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Mycobacterial Infections (H Bach, Section Editor)

Current Therapy for Nontuberculous Mycobacterial Pulmonary Disease

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Opinion statement

Pulmonary infections due to nontuberculous mycobacteria (NTM) occur commonly, are increasing in frequency, and pose many challenges to clinicians. Typically, NTM infections occur in the presence of structural lung disease such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), or bronchiectasis. Pharmacological therapy is the mainstay of treatment but should not be initiated until it is clear that the identification of NTM in bronchial secretions fulfills the criteria for active infection. Pathogenic NTM vary in their response to pharmacological therapy. Successful antimicrobial therapy must include the prolonged use of multiple agents simultaneously. Monotherapy is to be avoided. *Mycobacterium avium* complex (MAC) is the most common cause of NTM pulmonary infection, and clinical experience with this organism is extrapolated to guide the management of other NTM infections. MAC is best treated with a combination of a macrolide, a rifamycin, and ethambutol. *Mycobacterium kansasii* infections closely mimic active tuberculosis. In previously untreated patients, therapy with isoniazid, rifampin, and ethambutol is recommended. *Mycobacterium abscessus* is the most common rapidly-growing NTM pulmonary pathogen. It is very difficult to treat successfully with antimicrobial therapy, and the optimal drug treatment remains undefined. Surgical therapy has a limited but defined role in those with localized disease due to NTM, a significant complication such as life-threatening hemoptysis, or medically unresponsive disease. Surgical resection should be considered in appropriate patients especially in those with *M. abscessus*

infections. The referral of patients to clinicians with experience in treating NTM pulmonary infections is recommended to ensure appropriate monitoring of therapeutic response and pharmacologic toxicity. Many clinical questions concerning NTM pulmonary infections remain incompletely answered. It is hoped that the increased recognition of the burden inflicted by these infections is paralleled by advances in patient-centered research.

Introduction

Nontuberculous mycobacteria (NTM) refer to mycobacteria other than *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. Over 140 species of NTM have been identified, and at least 40 can cause pulmonary disease [1]. These organisms are ubiquitous in soil and water sources. Infections result from environmental exposure rather than person-to-person or animal-to-person transmission [1]. Species of NTM are broadly categorized as rapidly growing or slowly growing based on the presence of visible colonies on solid medium before or after 7 days, respectively [2]. Despite the many identified NTM organisms, the overwhelming majority of NTM pulmonary infections in the USA are attributable to *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium abscessus*. MAC includes *M. avium* and *M. intracellulare* and is also referred to as *Mycobacterium avium-intracellulare* (MAI). This review will limit discussion to the management of disease due to these organisms in HIV negative hosts.

Recent epidemiological studies in North America indicate that the prevalence of NTM lung disease is increasing, and similar trends are noted worldwide [3, 4]. The estimated cost of medical care for NTM in 2010 exceeded $800 million with over 70 % of that cost due to prescription medication cost [5].

The isolation of NTM exceeds that of *M. tuberculosis* in most laboratories in the USA [6]. Appropriate laboratory processing of specimens for NTM has been outlined by the Clinical and Laboratory Standards Institute (www.clsi.org). It is imperative that specimens from non-sterile body sites undergo digestion and decontamination procedures to prevent bacterial overgrowth. All cultures for NTM should be cultured using both liquid broth and solid media to maximize growth and timely identification [1].

Due to the frequency of environmental NTM exposure, isolation of NTM from bronchial secretions is not uncommon. Diagnosing active disease requires the fulfillment of clinical, microbiological, and radiologic criteria as defined by the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines (outlined in Table 1) [1]. NTM pulmonary infection is often seen in conjunction with underlying structural lung disease such as chronic obstructive pulmonary disease (COPD), bronchiectasis, or cystic fibrosis (CF). In 1989, Prince et al. first described a cohort of elderly women without known underlying lung disease or immunodeficiency who presented with NTM pulmonary infection [7]. Iseman further recognized that these patients often have coexistent pectus excavatum, scoliosis, and mitral valve prolapse [8]. This presentation of NTM infection in conjunction with nodular bronchiectasis in elderly females is increasingly recognized. Gastroesophageal reflux disease (GERD) is also often associated with NTM infections [4]. In a cohort of 58 patients with nodular bronchiectasis and NTM, one quarter of patients had GERD, most of whom lacked suggestive symptoms [9].

IFN-γ and interleukin-12 are central to the host defense of mycobacterium. Compared with appropriately matched controls, patients with nodular bronchiectasis and NTM have suppressed levels of interferon [10]. Neutralizing autoantibodies to interferon have been identified that appear to predispose to disseminated NTM infections. Their role in NTM thoracic infections is speculative [11, 12]. Interferon-γ and IL-12 upregulate tumor necrosis factor (TNF) as a mechanism to control mycobacterial infections. Similar to enhanced susceptibility to tuberculosis and endemic mycoses, the use of anti-TNF therapy has been recognized as a notable risk for NTM infections [13, 14].

Symptoms of NTM lung disease are often insidious and can include chronic or recurring cough, sputum production, dyspnea, fatigue, malaise, hemoptysis, fever, and weight loss [1]. Recognition that these symptoms are attributable to NTM infection in the setting of chronic lung disease, rather than progression of underlying disease, is often challenging and requires an appropriately high level of suspicion.

Treatment of NTM pulmonary disease depends on the causative species, antibiotic susceptibilities, and clinical and radiographic features of disease. The risks and benefits of treatment of NTM lung disease should be assessed on an individual basis, as the diagnosis does not always necessitate

Table 1. ATS/IDSA criteria for NTM pulmonary disease

Clinical	1. Pulmonary symptoms AND 2. Appropriate exclusion of other diagnoses
Radiographic	1. Nodular or cavitary opacities on chest radiograph OR 2. High-resolution computed tomography scan that shows multifocal bronchiectasis with small nodules
Microbiologic	1. Positive culture results from at least two separate expectorated sputum samples OR 2. Positive culture result from at least one bronchial wash or lavage OR 3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM

immediate institution of therapy [15]. Patient comorbidities and treatment cost should be considered carefully prior to initiation of treatment, particularly given the duration and potential toxicity of therapy.

Treatment

Pharmacologic treatment

Our understanding of the ideal treatment of NTM pulmonary disease is severely limited due to paucity of randomized controlled trials and by the multitude of NTM species. Treatment recommendations are guided primarily by clinical experience, expert opinion, and extrapolation from experience with the treatment of MAC and *M. abscessus*. Interestingly, and perhaps understandably, adherence to recommended therapy proposed by the ATS/IDSA has been shown to be exceedingly poor in clinical practice [16]. Appropriate antibiotic therapy for NTM pulmonary infections is dependent upon the infecting species and the clinical presentation. Although there are general recommendations regarding the management of the most common pulmonary pathogens, uncertainty persists in management of the less frequently encountered organisms. Prolonged therapy with multiple simultaneous antimicrobials is required.

Mycobacterium avium complex

The initial recommended therapy for *Mycobacterium avium* complex (MAC) or *Mycobacterium avium-intracellulare* (MAI) pulmonary infection is a triple-drug regimen consisting of a macrolide (clarithromycin or azithromycin), a rifamycin (rifampin or rifabutin), and ethambutol. Rifampin is more commonly utilized due to better tolerability and fewer drug interactions. Patients should be treated until sputum cultures are negative on therapy for at least 12 months [1].

There are two common radiographic forms of MAC lung disease, and treatment differs between the two. MAC lung disease commonly presents as nodular bronchiectasis, most often in elderly females. Patients with MAC in conjunction with nodular bronchiectasis can be treated successfully with intermittent rather than daily therapy, which increases the tolerability of the regimen

[17]. Each agent is given three times weekly (TIW). Drugs can be introduced sequentially if tolerability remains a concern. Jeong et al. retrospectively reviewed the results of therapy in 217 patients with noncavitary MAC treated with daily (n=118) or TIW (n=99) therapy. Discontinuation of ethambutol was required more frequently in those receiving daily therapy. Clinical outcomes, including symptomatic and radiographic improvement, and sputum conversion rates were similar between the two groups [18]. However, in patients with severe nodular bronchiectatic NTM disease, daily therapy should be utilized.

MAC pulmonary infection may also present as fibrocavitary disease. Fibrocavitary disease should be treated with daily, rather than TIW triple-drug therapy with a macrolide, ethambutol, and a rifamycin. For cases of severe fibrocavitary or extensive, multilobar MAC lung disease, an intravenous (IV) aminoglycoside such as amikacin or streptomycin is generally added for the first 2–3 months of therapy.

Because rifampin is known to decrease serum levels of clarithromycin, Miwa et al. prospectively compared triple-drug therapy with clarithromycin, ethambutol, and rifampin to a two-drug combination of clarithromycin and ethambutol in 119 patients with treatment-naïve pulmonary MAC. Sputum conversion rates at 12 months were not inferior in the two-drug therapy arm as compared with triple-drug therapy [19].

The ideal management of patients who fail to respond to initial drug therapy is uncertain. If initial therapy was provided TIW, conversion to daily therapy is warranted. Substituting rifabutin for rifampin at 150–300 mg/day or 300 mg TIW is suggested [20]. Rifabutin has greater in vitro activity against MAC, but close monitoring is required due to an increased number of drug interactions, including greater alterations in clarithromycin metabolism and more common gastrointestinal side effects.

For patients infected with macrolide-resistant MAC isolates, it is recommended that the macrolide be discontinued, and a parenteral aminoglycoside such as amikacin is begun. Additionally, adjunctive surgical resection is recommended. Griffith et al. reported a 79 % sputum conversion rate in patients treated with a parenteral agent and surgery [21]. However, MAC infections with macrolide-resistant MAC can be lethal. In 95 such patients, Morimoto demonstrated a survival curve that paralleled that of patients with multidrug-resistant tuberculosis [22].

Three recent randomized controlled trials have shown that prolonged macrolide antibiotic use in addition to inhaled bronchodilator therapy decreases exacerbations in patients with bronchiectasis with a history of frequent exacerbations [23–25]. Recognizing the propensity of macrolide monotherapy for inducing resistance in NTM and the prevalence of NTM infections in patients with bronchiectasis, the impact of this management approach on the development of macrolide-resistant NTM is not yet fully understood but raises concern.

Although uncommon, MAC may present as an isolated pleural infection leading to an exudative lymphocytic effusion. Standard antimicrobial therapy has been used successfully in this scenario [26]. Additionally, exposure to MAC with the use of indoor hot tubs or occupational water sources may result in a hypersensitivity pneumonitis. Avoidance of exposure to the contaminated water source is the mainstay of treatment for these patients although corticosteroids may offer additive benefit [27].

Drug intolerance can be a significant impediment to successful treatment of MAC lung disease. The risk of adverse effects, drug toxicities, and drug-drug

interactions is not insignificant with the multidrug regimens required, particularly in elderly individuals [1]. Often, dose reductions or drug substitutions are required for patients to successfully complete therapy. Although successful microbiologic conversion of sputum specimens to negative is quite favorable for patients able to complete macrolide-based regimens as prescribed, if one incorporates treatment dropouts and relapses, the cure rate with early macrolide-containing regimens when studied from 1994 to 2002 was only 56 % [28].

More recent observations describe not only a similarly high sputum conversion rates in patients that complete therapy but also a substantial need for modification of therapy due to intolerance. In a retrospective study by Sim et al., a favorable microbiologic outcome was noted in 79 % of patients (n=96) treated with a standardized multidrug regimen [29]. However, 29 % of patients needed to change treatment regimens due to side effects.

A retrospective review by Wallace et al. noted sputum conversion to culture negative without relapse in 84 % of patients that completed greater than 12 months of a macrolide-based treatment regimen [17]. Eighty percent of patients receiving daily therapy required modification of therapy due to drug intolerance. Tolerance improved with a TIW regimen, but this approach should be avoided in those with fibrocavitary disease. Similarly, in a review by Jeong et al., modification of initial antimicrobial therapy due to intolerance was common but significantly more frequent with daily regimens compared to intermittent therapy (46 vs. 21 %, respectively) [18].

M. kansasii

M. kansasii are slow-growing mycobacteria that commonly lead to pulmonary infections. In the largest and longest followed cohort of patients described, *M. kansasii* most commonly presented as an upper lobe cavitary lesion in patients with coexistent COPD, alcoholism, and peptic ulcer disease [30]. As opposed to other frequently encountered NTM isolates, in vitro drug susceptibility and clinical response often correlate well for *M. kansasii* [1]. Guidelines suggest a daily regimen of rifampin, ethambutol, and isoniazid with pyridoxine supplementation for initial treatment of *M. kansasii* pulmonary infection [1].

In patients with rifampin-resistant disease, an alternative three-drug regimen can be selected based on in vitro susceptibilities, including azithromycin or clarithromycin, moxifloxacin, ethambutol, trimethoprim-sulfamethoxazole, or streptomycin [1]. Patients should be treated until sputum cultures are negative on therapy for at least 12 months [1].

M. abscessus

M. abscessus are rapidly-growing mycobacteria that can be very challenging to treat, and treatment failure is common [2]. The *M. abscessus* complex encompasses *M. abscessus* subsp. *abscessus*, subsp. *massiliense*, and subsp. *bolletii*. Subspeciation of *M. abscessus* has potential clinical implications. Isolates of *M. abscessus* subsp. *abscessus* and subsp. *bolletii* have a functional erythromycin ribosomal methylase (erm) 41 gene that confers macrolide resistance despite in vitro susceptibility [31]. The gene is present but not functional is *M. abscessus* subsp. *massiliense*. Macrolide sensitivity in *M. abscessus* subsp. *massiliense* portends a better outcome with treatment.

There are no antimicrobial regimens with proven or predictable efficacy for treatment of *M. abscessus* disease [32]. This organism is inherently resistant to first-line antituberculous mycobacterial agents, including isoniazid, ethambutol, rifampin, and pyrazinamide. Antimicrobial susceptibilities should be performed routinely for all clinically significant isolates. Susceptibility testing for amikacin, cefoxitin, clarithromycin, ciprofloxacin, doxycycline, imipenem, linezolid, moxifloxacin, trimethoprim-sulfamethoxazole, and tobramycin is recommended [33]. However, physicians should interpret such susceptibilities with caution as correlations between in vitro susceptibility and in vivo response can be unreliable.

In practice, treatment of *M. abscessus* is highly variable and should be guided by antimicrobial susceptibilities and drug tolerance. Treatment of *M. abscessus* with a combination of a macrolide in conjunction with one or two parental agents is generally employed. The most commonly used intravenous drugs are amikacin, imipenem, and cefoxitin. Tigecycline can also be considered, but adverse effects, particularly nausea and vomiting, are very common [34]. Wallace et al. described 52 patients with either *M. abscessus* or *Mycobacterium chelonae* infections. Tigecycline was given in conjunction with other agents for >1 month, and this resulted in clinical improvement in >60 % of patients, but nausea and vomiting complicated therapy in nearly all [34]. Inhaled amikacin may be helpful in the management of *M. abscessus* but has significant adverse effects including hemoptysis and dysphonia (Table 2) [35].

All patients with *M. abscessus* pulmonary disease should be evaluated for potential surgical intervention. Although patients treated with multidrug antimicrobial therapy alone have similar outcomes to those treated with a combination of antimicrobials and surgery, combination therapy may offer a prolonged microbiologic response [36].

Surgery

Surgery offers an adjuvant role in patients with localized disease due to NTM when the response to therapy is inadequate, antimicrobial therapy is poorly tolerated, or when complications from infections such as life-threatening hemoptysis occur despite appropriate drug therapy. It is typically recommended that surgery be performed in conjunction with appropriate antimicrobial therapy. In a series of 28 patients with pulmonary MAC, surgical resection was performed primarily due to failure of medical therapy (54 %). Persistent air leak requiring surgical resection occurred in 18 % of patients, and there were two early postoperative deaths. Relapse only occurred in a single patient [37]. Sharaishi et al. described their experience with 60 consecutive patients with localized NTM infections—nearly all due to MAC (92 %). Surgery was performed due to inadequate response to antimicrobial therapy in most patients. There were no operative deaths, and all patients attained sputum-negative status postoperatively with a relapse reported in only 3 % of patients [38]. Additionally, for patients with pulmonary infections from NTM for which antimicrobial therapy has not demonstrated effectiveness, surgical resection may be considered. Goto et al. reported a curative left upper lobectomy for a patient with *M. chelonae* infection [39]. It is recommended that surgical resection be reserved for those with an FEV1 exceeding 30 % [1].

Table 2. Common antimicrobial dosages and adverse effects

Antimicrobial	Dosages	Comments:
Azithromycin (PO)	250–300 mg daily 500–600 mg TIW[a]	• Diarrhea, nausea, vomiting • Hepatotoxicity→monitor liver enzymes • Decreased hearing→interval audiometry • Headache • Prolonged QT interval
Clarithromycin (PO)	500–1000 mg daily[b] 1000 mg TIW[a]	• See comments for azithromycin above • Metallic taste→consider split (BID) dosing
Ethambutol (PO)	15 mg/kg daily 25 mg/kg TIW[a]	• Optic neuritis -Monitor visual acuity and red-green color discrimination • Peripheral neuropathy • Hyperuricemia
Rifampin (PO)	450–600 mg daily[b] 600 mg TIW[a]	• Nausea, vomiting→Consider split (BID) dosing • Hepatotoxicity→monitor liver enzymes • Hypersensitivity reaction (fever, rash) or flu-like illness • Orange discoloration of urine and secretions • Thrombocytopenia→monitor platelet count • Renal failure→monitor renal function • Many drug interactions
Rifabutin (PO)	150–300 mg daily[b] 300 mg TIW[a]	• See comments on rifampin (above) • Polyarthralgias, polymyalgias • Leukopenia, granulocytopenia→monitor CBC • Ocular toxicity (uveitis)→monitor visual acuity • Serum levels increased by clarithromycin
Ciprofloxacin (PO)	500 mg BID	• Nausea, vomiting, diarrhea • Prolonged QT interval • Tendonitis • Insomnia, headache, agitation, anxiety
Moxifloxacin (PO)	400 mg daily	• See comments on ciprofloxacin (above)
Isoniazid (PO)	5 mg/kg/day (max 300 mg daily)	• Hepatotoxicity→monitor liver enzymes • Hypersensitivity reaction (fever, rash) • Peripheral neuropathy (pyridoxine deficiency) -Supplement pyridoxine 50 mg/day
Amikacin (IV)	8–mg/kg TIW	• Auditory, vestibular toxicity -Interval audiometry and vestibular testing • Nephrotoxicity→monitor renal function
Amikacin (Inhaled)	15 mg/kg/daily	• Dysphonia, sore throat -Gradual up-titration of dose to assess tolerance • Oral candidiasis • See comments on Amikacin (IV) above
Streptomycin (IV or IM)	8–25 mg/kg TIW	• See comments on Amikacin (IV) above
Tigecycline (IV)	50 mg BID	• Nausea, vomiting→may require dose reduction -Consider pre-medicating with anti-emetic
Imipenem (IV)	1–2 g q6–8 h	• Nausea, vomiting, diarrhea • Central nervous system toxicity (seizures, confusion) • Hepatotoxicity→monitor liver enzymes • Hypersensitivity reaction (anaphylaxis, rash) • Anemia, leukopenia, thrombocytopenia→monitor CBC
Cefoxitin (IV)	200 mg/kg/day	• Hypersensitivity (rash, fever) • Anemia, leukopenia, thrombocytopenia→monitor CBC

Table 2. (continued)

Antimicrobial	Dosages	Comments:
Doxycycline	100 mg BID	• Nausea, vomiting, diarrhea • Photosensitivity
Linezolid	300–600 mg BID	• Anemia, leukopenia, thrombocytopenia→monitor CBC • Nausea, vomiting, diarrhea • Peripheral neuropathy
Sulfamethoxazole	1 g TID	• Nausea, vomiting, diarrhea • Anemia, thrombocytopenia, leukopenia→monitor CBC • Hypersensitivity, including Stevens-Johnson syndrome

TIW three times weekly, *BID* twice daily, *TID* three times daily, *PO* oral, *IV* intravenous, *IM* intramuscular, *CBC* complete blood count, *q* every
[a]Nodular/bronchiectatic MAC only
[b]Lower dose for weight <50 kg

Summary

NTM pulmonary infections are increasingly identified. Although there have been notable advances in species identification and culturing techniques, significant gaps in our understanding of the disease remain. Shared characteristics of infected patients have been recognized, but prospective identification of host susceptibility is incomplete. Furthermore, treatment of most NTM infections is based on clinical experience, in vitro susceptibility testing, and expert opinion. The current therapies are arduous, expensive, and incompletely effective. Successful treatment has been mostly defined as sustained culture negativity as opposed to patient-centered outcomes. However, there is increasing research interest in these infections, which ideally will translate into meaningful improvements in therapies and patient outcomes.

Compliance with Ethics Guidelines

Conflict of Interest

Margaret M. Johnson declares that she has no conflict of interest. Hilary P. Steele declares that she has no conflict of interest. Lisa M. Brumble declares that she has no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

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