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Mycobacterial Infections (J Esteban, Section Editor)

Current Opinions in the Treatment of Pulmonary Nontuberculous Mycobacteria in Non-Cystic Fibrosis Patients: *Mycobacterium abscessus* Group, *Mycobacterium avium* Complex, and *Mycobacterium kansasii*

Barbara A. Brown-Elliott, MS, MT(ASCP)SM[1,*]
Julie V. Philley, MD[2]
Jeana L. Benwill, MD[2]
Richard J. Wallace Jr., MD[1,2]

Address
[*,1]Mycobacteria/Nocardia Laboratory, The University of Texas Health Science Center at Tyler, Tyler, TX, USA
Email: Barbara.Elliott@uthct.edu
[2]Department of Medicine, The University of Texas Health Science Center at Tyler, Tyler, TX, USA

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Opinion statement

Treatment of pulmonary infections caused by *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii* involves multidrug oral therapy with a macrolide (azithromycin or clarithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). Patients with *M. kansasii* rapidly respond to a regimen of intermittent (three times weekly) or daily administration of this three-drug regimen. Patients with MAC respond more slowly and often require adjustment of the multidrug regimen because of drug intolerance. The usual treatment for patients with MAC nodular disease takes 15–18 months, with a goal of 12 months of negative cultures. Recent studies support the use of a three-times weekly oral treatment regimen for patients with macrolide-susceptible nodular MAC disease. Patients with upper lobe fibro-cavitary MAC, macrolide-resistant MAC, or severe nodular

bronchiectatic disease are usually treated with a daily multidrug regimen supplemented with an injectable antibiotic (amikacin or streptomycin) or, most recently, inhaled preparations of amikacin. Patients with cavitary changes and/or those with macrolide-resistant isolates are often associated with poor treatment response and may require surgical resection in addition to their drug therapy. In contrast to patients with lung disease due to MAC and *M. kansasii*, the presence of a functional erythromycin ribosomal methylase (*erm*) gene in the majority of isolates of *Mycobacterium abscessus* (*M. abscessus* subsp. *abscessus*) blocks the activity of macrolides and precludes an effective oral drug regimen for most of these patients. Treatment regimens for macrolide-resistant *M. abscessus* require long-term intravenous access and parenteral drug combinations of amikacin, cefoxitin, imipenem, and/or tigecycline. Because of the inconvenience of dosing cefoxitin, a regimen of imipenem and amikacin may be preferred. Cure with these agents is infrequent because of the long-term toxicity and expense of these agents. Other treatment options are currently dismal. The role of newer antimicrobials such as tedizolid and bedaquiline has not been evaluated. Approximately 15 % of isolates of subsp. *abscessus* and all isolates of subsp. *massiliense* (infrequent in the USA) have a nonfunctional *erm* gene and are macrolide susceptible, making an oral macrolide an important treatment component and increasing the likelihood of long-term cure of the infection.

Introduction

Species identification

Since the description of the first nontuberculous mycobacteria in the late 1800s, the recognition of nontuberculous mycobacteria (NTM) species has dramatically increased to more than 150 species and subspecies, currently largely due to the advent of molecular technology and the increase in susceptible hosts. NTM have traditionally been divided into the rapidly growing mycobacteria (RGM) species, which grow in less than 7 days, and the slowly growing species, which require more than 7 days of incubation for mature growth on solid media. Among the RGM, the *Mycobacterium abscessus* group is the most commonly encountered mycobacteria in pulmonary disease, while *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium xenopi* (outside the USA) are the slowly growing species that most often cause pulmonary diseases [1]. Publications describing the diagnostic criteria for pulmonary NTM disease and laboratory documents providing guidelines for detection, molecular identification, and antimycobacterial susceptibility testing of mycobacteria have increased the awareness of NTM treatment [1–4].

The '*M. abscessus* group' is the subject of current taxonomic controversy. Some investigators consider the '*M. abscessus* group' to be composed of three subspecies: *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, *and M. abscessus* subsp. *bolletii*, each of which were previously considered as full species prior to recent clinical and molecular taxonomy studies [5••, 6–8]. However, a 2011 study proposed the existence of only two subspecies: *M. abscessus* subsp. *abscessus* (for brevity referred to as *M. abscessus* hereafter) and *M. abscessus* subsp. *bolletii* (which includes both the former *M. abscessus* subsp. *massiliense* and *M. abscessus* subsp. *bolletii*). Because *M. abscessus* subsp. *bolletii* was named first, its name would receive priority by taxonomic rules and *M. abscessus* subsp. *massiliense* would be only taxonomic history [7]. Subspecies *massiliense* but not subsp. *bolletii* are of major clinical interest; therefore, many labs have continued to use the three subspecies names. Recent studies now suggest there are indeed three subspecies [9••].

Similarly, the slowly growing NTM have increased to approximately 75 species, with the MAC (*Mycobacterium intracellulare*, *M. avium*, and 'MAC-X' species) currently representing the most often isolated species of this group in clinical laboratories globally [10••].

Originally, the MAC was composed of two species, *M. avium* and *M. intracellulare* [1]. Isolates that

were positive with a MAC molecular probe but negative with the individual probes for *M. avium* and *M. intracellulare* were subsequently found and referred to as 'MAC-X'. Subsequently, *M. avium* was separated into four subspecies: *M. avium* subsp. *avium*, *M. avium* subsp. *sylvaticum*, *M. avium* subsp. *hominissuis*, and *M. avium* subsp. *paratuberculosis*, with *M. hominissuis* the cause of human lung disease within the *M. avium* species [11, 12]. Subsequent molecular taxonomic studies have shown that there are multiple species within the former 'MAC-X' group. These include at least seven pathogenic species: *M. chimaera*, *M. vulneris*, *M. marseillense*, *M. timonense*, *M. arosiense*, *M. bouchedurhonense*, and *M. colombiense*.

M. kansasii is currently considered the third most commonly isolated species of NTM in pulmonary disease in many countries, including the USA [1, 13•]. In contrast to MAC and the *M. abscessus* group (probably the second most commonly encountered NTM), *M. kansasii* is considered rapidly responsive to treatment as directed by laboratory data.

Laboratory diagnosis

The laborious, inefficient, and inaccurate (especially as it relates to newer species) conventional identification methods using biochemical schemes and chemotaxonomic methods such as high-performance liquid chromatography (HPLC) are rapidly being replaced by more rapid and definitive molecular gene sequencing or, even more recently, proteomic methods. Although the latter method has not yet been widely validated, proteomic methods using matrix-assisted laser desorption ionization mass spectrometry-time-of-flight (MALDI-TOF) are being used in large reference and clinical laboratories to identify some NTM [14, 15]. As with molecular methods, proteomic methods require quality-controlled commercial or in-house databases for definitive identification of species. The development of a database is a labor-intensive and time-consuming process requiring highly experienced technologists, and it is not possible without analyzing large numbers of isolates [16]. Commercial web-based systems such as MicroSeq (Applied Biosystems, Carlsbad, CA, USA), SmartGene (Smart Gene Inc., Raleigh, NC, USA) or RipSeq (Isentio, Paradis, Norway) may facilitate sequence analysis but should be carefully checked against reference strain sequences, as some systems have been slow to add newer species or make changes in taxonomic status of organisms.

16S ribosomal RNA (rRNA) gene sequencing is currently the most commonly sequenced gene for species identification [2]. The recent recognition of interspecies gene combinations in gene sequences has necessitated the use of multi-gene-based identification and typing methods for many RGM species or subspecies, including the *M. abscessus* group [9••, 17, 18, 19••, 20].

For differentiation of subspecies within *M. abscessus*, most investigators recommend the *rpoB* gene sequence be performed and supplemented with sequencing of the *hsp65* gene or polymerase chain reaction (PCR) restriction enzyme analysis (PRA) [20] or another gene sequence [19••] such as *erm* gene [21].

Antimicrobial susceptibility testing

The current Clinical and Laboratory Standards Institute (CLSI) guidelines for NTM susceptibility testing recommend the broth microdilution method for both RGM and slowly growing species. Importantly, recommended antimicrobial breakpoints are only applicable as long as CLSI standard methods are used.

The most recent addition to the susceptibility recommendations involves the implementation of 14-day extended clarithromycin readings to detect isolates of RGM with inducible macrolide resistance.

For differentiating the three subspecies of *M. abscessus*, the major apparent difference is macrolide susceptibility among the *M. abscessus* subsp. *massiliense* in comparison with macrolide resistance in the majority of the *M. abscessus* [22••]. This susceptibility is due to the absence of a functional erythromycin methylase gene (*erm*) in *M. abscessus* subsp. *massiliense* in contrast to *M. abscessus* with an intact (functional) *erm* gene, which induces macrolide resistance [21, 22••]. The most recent finding of an isolate of *M. abscessus* subsp. *massiliense* with an *erm* gene complicates the picture and is discussed in this article.

Recent studies have shown that clinical response for only two antimicrobials (amikacin and clarithromycin) are correlated to laboratory susceptibility (minimal inhibitory concentration [MICs]) with MAC [23•, 24••]. Previous studies with MAC show a lack of correlation of in vitro MICs to clinical response to other (antituberculous) antimicrobials, including ethambutol, streptomycin, rifampin, and rifabutin [25••]. Thus, the American Thoracic Society (ATS) and Infectious Disease Association of America (IDSA), along with the CLSI, have recommended reporting susceptibility results for only clarithromycin with MAC, although

clinical regimens should include a rifamycin and ethambutol [1, 3]. It is likely that new testing recommendations will soon include amikacin [26••].

Current CLSI guidelines for antimicrobial susceptibility testing of *M. kansasii* recommend in vitro testing of rifampin and clarithromycin only, unless the isolate is resistant to rifampin. In those cases, since treatment failure is usually associated with rifampin resistance or in unusual situations of drug intolerance, a secondary panel of antimicrobials, including amikacin, ciprofloxacin, ethambutol, linezolid, moxifloxacin, rifabutin, and trimethoprim-sulfamethoxazole, should be tested. Isoniazid and streptomycin may have clinical efficacy, but breakpoints to establish susceptibility and resistance have not yet been established [3]. Susceptibility testing should be repeated, and identification of the isolate should be confirmed, by genetic sequencing if the patient remains culture positive after 3 months of appropriate therapy [3].

The number of NTM species causing disease continue to increase. Although data are currently inadequate to recommend specific antimicrobial testing methods and breakpoints for these species, the CLSI recommends broth microdilution and application of the primary and secondary panel used for rifampin-resistant isolates of *M. kansasii* for testing of these species [3].

Epidemiology

Previously, NTM have not been considered as communicable human to human. In the USA, NTM are not mandatorily reported and thus only estimates of the incidence and prevalence of NTM infections are available in most areas.

However, recent reports in cystic fibrosis clinics have shown multiple patients infected with the same clonal strain of *M. abscessus* subsp. *massiliense*. This finding seems to suggest that transmission may be possible among immunocompromised individuals [9••, 10••, 27••]. If this transmission is proven true, there are far reaching implications that may necessitate changing infection control guidelines in cystic fibrosis centers.

The incidence of NTM in the USA (predominantly MAC, *M. kansasii*, and, more rarely, *M. abscessus*) has been associated with specific geographical areas, which may be related to differing water supplies [28, 29]. Tap water and biofilms in the pipe system appear to be specific sources for some NTM species, including *M. avium* [30, 31, 32•, 33],*M. kansasii*, *M. xenopi* (hot water) [34], and *Mycobacterium simiae* [29]. Increasing reports of the relationship of the formation of biofilms and NTM disease have prompted ecological and environmental studies to investigate and assess the patient exposure risk and the efficacy of prevention measures associated with biofilms in drinking water systems, pipe surfaces, medical devices such as catheters, and other surfaces to which biofilms can adhere. The fact that NTM grow and persist in water distribution systems and readily form biofilms suggests that they can also persist in household plumbing systems. [33] Falkinham reported in a 2007–2009 study that NTM were recovered significantly more often in households with water heater temperatures <125 °F than in those with temperatures >130 °F. [33] In addition to allowing NTM to adhere and live on artificial surfaces, biofilms also provide a protective shield against disinfectants [35, 36]. NTM associated with biofilms are known to be more resistant to biocides [35]. However, resistance to antimicrobials of specific NTM associated with biofilms is still being investigated [35]. A 2007 study showed that biofilm-grown cells of *M. avium* exposed to clarithromycin in catheters were significantly more resistant to the antimicrobial than were organisms grown in a suspension with clarithromycin present [37]. Only transparent colonies were detected among the persisters, as would be expected because the transparent colonies of *M. avium* are known to be more antibiotic resistant than opaque colony types [37].

Biofilms have been identified as important sources of nosocomial infections, including association with outbreaks involving bronchoscopes, endoscope washers, ice machines, and other instruments associated with tap or distilled water [36, 38]. Intriguingly, some species of MAC (i.e., MAC-X) have been recovered from the tap water of patients with MAC lung disease [32•, 33]. Recent studies showed that the household water of patients with MAC thought to contain *M. intracellulare* did not contain that species but actually contained other species of MAC, including predominantly *M. chimaera* (73 %) and other MAC-X species (20 %) despite the majority of patients being infected with *M. intracellulare* [32•]. This study was the first recognition of *M. chimaera* in household water of patients with MAC lung disease and clearly emphasizes the importance of species differentiation among isolates of MAC.

These studies suggest that the reservoir for *M. intracellulare* is the environment outside the home, with commercial or natural soils used in planting and gardening the most likely source.

Treatment of *Mycobacterium avium* complex (MAC)

According to the most recent ATS/IDSA guidelines, the diagnosis of NTM lung disease requires a combination of patient symptoms, characteristic radiographic findings, and appropriate microbiologic data [1]. Current treatment guidelines by the ATS/IDSA recommend a macrolide regimen (clarithromycin/azithromycin, rifampin/rifabutin, and ethambutol with or without streptomycin/amikacin). Treatment is not appropriate for all individuals, and care must be taken to identify appropriate timing and medication regimens to ensure successful therapy. MAC, the most common species of NTM in the USA, can present in multiple ways clinically and radiographically, thus treatment options must be tailored individually. Nodular bronchiectasis disease can be best treated with three-times weekly therapy. This method is as effective as daily therapy and is accompanied by fewer side effects [24••]. It is the current treatment of choice recommended by the ATS and IDSA. In 2001, the British Thoracic Society published the first randomized controlled clinical trial describing treatment regimens for patients with MAC. However, because this regimen did not include a macrolide, it cannot be recommended for treatment of patients with MAC [39].

Upper lobe fibrocavitary disease is more common in individuals with advanced lung disease, and daily antimicrobial therapy in combination with an injectable aminoglycoside is warranted, although no clinical trials have compared this treatment regimen with a three-times weekly regiment. In addition to medication, other treatment modalities include smoking cessation, surgical consideration, airway clearance, exercise, and avoidance of environmental sources. The primary microbiologic goal of therapy for both disease types of MAC is 12 months of negative sputum cultures while on therapy. Macrolide-resistant MAC lung disease poses a formidable challenge to treating physicians and patients and is difficult, if even possible, to treat. Most specialists agree that prevention of resistance is key and therefore recommend adequate companion drugs to accompany macrolide therapy for all regimens. Once an isolate becomes resistant, continued macrolide therapy is not indicated except where the drug is also being used as an anti-inflammatory agent in the setting of bronchiectasis. Macrolide-resistant MAC lung disease should be referred to a center that specializes in treatment of NTM.

Pharmacologic treatment

- Nodular bronchiectasis is typically treated with three-times weekly dosing of clarithromycin 1,000 mg or azithromycin 500 mg, ethambutol 25 mg/kg, and rifampin 600 mg (or rifabutin 150–300 mg) as recommended by the ATS (see Table 1) [1]. Dosing adjustments are

usually needed for patients who weigh less than 50 kg or who are 80 years or older. Severe cases, including reinfection or relapse, may require the addition of a three-times weekly injectable aminoglycoside (amikacin or streptomycin). Inhaled amikacin may provide another option for therapy [40••] (see Table 1).

- A macrolide with a single companion drug, ethambutol, may be adequate for minimal nodular bronchiectatic MAC disease if the patient is intolerant to a rifamycin, but data are limited. One study of 119 patients (60 on the two-drug regimen) in Japan demonstrated no significant differences in treatment response rate between 59 patients receiving the three-drug regimen compared with those receiving the two-drug regimen, although no follow-up data were provided [41]. Patients are considered treatment failures if they have not had a response (microbiologic, clinical, or radiographic) after 6 months of appropriate therapy or achieved culture negativity of sputum after 12 months of therapy.
- Cavitary upper lobe MAC disease or extensive nodular bronchiectatic disease is treated with a daily regimen that includes clarithromycin 500–1,000 mg/day or azithromycin 250 mg/day, ethambutol 15 mg/kg per day and rifampin 10 mg/kg per day (maximum 600 mg) or rifabutin 150–300 mg/day (although in the latter setting, the drugs are often poorly tolerated) (see Table 1). Three times weekly therapy may be sufficient, but limited data are available. For patients with upper lobe cavitary changes on either daily or three times weekly oral drugs, intravenous or intramuscular amikacin or streptomycin at a dose of approximately 7–10 mg/kg three times weekly for at least the first 3 months is recommended.
- Use of a quinolone and a macrolide and macrolide monotherapy are not recommended due to poor response and the frequent emergence of macrolide resistance [42, 43].
- The best clinical response is to the first course of MAC treatment; therefore, adherence to and use of a multi-drug regimen are essential. Early specialist referral in patients with complex disease is generally warranted.

Susceptibility testing

- Treatment of MAC is complicated by antimicrobial resistance to some agents and the lack of correlation of in vitro MIC data for agents other than amikacin and clarithromycin [10••, 44••]. More simply, the only drugs proven to correlate with a clinical response in MAC lung disease are macrolides and, as discovered recently, amikacin [26••].
- Repeat susceptibility testing is necessary in individuals who have not had a response (microbiologic, clinical, or radiographic) after 6 months of appropriate therapy, reinfection, and relapse isolates.
- Macrolide-resistant MAC cases are universally difficult to treat and should be referred to a specialty center.

Table 1. Adult treatment regimens[a] of *Mycobacterium avium* Complex (MAC), *Mycobacterium abscessus*, and *Mycobacterium kansasii*

Organism/disease	Antimicrobial treatment	Regimen	Duration
MAC/nodular bronchiectasis (macrolide susceptible)	Clarithromycin (15 mg/kg up to 1,000 mg) in 2 divided doses (usually 500 mg bid) **or** Azithromycin (500 mg)	3 × weekly	Until negative cultures x 12 months
	Rifampin (600 mg) **or**	3 × weekly	
	Rifabutin (150–300 mg)		
	Ethambutol (25 mg/kg)	3 × weekly	
	Amikacin (7–10 mg/kg IV or 500 mg inhaled)[b] **or**		
	Streptomycin (7–10 mg/kg IV or IM)[b]	Once daily, 3 × weekly	
MAC/cavitary[c] (macrolide susceptible)	Clarithromycin (15 mg/kg up to 1,000 mg) in 2 divided doses **or** Azithromycin (250 mg)	Daily	Until negative cultures for 12 months
	Rifampin (10 mg/kg; max 600 mg) **or**	Daily	
	Rifabutin (150–300 mg)		
	Ethambutol (15 mg/kg)	Daily	
	Amikacin (7–10 mg/kg IV)[b] **or**	Once daily, 3 × weekly	
	Streptomycin (7–10 mg/kg IM or IV)[b]		
MAC/nodular bronchiectasis[d] or cavitary[c] (macrolide resistant)	Rifampin (600 mg) **or** Rifabutin (150–300 mg)	Daily (all drugs)	Until negative cultures x 12 months
	Ethambutol (15 mg/kg)		
	Amikacin (7–10 mg/kg)[b] **or**	Once daily, 3 × weekly	
	Streptomycin (7–10 mg/kg)[b]		
M. abscessus subsp. *abscessus*, *M. abscessus* subsp. *bolletii* (macrolide resistant due to functional *erm* gene)	Amikacin (7–10 mg/kg IV or 500 mg inhaled)[b] **or** Imipenem (1,000 mg bid) **or** Cefoxitin (4 g bid) **and/or** Tigecycline[e] (25–50 mg) as tolerated **and/or** Linezolid (600 mg)	Daily (all drugs)	Usually 6 months depending on response[f]
M. abscessus subsp. *massiliense* or subsp. *abscessus* (macrolide susceptible due to non-functional *erm* gene)	Clarithromycin (1,000 mg) **or** Azithromycin (500 mg) Imipenem (500 mg bid) **or** Cefoxitin (4 g bid) **and/or** Tigecycline[e] (25–50 mg) Amikacin (7–15 mg/kg IV or 500 mg inhaled)[b]	Daily (all drugs)	Until negative cultures x 12 months
M. kansasii (Rifampin susceptible)	Clarithromycin (1,000 mg) **or**	3 × weekly (all drugs)	

Table 1. (continued)

Organism/disease	Antimicrobial treatment	Regimen	Duration
	Azithromycin (500 mg) Rifampin (600 mg) Ethambutol (25 mg/kg)		Until negative cultures x 12 months
M. kansasii (rifampin resistant)	Clarithromycin (1,000 mg) **or** Azithromycin (500 mg) Rifabutin (150–300 mg) Ethambutol (25 mg/kg) **and/or** combinations of secondary antimicrobials based on in vitro susceptibility testing: amikacin, moxifloxacin, trimethoprim sulfamethoxazole **and/or** linezolid, plus ethambutol, macrolide	3 × weekly or daily (all drugs)	Until negative cultures x 12 months)

bid twice daily, *IM* intramuscular, *IV* intravenous, *MAC Mycobacterium avium* complex
[a]Dosing adjustments needed for patients who weigh <50 kg and/or are ≥80 years old
[b]For severe disease, reinfection, or relapse cases. Dosage adjusted to achieve peak serum levels of 20–25 µg/mL
[c]If large cavity or treatment failure, consider surgical resection
[d]Inhaled amikacin (500 mg) thrice weekly, once daily, may be considered for patients with macrolide-resistant MAC and nodular bronchiectasis
[e]Dosage adjusted for tolerability factors (age, weight, specific health status). Nausea, anorexia secondary to drug dosage
[f]Symptomatic or radiographic improvement, or reduced colony counts in culture may be more realistic goals

Surgical management

- Multiple studies have described surgical intervention in the era of macrolide use with relatively low operative mortality [45–48]. The reports of surgical therapy for NTM disease thus far do not establish consensus guidelines for selecting the best patient candidates for surgery, choosing the most advantageous timing for operative intervention, and choosing the specific surgical procedures with the best risk/benefit ratio in various clinical circumstances.
- Most specialists agree that adjunctive surgical intervention in the hands of an experienced multidisciplinary team and center offers benefit to a select population of patients who have either NTM disease due to MAC that is difficult to treat with antibiotic therapy or who have not responded favorably in spite of aggressive medical therapy. Aggressive and appropriate antibiotic therapy should accompany surgical intervention.

Airway clearance

- Data are limited regarding the use of bronchodilators, inhaled corticosteroids, and hypertonic saline for the treatment of NTM lung disease.
- Many specialists agree that bronchodilation followed by the inhalation of hypertonic saline (3–7 %) with some type of chest physiotherapy (i.e. cough techniques, flutter valves, vest) provides some patients assistance with sputum expectoration.

Diet and lifestyle

- Data support that at least some patients acquire NTM pathogens, including *M. avium*, from household plumbing [49, 50]. However, how much of a risk NTM in municipal water and household plumbing present and whether these water sources are the major source of NTM for most patients with NTM lung disease is still unknown. Additionally, the identification of species within MAC in household water samples continues to evolve [32•]. Recent studies have demonstrated that *M. intracellulare* is not present in household plumbing.
- It is not certain that avoidance of showers without avoidance of other potential aerosol-generating activities associated with running water in the home would eliminate the risk of household NTM transmission. Increasing the temperature of the hot water heater to >130 °F or changing shower heads at regular intervals might decrease the risk of NTM transmission but the impact of these interventions are not known [33].
- MAC can be isolated from soil; however, whether exposure to specific soil-based sources of MAC organisms may contribute to the development of NTM lung disease is unknown. It is unclear whether avoidance

of soil and/or soil-based activities would minimize the risk of acquiring NTM lung disease.

- There is no evidence to support any role for dietary changes in the treatment of MAC lung disease. Maintaining adequate caloric intake, body mass index (BMI), and following pre-albumin levels as a marker of nutrition may be helpful.
- Exercise, including pulmonary rehabilitation, is encouraged in individuals with chronic lung disease, but this has not been studied in NTM lung disease. Aerobic activity and deep breathing activities such as in yoga are generally thought to be helpful.

Emerging or unproven therapies

- Nebulized commercial amikacin in place of intravenous amikacin has been used for many years, but there are few studies of its safety, efficacy, when and where to use it, and what doses at what frequency. Susceptibility testing of amikacin with both MAC and *M. abscessus* is currently available, although the former has not yet been addressed by the CLSI [26••].
- An investigational liposomal form of inhaled amikacin has been recently studied in a multi-center randomized trial in patients with refractory MAC and *M. abscessus* lung disease. The majority of patients are still receiving therapy. Further information regarding results of this trial are forthcoming [51].
- The new diarylquinoline, bedaquiline, recently approved for multidrug-resistant tuberculosis has been shown to have in vitro activity against MAC and may provide another oral alternative for patients with severe disease [52]. Randomized controlled trials are needed to delineate future use.
- The role of clofazimine in the treatment of MAC lung disease is not clear; little is understood about long-term efficacy [53].

Treatment of the *Mycobacterium abscessus* group

The treatment of the *M. abscessus* group is difficult due to the inherent resistance of the organism to currently available antimicrobials and the lack of correlation of in vitro susceptibility data. Regimens include combinations of amikacin, cefoxitin, imipenem, linezolid, tigecycline, and a macrolide (depending upon the presence of a functional *erm* gene) (see Table 1). However, the most current NTM guidelines state that no antibiotic regimens have been shown to produce long-term sputum conversion [1]. This is true for most isolates of *M. abscessus* subsp. *abscessus* with a functional *erm* gene and subsequent macrolide resistance. Isolates with a non-functional *erm* gene (subsp. *massiliense* and about 15 % of isolates of subsp. *abscessus*) and subsequent macrolide susceptibility have a much better prognosis for cure. There is no consensus on duration of therapy and most experts rely on a combination of factors such as quantitative sputum cultures, resolution of symptoms, and radiographic response to determine length of therapy.

Pharmacological therapy

- The choice between azithromycin or clarithromycin is based on tolerability and drug interactions. Although a 2012 study by Choi et al. [54••] suggested that azithromycin may be a better macrolide than clarithromycin, this has not been assessed in clinical trials. The use of the macrolides is severely limited due to the majority of *M. abscessus* having an inducible *erm* gene [55•]. For *M. abscessus* subsp. *massiliense*, using a macrolide in combination with parenteral antibiotics remains a key component of therapy (see Table 1).
- Most *M. abscessus* group isolates are susceptible to amikacin, and it remains the most active available drug. However, due to its well known toxicities, its long-term use is limited. The effectiveness of the inhaled form of amikacin has been assessed in 20 treatment-refractory patients, 15 of whom had *M. abscessus* [40••]. Four patients had clearance of *M. abscessus* in their sputum. The role of inhaled amikacin in patients with *M. abscessus* will perhaps be better determined after the results of the randomized, placebo-controlled trial using liposomal amikacin for treatment-refractory patients is published. Mutational resistance to amikacin is a concern if additional effective drugs are not included, as mutational resistance occurs with a single base pair change in a single copy gene (16S rRNA gene) [40••].
- The use of the remaining drugs, including imipenem, cefoxitin, and linezolid should be based on the in vitro susceptibility data and tolerability of the drug. The ATS/IDSA guidelines recommend up to 12 mg/day of cefoxitin, but adverse effects limit that quantity of dosing [1]. It is commonly given at an intravenous dose of 4 g twice daily. Czaja et al. [56••] published pharmacokinetic data on continuous infusion of cefoxitin 2 g over 8 h in three patients with *M. abscessus*; only one patient achieved a steady state concentration in serum >16 [56••]. This study illustrates the paradox between dosing of cefoxitin and the inconsistent drug levels achieved. The treatment regimens are difficult secondary to adverse effects that limit standard dosing practices that are not used in *M. abscessus* infections.
- Tigecycline, the first clinically available injectable glycylcycline, can be used as part of a regimen in treating *M. abscessus*, but there are no established breakpoints, and the optimum dosage has yet to be determined. However, most isolates of *M. abscessus* have MICs ≤1 μg/mL [10••].Wallace et al. [57••] reported 52 patients with *M. abscessus* who received tigecycline as salvage therapy at an initial dose of 50 mg, with dose adjustment for tolerability. A total of 36 patients had pulmonary infection, and 16 (44.4 %), 11 (30.6 %), and nine (25 %) had clinical improvement, failed, and indeterminate response, respectively. Those who received tigecycline for ≥1 month had better clinical improvement and no deaths were attributed to tigecycline. Not surprisingly, nausea and vomiting were the most common adverse events in 33 (63.5 %) and 18 (34.6 %), respectively. This study is an important assessment of

the efficacy and safety of tigecycline as part of a salvage regimen for patients with *M. abscessus*.

Surgical management

- The use of surgery as part of the treatment approach in non-cystic fibrosis *M. abscessus* lung infection is regarded as a key component in combination with antimicrobials and has been shown to improve treatment responses and relapses [58, 59].
- The timing and extent of surgery must rely on a multidisciplinary team and center. The published morbidity and mortality associated with surgery has been low [46, 48].
- The role of lung transplantation in cystic fibrosis patients and active *M. abscessus* infection also requires a multidisciplinary team and center that are skilled in the management of potential *M. abscessus*-related complications. Cystic fibrosis patients with and without *M. abscessus* have had similar outcomes [60].

Airway clearance

- The approach and recommendations are the same for *M. abscessus* as for other NTM, including MAC.

Diet and lifestyle

- Less information is known regarding the direct acquisition of *M. abscessus* from its environmental niche compared with MAC. Studies have identified *M. abscessus* in water and have linked strains from patient isolates to potable water [28, 61].
- General recommendations regarding aerosolization of water, showering, and soil exposure do not exist because the mechanism by which patients acquire *M. abscessus* and the unknown reduction of risk of acquisition, if any, is unclear.
- The transmission of *M. abscessus* between cystic fibrosis patients has been reported [62]. Further investigation and evaluation is warranted, and this transmission cannot be applied broadly to the general public. It does appear to potentially pose a significant problem in this distinct group of patients.

Emerging therapies

- The new diarylquinoline, bedaquiline, has been shown to have in vitro activity against *M. abscessus* [52]. However, the role of bedaquiline in the current armamentarium of *M. abscessus* antimicrobials needs further assessment in clinical studies.

- The novel oxazolidinone, tedizolid (DA-7157), has excellent in vitro activity against *M. abscessus* and would also need to be tested in clinical trials [63].

Treatment of *Mycobacterium kansasii* pulmonary disease

Of the NTM involved in pulmonary disease, *M. kansasii* causes both cavitary disease and nodular disease in the setting of bronchiectasis, the former most similar to the clinical picture of *M. tuberculosis* [64]. Untreated strains of *M. kansasii* are susceptible to rifamycins (rifampin and rifabutin) with MICs ≤1 μg/mL [65]. Other than isoniazid, which is not currently recommended for reporting by the CLSI since no broth MIC breakpoints are available, MICs to other antimicrobials seem to correlate well with clinical response. In fact, clinical response has been so favorable that currently only rifampin and clarithromycin should be reported except in rare cases of drug intolerance or in cases in which the strain of *M. kansasii* has become rifampin resistant. In both situations, the cases should be carefully assessed by a physician experienced in treating these patients. In these situations, testing of ancillary agents such as amikacin, ethambutol, quinolones, linezolid, trimethoprim-sulfamethoxazole, tetracyclines, and rifabutin becomes important [1, 3]. Surprisingly, the prognosis for cure of *M. kansasii* infection, even in patients with rifampin-resistant isolates, is good [65].

A 2003 study by Griffith et al. suggests that an intermittent regimen (three times weekly) of rifampin (300–600 mg), ethambutol (25 mg/kg), and macrolide (clarithromycin or azithromycin, 1000 mg or 500 mg, respectively) is effective, less toxic, and less expensive than the standard 18-month daily dosage regimen [62] including rifampin, ethambutol, and isoniazid for rifampin-susceptible isolates of *M. kansasii* (see Table 1). In the intermittent regimen, the mean time to sputum conversion to negative culture was less than 2 months [64]. This regimen is currently being recommended for most cases of pulmonary *M. kansasii*[1, 64].

Compliance with Ethics Guidelines

Conflict of Interest

Barbara A. Brown-Elliott and Richard J. Wallace, Jr. have grants from Insmed, Amon G. Carter Foundation, Pfizer, and Cubist, and received support for travel to present study data at national meetings. All authors have participated in previous in vitro MIC studies and clinical trials and have received previous funding from Insmed (inhaled amikacin, Arikace), Pfizer Labs (tigecycline, azithromycin), Abbott Labs (clarithromycin), and Pharmacia Labs (rifabutin, linezolid) in addition to receiving research funding from Cubist (tedizolid) and a pending grant from Janssen Pharmaceuticals (bedaquiline) for future in vitro studies to be performed at The University of Texas Health Science Center at Tyler.

Human and Animal Rights and Informed Consent

All clinical trials involving human subjects were approved by the Instititutional Review Board at the University of Texas Health Science Center at Tyler.

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

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