatment is based on organism identification and susceptibility testing. Treatment is often prolonged and costly and can be complicated by adverse effects, drug interactions, and toxicity. Initial treatments include an oral macrolide, and dosing could be 3 times a week, depending on diagnosis. Adverse effects of antimicrobials for NTM require monitoring. Frequency of monitoring should be individualized according to age, comorbidities, concurrent medications, and overlapping drug toxicities. Further research is needed on the optimal strategy and monitoring frequency, as no studies to date have identified the optimal frequency or most cost-effective approach to monitoring for drug-related adverse reactions.[1] Drug-drug interactions, particularly in elderly patients, can make NTM treatment difficult.[77] An interdisciplinary team including infectious disease experts, pulmonologists, and clinical pharmacists is critical to formulate guideline-recommended treatment regimens for NTM-PD, educate patients, and monitor therapy.

Disclosures

The authors have declared no potential conflicts of interest.

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