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The Challenge of Pulmonary Nontuberculous Mycobacterial Infection

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Abstract

The incidence of nontuberculous mycobacterial (NTM) lung disease is increasing. Current treatment strategies are largely based on expert opinion. The lack of randomized clinical trials to inform treatment leave clinicians with many questions regarding the most effective and safe regimens. The risk-benefit ratio of therapy is often thought to favor observation given the chronic nature of the disease, multiple long-term antibiotics recommended for therapy, side effects associated with treatment, and perceived lack of efficacious therapies.

Keywords

nontuberculous mycobacterial (NTM) pulmonary disease; *Mycobacterium abscessus*; MAC; surgical therapy; antibiotic resistance

Introduction

Clinicians are encountering nontuberculous mycobacterial (NTM) disease more commonly. Treating this disease is not straightforward because of its chronic nature, lack of evidence based treatment strategies, and the fear of prolonged antibiotic therapy with its associated side effects. There are over 150 species of NTM currently recognized and this number will increase as molecular technology advances [1]. Current American Thoracic Society/ Infectious Diseases Society of America (ATS/IDSA) guidelines are largely based on expert

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Compliance with Ethics Guidelines

Conflict of Interest Statement

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opinion and there are few randomized controlled trials (RCTs) concerning treatment of NTM pulmonary disease [2]. Diagnosis can be difficult and there is little guidance for clinicians regarding long term monitoring of patients. Lack of concordance between *in vitro* susceptibility information and *in vivo* response is a problem.

Clinicians commonly have a perception of poor outcomes associated with treatment. A recent study from Canada examined differences in opinions between NTM “nonexperts” and “experts” regarding pulmonary *Mycobacterium avium* complex (MAC) disease. They found that “nonexperts” believed that fewer patients with positive cultures actually had disease and if they decided to treat used less aggressive regimens. Further, “experts” were more likely to think treatment would be successful [3].

A detailed review of diagnosis, treatment, and monitoring of all NTM species that cause pulmonary disease is beyond the scope of this article. However we hope to identify commonly encountered questions or challenges and review the currently available evidence as well as provide our own experience.

Epidemiology

NTM are ubiquitous environmental organisms found in water distribution systems and soil [2, 4]. NTM cause chronic, debilitating pulmonary disease primarily affecting HIV-negative people over age 45, as well as younger patients with cystic fibrosis (CF) [2, 5]. Approximately 55% of all cases occur in adults over age 65 [6, 7]. Pulmonary NTM disease disproportionately affects females and occurs more frequently in those with chronic underlying lung disease such as chronic obstructive pulmonary disease (COPD) and bronchiectasis [7, 8]. Studies have shown NTM to be strongly associated with non-CF bronchiectasis [7, 9]. An estimated 2-10% of non-CF bronchiectasis patients will be infected with NTM at any given time, and in one retrospective study, 30% were diagnosed with NTM disease over a 7-year period [10-13].

Recent studies found that the incidence and/or prevalence of NTM disease increased 2-6% per year [6, 8, 14]. This increase is even more dramatic at 8.7% per year from 1997 to 2007 in the Medicare population [15]. In Oregon, the annual incidence of pulmonary NTM disease from 2007-2012 ranged from 0.8/100,000 in females less than 50 years old to 30/100,000 in females 80 years and older [6]. Of note, the female predominance occurred in patients over age 60, and while there were fewer cases in younger patients they were more frequently male [6]. In all studies, MAC caused 80-86% of NTM pulmonary disease and *Mycobacterium abscessus* 6-13% (Table 1) [6-8, 14, 16]. In a recent analysis of a national cause of death database, NTM related deaths increased from 1999 to 2010, with a combined age-adjusted mortality rate of 0.1/100,000 person-years [17].

Diagnosis and Decision to Treat

The current ATS/IDSA guidelines published in 2007 have both clinical and microbiologic criteria that must be met for the diagnosis of pulmonary NTM disease [2]. These diagnostic criteria at least partially account for NTM being environmental organisms and that exposure is likely widespread [18]. Accordingly, sputum culture evidence of repeated isolation of

NTM is required to confirm that it is not a transient event (reflecting colonization or contamination of the upper airway). These criteria “fit best” with MAC, *Mycobacterium kansasii*, and *M abscessus* because at the time of publication there was little evidence available on other NTM species.

We commonly encounter patients who have characteristic symptoms and imaging findings of NTM lung disease but do not meet the microbiologic criteria. There are no studies in this group of patients regarding the best diagnostic strategy. In this group we collect multiple sputum samples (either self expectorated or induced) over a short period of time. If still unable to meet the microbiologic diagnosis, then we consider bronchoscopy. If still unable to isolate, NTM we will continue to follow patients with intermittent collection of sputum and close monitoring of symptoms.

A diagnosis of NTM lung disease does not mean that therapy must be started, as this decision should be based on the risks and benefits of therapy for individual patients. In some treatment should be started as soon as possible, such as those with cavitary disease, significant symptoms, or with underlying immunosuppression. In others such as those with minimal symptoms or mild imaging findings, treatment can potentially be delayed as long as the patients have close follow-up to monitor for progression.

We believe that in most patients, pulmonary MAC disease will progress (albeit slowly) over time, and it is a disservice to most patients to simply ignore a single culture as contamination without monitoring for at least some period of time [19]. The question of how frequently to repeat chest imaging (computerized tomography (CT) scans) is more difficult, but a repeat scan at 3-6 months after the first scan is reasonable to assess for disease progression. For *M abscessus* disease, progression is also often slow, although frequently more rapid than that observed for MAC. This should be kept in mind when making decisions regarding microbiologic or radiologic surveillance for disease progression.

Disease Types

Monitoring and treatment recommendations will need to be modified depending on the type of NTM lung disease present. For MAC there are two typical disease types. The first is an upper lobe fibrocavitary disease more commonly seen in men with underlying COPD and a history of smoking [20]. The second is a nodular bronchiectatic form of disease often called “Lady Windermere’s” syndrome [21]. It is most commonly found in women, without significant underlying lung disease (other than bronchiectasis) and with other associated features such as low body mass index (BMI), white race, lack of smoking history, and associated anatomic abnormalities [12, 22, 23]. The reasons for this association are unknown and there is speculation that there is an unidentified defect in the immune system that is playing a role as some studies have found altered levels of interleukin-10 and interferon-gamma [24]. There can be overlap among these disease subtypes. Those with nodular bronchiectatic disease can later develop cavities. Males frequently present with the nodular bronchiectatic subtype.

The descriptions above have been classically associated with MAC, however other species such as *M abscessus* present similarly [25], while some organisms like *Mycobacterium*

xenopi present more frequently with cavities, nodules, consolidation or ground-glass opacities [26]. The fibrocavitary form of disease may progress more quickly and should be treated [19]. Some studies have suggested increased mortality with cavitary disease [27].

NTM Identification and Susceptibility

NTM should be identified to the species level (other than MAC). They are often divided into rapid and slow growers depending on how long it takes to grow visible colonies. There are commercial DNA probes available for select species (MAC, *M. kansasii*, and *Mycobacterium goodii*).

For MAC, current guidelines recommend drug susceptibility testing for clarithromycin only, since clinical response is known to correlate only with macrolide susceptibility [2, 28]. There are no recommendations for routine testing for other antimicrobial agents. Some studies suggest no correlation between rifampin or ethambutol susceptibility results and clinical response to therapy [28, 29]. A recent study showed that *in vitro* resistance to amikacin was associated with treatment failure [30]. However, this was a very small study and the long-term clinical relevance is unknown. When a clinician orders a susceptibility panel, they will receive information on antimicrobial agents other than clarithromycin. At present there is no guidance on how to use this additional information.

M. abscessus poses a particular challenge to clinicians because of its multi-drug resistant nature, such that few drugs have *in vitro* activity. Early laboratory reports generally identified rapid growers either as one of two distinct complexes: *Mycobacterium chelonae* complex or *Mycobacterium fortuitum* complex [31]. Such isolates were generally not speciated further. Later it was discovered that *M. abscessus* and *M. chelonae* were different species with differing *in vitro* antibiotic resistance profiles. However, despite the potential clinical ramifications of distinguishing between these two species, many laboratories are unable to identify this organism at the appropriate species level and the reports will often identify this species as “*M. chelonae/abscessus*” complex.

It has been proposed that isolates previously identified as *M. abscessus* be taxonomically split into 3 subspecies: *M. abscessus* subsp. *bolletii*, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense*. There is no universally accepted designation for the correct species or subspecies [32]. The inducible macrolide resistance gene, the erythromycin methylase 41 ((*erm*(41)) gene impairs binding of macrolides to ribosomes [33]. This resistance is not reflected in standard culture reports as it is “induced” by exposure to macrolides *in vivo*. In order to be identified *in vitro* cultures would have to be incubated for a longer period of time than is standard. This distinction is important for treatment because *M. abscessus* subsp. *massiliense* lacks an active *erm* gene while the other two subspecies in general have active *erm* genes [34, 35]. Some studies have shown that up to 20% of *M. abscessus* subsp. *abscessus* retain *in vivo* susceptibility [36] highlighting the need for techniques to identify isolates to the subspecies level and in some cases incubate isolates of *M. abscessus* for longer periods of time to determine minimum inhibitory concentrations (MICs) for clarithromycin (i.e. rule out the presence of inducible macrolide resistance) [32, 37]. Multiple additional antibiotic resistance mechanisms, in particular for *M. abscessus*

subsp abscessus, further complicate treatment and require study to develop techniques to correctly identify them for clinicians.

Treatment

There are a limited number of studies regarding the treatment of NTM pulmonary disease and currently no drugs have been approved by the Food and Drug Administration (FDA) for the treatment of NTM pulmonary disease. ATS/IDSA guidelines are based largely on expert opinion and offer the most guidance for MAC, *M kansasii*, and *M abscessus*. The current evidence base is largely composed of single-center observational studies. We will focus on MAC and *M abscessus* but briefly mention treatment of some other NTM species (Table 2).

In studies, success is usually defined as “conversion” of cultures to negative. There is little information regarding functional assessments such as six-minute walk tests or pulmonary functions tests. Reported changes in symptoms are difficult to interpret, in particular in patients with other underlying pulmonary diseases. In practice, the goals of treatment are improving quality of life, reducing bacillary load, and halting progression of lung damage.

MAC

The ATS/IDSA guidelines recommend multidrug macrolide based regimens with ethambutol and rifampin/rifabutin for MAC as well as intravenous (IV) therapy with streptomycin or amikacin for extensive disease (cavitary) [2]. Early studies of therapy that included macrolides found approximately 56 % were treatment successes (defined as “eradication of organism without relapse over a period of several years after treatment has been discontinued”) [38] however these were noncontrolled trials with small numbers of patients. A meta-analysis of treatment regimens for MAC (including both disseminated and pulmonary disease) by Xu et al. found an estimated pooled treatment success of 39% and significantly higher success, 42% vs. 28%, with macrolide-based regimens [39]. Wallace et al. performed a single center retrospective study examining the efficacy of macrolide/azalide-containing regimens for nodular/bronchiectatic disease in 180 MAC patients. Eighty-six percent achieved negative cultures with a 3-drug regimen [40]. Macrolide resistance has been associated with treatment failure. Single drug therapy with a macrolide and combination therapy with a macrolide and fluoroquinolone have been shown to promote development of macrolide resistance [41].

ATS/IDSA guidelines recommend 3 times a week (TIW) therapy for nodular/bronchiectatic disease and daily therapy for cavitary disease. There has been some debate regarding the efficacy of TIW therapy and some advocate starting daily therapy in all patients. Wallace et al. found increased need for modification of treatment regimens with daily therapy (80% vs. 1%, $p=0.0001$) and no difference in culture conversion rates between TIW and daily therapy. In addition, no patient developed macrolide resistance [40]. Jeong et al. found no difference in symptomatic or radiographic improvement, sputum culture conversion, time to culture conversion, or microbiologic recurrence between TIW and daily therapy [42].

Given the recommendations for prolonged multi-drug therapy some patients become intolerant of one or more drugs and it is often unclear how to continue therapy. Is it better to

add a second-line antimicrobial or continue with two-drug therapy? In a preliminary open-label study Miwa et al. randomly assigned untreated, newly diagnosed pulmonary MAC patients to 2-drug (clarithromycin and ethambutol) vs. 3-drug (clarithromycin, ethambutol, and rifampin) therapy. They found that the 2-drug regimen was non-inferior to the 3-drug regimen with sputum conversion in 55% and 41% respectively [43].

There is a perception that side effects often preclude treatment or lead to early discontinuation of treatment in many patients. In our experience most patients can tolerate therapy and finish prescribed course of therapy with use of better tolerated medications such as azithromycin, changes in dosing (i.e., daily to TIW), and counseling regarding medication administration. Recent studies have found only 9-15% of those treated with macrolide/azalide regimens had to discontinue therapy before 12 months due to adverse events [40, 42].

M abscessus—Regarding *M abscessus* lung disease the guidelines state, “there are no drug regimens of proven or predictable efficacy” and that multidrug regimens that include a macrolide may lead to symptomatic improvement [2]. Current recommendations from centers with experience treating NTM disease recommend starting therapy with 2 IV agents as well as an oral macrolide for 2-4 months and then later stepping down to 2-3 active agents (a combination of oral and possibly inhaled agents) [31]. The particular agents chosen depend on the NTM species causing disease with acknowledgement of the limitations of susceptibility data. Also, given the resistance to macrolides discussed above in some species/subspecies, it is unknown if addition of a macrolide offers any benefit with regard to NTM therapy.

For *M abscessus*, we usually start IV amikacin at 10 mg/kg TIW in combination with imipenem, tigecycline, or cefoxitin along with a 3rd oral agent. It has been our experience that TIW amikacin is better tolerated than daily therapy and is effective. Studies are needed to confirm the efficacy of TIW amikacin compared to daily therapy. The addition of a 3rd agent depends on knowledge of the particular species or subspecies causing disease. After 2-4 months we attempt to step down therapy to a combination of oral and inhaled agents based on the NTM species, antibiotic susceptibilities, and patient tolerance.

The question of whether azithromycin vs. clarithromycin is a better choice has been raised. Choi et al. found significantly greater induction of the erm(41) in *M abscessus* isolates after exposure to clarithromycin compared to azithromycin and no induction in *M massiliense* isolates [44]. Conversely, another study found that in clinical isolates of *M abscessus* and *M chelonae* there was no difference in inducible resistance between azithromycin and clarithromycin [45]. We support the use of azithromycin over clarithromycin as it has a more favorable side effect profile and is better tolerated by patients.

Historically, studies have shown that outcomes of treatment are poor for *M abscessus* and that adverse events are frequent [25]. A retrospective study of 69 patients with *M abscessus* pulmonary disease treated at National Jewish Health in Denver, Colorado found that at least one drug was stopped because of adverse effects in 65% of patients, and 35% of those on IV amikacin had an adverse event [46]. More recent studies found outcomes are better for *M*

massiliense than *M abscessus* [47]. Studies from South Korea have found a sputum conversion rate of 100% among those with *M massiliense* (n=34) compared to 50% with *M abscessus* (n=24) as well as radiographic improvement in 88% vs. 33% [48]. A case series of pulmonary and extrapulmonary *M abscessus* patients found that adverse events were more frequent in those treated with daily vs. intermittent IV amikacin [49].

Other Antibiotic Options

Current guidelines focus primarily on initial regimens but how to modify therapy if a patient isn't responding, is worsening, or becomes intolerant to a drug is less clear. It is important to continue to identify and study new or existing agents that could potentially be used to treat NTM lung disease [50-52].

Providers have used inhaled amikacin for a number of years but until recently there was little data regarding efficacy and safety. A case series reported 5 of 6 patients treated with inhaled amikacin had symptomatic improvement (4 had negative sputum cultures at 6 months) [53]. Twenty-five percent of those treated between 2003 and 2010 with inhaled amikacin at the National Institutes of Health (NIH) had persistently negative cultures (n=20, followed for a median of 19 months). Thirty-five percent had to stop therapy due to side effects [50]. The large number of side effects may have been due to the dosages of amikacin utilized in this study (goal dose of 500 mg twice a day). A recent multicenter clinical trial evaluated the efficacy of inhaled liposomal amikacin in recalcitrant disease. They found a statistically significant difference in the proportion of patients with MAC who achieved early culture conversion (at day 28). This was sustained through days 56 and 84. They also had significant improvements in six-minute walk tests [54, 55]. A subsequent phase 3 study is currently underway of this compound.

Clofazimine is a riminophenazine currently approved by the Food and Drug Administration (FDA) for the treatment of leprosy. Interest in clofazimine as a therapy for other mycobacterial diseases including multidrug resistant tuberculosis and NTM disease has emerged [56, 57]. In the U.S., clofazimine is currently available via the FDA for non-leprosy mycobacterial cases under an expanded access single patient investigational new drug (SPIND) application that requires individual institutional review board (IRB) approved protocols. Clofazimine shows *in vitro* susceptibility against many NTM including MAC and *M abscessus* [58-60]. In some studies, approximately 65% of those treated with regimens containing clofazimine have converted cultures to negative [61, 62]. A study from South Korea of MAC patients who failed standard therapy showed only 15.4% of those treated with clofazimine containing regimens had "favorable" treatment response; however the majority (82.4%) had fibrocavitary disease [63].

In a retrospective review of 52 patients with *M abscesses* and *M chelonae* treated with tigecycline, more than 60% of those who were treated for at least one month showed improvement. Ninety-four percent reported adverse events (most commonly nausea) with 56% considered serious [64]. Almost half of these patients received 100 mg daily of tigecycline likely contributing to the high number of adverse events. We frequently use tigecycline in patients with *M abscessus* lung disease and start treatment at 50 mg once a day.

The tolerability of linezolid was recently evaluated via a retrospective cohort study at 6 NTM treatment centers in North America. Among 102 patients with NTM disease (78% with pulmonary disease), 46 (45%) developed adverse events attributed to linezolid after a median of 19.9 weeks. Eighty-seven percent of those with adverse events stopped therapy but 42.5% were later able to restart therapy for a median duration of 17.3 weeks [52]. The most commonly used dose was 600 mg once a day. RCTs are needed to confirm the tolerability and efficacy of linezolid in the treatment of NTM lung disease.

Koh et al. examined the efficacy of a moxifloxacin containing regimen for refractory MAC lung disease in 41 patients. Twelve patients (29%) achieved negative cultures (median time to sputum conversion 91 days). Treatment success did not correlate with baseline *in vitro* sensitivity to fluoroquinolones [65]. No patients with clarithromycin resistance at baseline achieved negative sputum cultures. Out of 18 “treatment failures” 7 developed clarithromycin resistance

Surgery

Surgery should be considered for those with localized disease who are appropriate surgical candidates (Figure 1). Mitchell et al. proposed 3 indications for surgery: failure of medical therapy, symptom relief, and to slow progression of disease [71].

Shiraishi et al. conducted a retrospective review of 60 patients who met ATS/IDSA disease criteria and underwent resection for localized NTM lung disease 2007-2011. All patients received preoperative antibiotics, there were no postoperative deaths, and all had negative sputums postoperatively. Eight patients (13%) had a total of 11 complications and only 2 had relapse during the study period [72].

A retrospective review of 70 patients in South Korea who underwent surgery from 2007 to 2013 reported 15 patients (21%) experienced postoperative complications including one death. The majority of surgeries were lobectomies or pneumonectomies rather than minimal resection and only 36% were performed using video-assisted thoracoscopic surgery (VATS). Fifty seven (81%) had negative sputum cultures [73].

Mitchell et al. reviewed 171 patients who underwent thoracoscopic lobectomy or segmentectomy between 2004 and 2010 at University of Colorado/National Jewish Health. They observed no operative mortality and complications in 19 (8.9%), most commonly prolonged air leak and atrial fibrillation. Ten patients required conversion to thoracotomy [74].

Overall studies have found low rates of postoperative mortality and complications ranging from approximately 9 to 21% with lower rates in those who undergo targeted resection for localized disease using a thoracoscopic approach. It has been our experience that surgery is often not suggested to eligible patients until disease has progressed making them less suitable surgical candidates. We advocate referring eligible patients to experienced centers early in their treatment course. Surgery should be performed in a center with a multidisciplinary team with close attention to pre-, peri-, and post-surgery antibiotic regimens as well as surgical technique to limit spread of infection during surgery, prevent

postoperative complications, and ensure best chance of disease control/cure. There are no RCTs comparing adjunctive surgical therapy to medical-only therapy, but it is our experience that limited resection via VATS of advanced areas of bronchiectasis or NTM disease can improve cough and mitigate the need for chronic antibiotic therapy in the future.

Monitoring During and After Treatment

Current guidelines recommend treating for 12 months after a patient achieves a negative culture [2]. In addition to standard monitoring for IV therapy, we monitor drug levels of oral medications, as a considerable proportion of patients will have sub-therapeutic levels [75, 76]. To date, no studies have evaluated whether “therapeutic” drug levels correlate with clinical outcome.

There are no accepted guidelines on how to follow patients during and after therapy. During therapy we see patients frequently (approximately every 3 months) to evaluate response to and tolerance of therapy. We attempt to repeat sputum cultures every 3 months but not all patients are able to provide adequate sputum for repeat cultures. If a patient is unable to produce another sputum culture, we take this as a sign of negative cultures (as long as symptoms and imaging are improving). We perform a CT scan prior to therapy start and prior to stopping therapy (to help aid in decision to stop therapy). We avoid repeat CT scans unless a patient is not improving. Chest x-rays can often be used to follow cavitory disease.

Wallace et al. found that 74 of 155 patients with MAC had microbiologic recurrence after completion of therapy and that 75% of these were due to a new isolate (representing new infection and not relapse) [40]. Over time a large number of patients will become reinfectd or recrudescence therefore these patients need lifelong monitoring.

Conclusions

NTM pulmonary disease is a chronic disease and current treatment strategies are largely based on expert opinion and small single center studies. Studies for MAC have found adequate outcomes in patients who received regimens in compliance with ATS/IDSA guidelines. Adjemian et al. examined adherence to published treatment guidelines in a group composed primarily of pulmonary and infectious disease specialists. They found that less than 15% of antibiotic regimens followed current guidelines and up to 30% prescribed regimens that might promote the development of antibiotic resistance [77]. Better adherence to these guidelines could potentially improve outcomes. However, it is unclear if the outcomes commonly used in studies to define “success” (culture conversion) are the most meaningful given the chronic nature of NTM pulmonary disease. Despite the perception that many patients are unable to finish therapy due to side effects, published data [40, 42] and our experience, support that most patients are able to successfully complete therapy.

For *M abscessus* complex, routine use of laboratory techniques to better identify subspecies and antibiotic resistance would assist physicians and patients in choosing therapy in the future. Early referral of patients to centers experience in the surgical management of NTM lung disease cannot be overemphasized.

At the time of this publication, review of the NIH clinical trials database revealed only one randomized trial on the treatment of NTM pulmonary disease currently recruiting (the previously mentioned inhaled liposomal amikacin trial in recalcitrant MAC) [78]. Because of the chronic nature of NTM pulmonary disease (as well as the medications and monitoring needed to ensure adequate therapy), the costs of treating NTM disease are not insignificant. Ballarino et al. estimated the median medication cost to be \$19,876 (range, \$398-70,917) [79]. From 2001-2012, hospital costs associated with NTM pulmonary disease totaled \$970, 643, 222 and increased significantly each year ($p=0.001$) [80]. It is vital that more studies (in particular RCTs) examining the efficacy and safety of antibiotics regimens in treating NTM lung disease are developed and funded.

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Figure 1.
NTM pulmonary disease amenable to surgical resection

Table 1

Key Studies of Incidence/Prevalence and Species Associated with Pulmonary NTM Disease in the United States

Study location, years	N	Annual incidence/prevalence	% MAC	% <i>M abscessus/chelonae</i>	Other key species ≥5%
Oregon, 2007-2012 [6]	1146	Incidence: 5.6/100,000	86	6	n/a
NYC, 2000-2004 [16]	81	n/a	80	13	<i>M fortuitum</i> , <i>M kansasii</i> , <i>M xenopi</i>
Four integrated health care delivery systems, US, 1994-2006 [8]	1865	Prevalence: 5.5/100,000	80	12	<i>M fortuitum</i> , <i>M kansasii</i>

MAC=*Mycobacterium avium* complex, N=number, n/a=not applicable, NYC=New York City, US=United States

Table 2

Clinical pearls and potential starting regimens for some commonly encountered NTM species (Based on current ATS/IDSA guidelines [2] as well as our practice)

NTM Species	Clinical pearls	Initial/starting regimens
MAC	Avoid macrolide monotherapy or 2 drug therapy with macrolide and fluoroquinolone Intermittent regimens are not recommended for cavitary disease	Nodular bronchiectatic disease: azithromycin 500 mg ¹ , rifampin 600 mg ² , and ethambutol 25 mg/kg TIW or azithromycin 250 mg ¹ , rifampin 600 mg ² , and ethambutol 15 mg/kg daily Fibrocavitary: Azithromycin 250 mg ¹ , rifampin 600 mg ² , and ethambutol 15 mg/kg daily with consideration for IV amikacin 10 mg/kg TIW for up to 3 months
<i>M abscessus</i> complex	High levels of resistance to most oral antibiotics Knowledge of subspecies needed to determine most efficacious regimen	2 IV agents plus an oral agent with the exact regimen dependent on knowledge of subspecies and antibiotic resistance --IV options include amikacin 10 mg/kg TIW +/- imipenem 1000 mg BID, cefoxitin 1-2 grams every 6-8 hours, and tigecycline 25-50 mg daily --oral options include azithromycin 250 mg daily ¹ , clofazimine 100 mg daily (possible step-down to 50 mg daily after 2 weeks), fluoroquinolones (moxifloxacin 400 mg daily), linezolid 600 mg daily Step down therapy after initial IV therapy (at least 2-3 months) is complete with a combination of oral and inhaled agents
<i>M chelonae</i>	More favorable antibiotic resistance profile than <i>M abscessus</i> complex Known in vitro resistance to cefoxitin [66] Tobramycin can be used for <i>M chelonae</i> but usually not for other rapid growers	Azithromycin 250 mg daily ¹ , tobramycin 5 mg/kg per day divided into 2-3 doses TIW, imipenem 1000 mg BID daily Step down therapy after initial IV therapy (at least 2-3 months) is complete with a combination of oral and inhaled agents
<i>M fortuitum</i>	Usually susceptible to multiple oral agents Active erm gene so macrolides may not be effective [67-69] Often associated with reflux	Amikacin 10 mg/kg TIW and at least 2 agents with <i>in vitro</i> activity (will often use another IV agent and one oral agent) --Oral options include: fluoroquinolones (moxifloxacin 400 mg daily or levofloxacin 500-750 mg daily), doxycycline 100-200 mg daily, and trimethoprim-sulfamethoxazole 1 double strength tablet BID Step down therapy after IV therapy (at least 2-3 months) is complete with a combination of oral and inhaled agents
<i>M gordonae</i>	Uncommon cause of lung disease and usually considered a contaminant	
<i>M kansasii</i>	Drug susceptibility testing for rifampin is recommended Responds well to treatment Often presents similar to tuberculosis with upper lobe cavitary disease	Isoniazid 300 mg, rifampin 600 mg ² , ethambutol 15 mg/kg, and pyridoxine 50 mg daily is recommended in the ATS/IDSA guidelines 2007 however a macrolide or fluoroquinolone could be substituted for isoniazid If rifampin resistance is present, a 3 drug regimen based on <i>in vitro</i> susceptibilities is recommended
<i>M xenopi</i>	Patient tend to have a lot comorbidities and immunosuppression is common [70]	Isoniazid 300 mg, rifampin 600 mg ² , ethambutol 15 mg/kg, azithromycin 250 mg daily, +/- amikacin 10 mg/kg TIW depending on disease severity

BID=twice daily, IV=intravenous, MAC=*Mycobacterium avium* complex, TIW=three times a week

¹ We prefer azithromycin over clarithromycin due to its more favorable side effect profile but clarithromycin could be substituted for azithromycin at a dose of 500 mg bid (whether it is administered daily or TIW)

² Rifabutin could be substituted for rifampin with a dosage of 150-300 mg daily or 300 mg TIW