Treatment of *Mycobacterium abscessus* Complex

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Abstract

Of the nontuberculous mycobacteria (NTMs) causing lung disease, members of the *Mycobacterium abscessus* complex (MABc) present a formidable obstacle to successful management. This challenge starts from a poorly understood pathogenesis, continues with complicated subspecies variation in treatment response, and extends to the multidrug-resistant nature of these organisms. The disease often necessitates the use of intravenous therapy, toxic drug combinations, and, in some cases, lung resection. Like many NTMs, MABc treatment requires prolonged therapy with multiple medications, and pulmonary disease in some subspecies can be impossible to eradicate or cure. This disease also represents a frequent and unique problem in certain populations, including cystic fibrosis and lung transplant recipients, and providers who manage such patients should be familiar with how MABc disease influences management. Because of the rising prevalence of the MABc, especially in patients with complicated underlying pulmonary disease, it is increasingly necessary for infectious diseases and pulmonary medicine clinicians to understand the unique aspects of MABc management and understand when to obtain expert consultation in the care of these patients.

Keywords
- *Mycobacterium abscessus* treatment
- *Mycobacterium abscessus*
- *Mycobacterium massiliense*
- *Mycobacterium bolletii*
- bronchiectasis
- cystic fibrosis

Mycobacterium abscessus complex (MABc) is the second most common nontuberculous mycobacteria (NTM) grouping causing human disease after *Mycobacterium avium* complex (MAC).[1,2] MABc causes a wide spectrum of human disease, most commonly pulmonary disease, although it can cause soft tissue disease, bone disease, and disseminated disease in immunocompromised hosts.[1,3] The spectrum of infection severity is heterogeneous, ranging from asymptomatic colonization to progressive and mortal disease.[4,5] Unfortunately, MABc is a highly drug-resistant organism and few oral antibiotics show in vitro activity, making long-term treatment of this infection extremely complicated.[1,4,5] In this article, we will review the treatment of MABc pulmonary disease as well as its epidemiology, disease manifestations, and aspects of its diagnosis that are germane to disease management.

Microbiology and Epidemiology

Mycobacterium abscessus Complex Taxonomy

MABc is one of a group of NTM "rapid growers," which includes *Mycobacterium fortuitum* complex, *Mycobacterium chelonae*, and MABc, all having the characteristic of growing within 7 days on solid media subculture (faster in liquid media) as well as the ability to grow in standard blood culture.[1,5] It was only in 1992 that MABc organisms could be identified as distinct from *M. chelonae* and thus these organisms are undifferentiated in literature published before that time.[1,5,6] As recently as 2006, *M. abscessus* was reclassified to represent a complex containing three subspecies: *M. abscessus*, *Mycobacterium massiliense*, and *Mycobacterium bolletii*.[1,5] Over the subsequent 7 years, the taxonomic and nomenclature classifications for these organisms have

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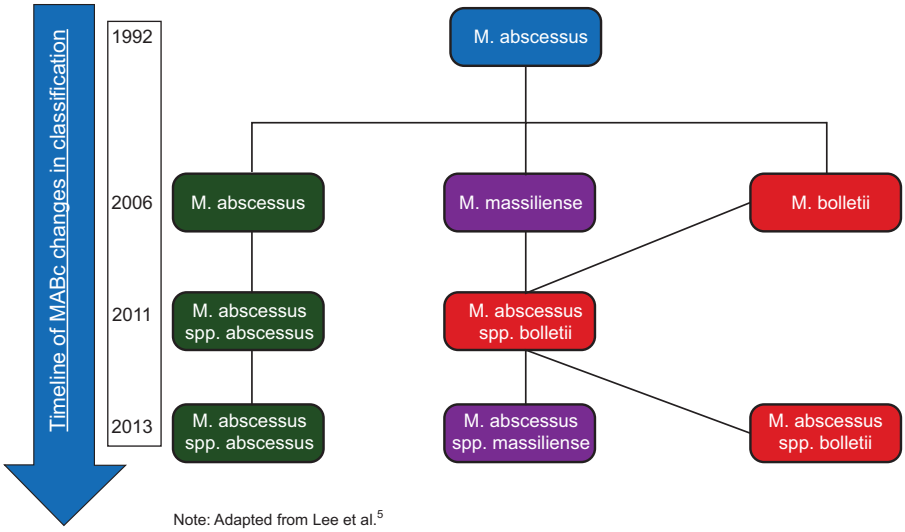

Fig. 1 Changes over time to subspecies organization of MABc. (Adapted from Lee et al.[5])

undergone additional changes resulting in the current understanding of MABc (►**Fig. 1**).[5] It can be difficult to analyze literature regarding "*M. abscessus*" treatment as many studies do not separately analyze these subspecies, which have differential drug susceptibilities and accordingly differential treatment success. Additionally, since early studies did not differentiate between *M. abscessus* and *M. chelonae*, it is difficult to judge the results of these studies, as *M. chelonae* is often a colonizer or contaminant.[1]

Organism Microbiology

Several microbiologic features of MABc are important to highlight because of their implications for disease management. First, like many NTM species, these organisms are ubiquitous in soil and water environments.[1,7,8] As a result, patients with an underlying predilection to initial infection (e.g., bronchiectasis, other structural lung disease) have a high risk of reinfection after adequate treatment, as well as a risk of infection with different strains of the same organism.[9,10] Second, the organisms have a propensity for biofilm formation. This protects them not only from the immune response but also from antibiotics, both of which make true eradication very difficult.[8,11] Third, the presence or absence of a functional *erm gene* (RNA methylase gene), discussed in more detail in next sections, has important implications for drug resistance to macrolide antibiotics. Since this drug class constitutes the most effective oral antibiotic for susceptible NTM organisms, this biology is crucial to treatment choice and response.[12–14] Fourth and least well understood, there appears to be other genotypic variations within the MABc subspecies that influence disease manifestations and treatment response.[15–17]

Disease Epidemiology

Along with most other NTM infections, the incidence and prevalence of MABc pulmonary infections appears to be increasing, although it is unclear what role increased awareness and improved diagnostics is playing in this process.[18–20] Of the complex subspecies (subsp), subsp *abscessus* is generally the most common, although there are notable geographic variations in this finding with subsp *massiliense* even more prevalent in some regions (►**Table 1**).[4] Since not all

Table 1 *MABc* propotions of *M. abscessus*, *M. massiliense*, *M. bolletii*

Study	Location	Total number	*M. abscessus* (%)	*M. massiliense* (%)	*M. bolletii* (%)
Zelazny, 2009[143]	United States	40	67.5	27.5	5
van Ingen, 2009[22]	Netherlands	39	64	21	15
Roux, 2009[24]	France	50	60	22	18
Harada 2012[144]	Japan	102	71	26	3
Yoshida 2013[46]	Japan	143	63	35	2
Nakanaga, 2014[35]	Japan	115	60	37	3
Huang, 2013[105]	Taiwan	79	43	56	1
Kim, 2008[145]	South Korea	126	53	45	2
Koh, 2011[23]	South Korea	158	44	55	1
Lee, 2014[146]	South Korea	404	50	49	1

Note: Adapted from Koh et al.[4]

laboratories can perform subspecies identification and the process of getting results from a reference laboratory can take many weeks, knowledge of local epidemiology can be helpful in crafting empiric antibiotic regimens if they are needed while waiting further subspecies identification. That said, since subsp *abscessus* is the most drug-resistant of the group and since in no region is the prevalence low enough to ignore, empiric treatment of MABc should consider subsp *abscessus*.

Another nuance in the evaluation of MABc literature and clinical management of the disease is the fact that in the respiratory tract, culture positivity (infection) does not inherently mean disease.[1,21] In the lungs, all subspecies can behave in a nonpathogenic way, essentially "colonizing" the airway with minimal clinical impact.[1,21,22] Other times, the organisms can cause airway inflammation *without* causing parenchymal lung disease. In both situations, infection can become progressive within the airway and surrounding lung parenchyma, ultimately causing disease. Sputum culture positivity does not definitively indicate which situation is true in a patient at any given moment.[1] This has implications for treatment but also for interpreting literature in which it is not always clear whether patients included in studies have "colonization" versus "disease," which can change reporting on manifestations and treatment response; therefore, this word of caution must be kept in mind when interpreting published literature.

Clinical Features of *Mycobacterium abscessus* Complex Pulmonary Disease

An overwhelming majority of the cases of MABc pulmonary infection and disease occur in hosts with underlying lung disease.[9,15,22,23] This can be airway disease such as bronchiectasis, which allows accumulation of and prevents clearance of environmental colonizing microorganisms, or parenchymal disease such as emphysema or pulmonary fibrosis, which by causing destruction and impaired circulation at the tissue level inhibits immune surveillance against and clearance of foreign microbes. This susceptibility to infection is particularly pronounced in patients with cystic fibrosis (CF), who have bronchiectasis but also airway ciliary deficiencies creating a unique clinical phenotype covered in detail later in this review.[24–26] Because all the above physiology allows other organisms to gain easier access to the respiratory tree as well, individuals with MABc pulmonary infection are usually colonized with and often infected with other pathogens.[9,27] Treatment sometimes needs to take these organisms into account or clinicians need to consider a superinfection with these other organisms as one of the possible reasons for worsening in a MABc patient on therapy. There is a poorly understood interplay of the lung microbiome here, and in some patients, treatment of MABc allows other pathogens to flare (and vice versa) as organisms compete for resources within the airway.[28,29]

MABc pulmonary infection typically presents in an indolent fashion with waxing and waning symptoms, and many patients do not have significant progression for months or years after infection.[1,21,30,31] In light of this, treatment initiation is not always indicated even if disease criteria described below is met, and when it is indicated, this is rarely urgent.[1] Like MAC, the presentation is typically scattered nodular infiltrates in or around areas of structural lung disease.[1,9,15] Also like MAC, less commonly the disease can be cavity-forming or superinfect structural lung cavities, and it is not clear whether or not cavity formation is more common with MABc or MAC.[15,32] Because of the higher mycobacterial burden and less optimal blood supply within these areas of cavitary physiology, the presence of cavities has implication for treatment decisions.[1] Coinfection with MAC is not uncommon and MABc can be seen in up to 50% of pulmonary MAC cases in some series.[9,30] An estimated 15 to 30% of MABc cases have MAC isolated from their sputum as well.[33] Coinfection presents a clinical conundrum as it can be difficult to ascertain which organism is playing a pathogenic role (or if both are) and should be targeted for therapy.[1,33]

Diagnosis of Infection versus Disease

The identification of MABc is still largely culture-based, although new technologies are revolutionizing laboratory-based diagnostics in this area.[34,35] However, microbe identification (infection) does not equal disease, especially in pulmonary specimens, so pulmonary disease diagnosis is worth reviewing in any discussion of treatment. American Thoracic Society guidelines for pulmonary NTM disease are listed below:[1]

- Symptoms attributable to an infection with the organism.
- At least two positive sputum cultures or one positive bronchoalveolar lavage or lung biopsy culture with the organism.
- Radiographic changes compatible with infection with the organism.

In addition to the potential of nonpathogenic colonization, organisms in MABc can occasionally be contaminants of the laboratory process because of their prevalence in nonsterile environments; thus, as with most infectious diseases, isolation from a site without clinical evidence of pathology should be viewed with suspicion.[1,7]

Drug Resistance and Susceptibility Testing

As mentioned previously, organisms in the MABc are highly drug resistant and understanding their resistance properties and laboratory ways to identify them is a crucial part of treatment.

Slow Growth

Compared with most other pathogens, even rapid-growing mycobacteria are slow growing. This property creates treatment difficulties for multiple reasons. Since many antibiotics work at least partly on dividing pathogens, slow cell replication means slower rates of antibiotic activity. Of the antibiotics typically used to treat MABc, this property limits the efficacy of β-lactams (BLs) and means most of the antibiotic classes used

rely on targeting ribosomal protein synthesis, which is not dependent on bacterial division (macrolides, tetracyclines, aminoglycosides, fluoroquinolones, oxazolidinones).[36] The slow growth of the organisms also makes culture-based susceptibility testing time-consuming and difficult.

Waxy Cell Wall Barrier

The cell wall of MABc has a high lipid content, creating a waxy barrier that is difficult for antibiotics to penetrate.[37] This fact alone is potentially sufficient to confer resistance to many BLs and likely impairs susceptibility to aminoglycosides.[38] Even when not completely impermeable, by lowering the antibiotic concentration within the bacteria, the cell wall plays a role in allowing other resistance mechanisms to be protective when they would otherwise be overwhelmed by high enough antibiotic concentrations.[39]

Biofilm Formation

Biofilm formation is protective for many microbial organisms by creating a surrounding environment that is poorly penetrated by the immune system and antibiotics. Biofilms also create an environment within which bacteria can survive despite less metabolic activity, rendering them more resistant not only to antibiotics that target cell division but also to protein synthesis and adenosine triphosphate (ATP) synthesis processes.[11,40] MABc has been described to form these biofilms in airways, alveoli, and pulmonary cavities, which likely explains part of its resistance to treatment and the difficulty with infection eradication.[11,41,42]

Drug-Neutralizing Enzymes and Export Systems

There are many neutralizing enzymes and drug export systems that enhance the ability of MABc to survive antibiotic exposure (►**Table 2**), including an adenosine diphosphate (ADP)-ribosyltransferase and mono-oxygenase that may confer the complexes known rifampin resistance.[36,43] The most importance of these resistance mechanisms is an inducible *erm* gene which is present in some members of the MABc and confers macrolide resistance that is expressed upon macrolide exposure.[44] This mechanism is notable both for the important role macrolides play in management of NTM infections and because of the difficulty in identifying its presence. Since it is an inducible enzyme, the mechanism will not be picked up on in vitro antibiotic susceptibility testing unless this testing is done after incubating the organism in the presence of macrolides for 14 days.[1,44] As a result, the Clinical and Laboratory Standards Institute (CLSI) recommends that macrolide testing for this complex include prolonged incubation testing for inducible macrolide resistance.[1,45] Additionally, the *erm* gene can be present and inactive, so molecular tests that only probe for the presence of the gene do not conclusively prove macrolide resistance.[14,36] Since many laboratories are not capable of performing prolonged drug incubation and do not have the molecular diagnostics to either identify the *erm* gene or identify if it is active, accurate macrolide susceptibility testing may require sending the isolate to a mycobacterial-specific reference laboratory. Labs that report macrolide susceptibility without performing appropriate testing may provide results that mislead the untrained provider leading to suboptimal treatment regimens. An active *erm* gene is present in most MABc subsp *abscessus* isolates, in some subsp *bolletii*, and in a small proportion of subsp *massiliense*.[12,13,46]

Genetic Polymorphisms

Because of specific genetic polymorphisms within the MABc, these organisms are less susceptible to antibiotics than most other mycobacteria (higher minimum inhibitory concentrations, MICs). Classic in this regard are a couple base-pair substitutions in the *embB* ethambutol resistance determining region which confer high-level (MICs $>$ 64 mg/L) ethambutol resistance to all members of the MABc.[47] Although the MABc is not intrinsically resistant to fluoroquinolones, only a

Table 2 Possible mechanisms of resistance of *MABc*

Antibiotic	*Locus and genes*	Proteins involved	Resistance mechanism
Hydrophilic antibiotics	–	–	Selective permeability of cell envelope
Aminoglycosides	*MAB_4395*	Aminoglycoside 2-N-acetyltransferase	Antibiotic-modifying enzymes
	MAB_0327	Aminoglycoside phosphotransferases	
	MAB_0951		
	MAB_3637c		
	MAB_4910c		
	MAB_4395		
Rifampicin	*MAB_0951*	Rifampicin ADP-ribosyltransferase	–
Beta-lactams	*MAB_2875*	Beta-lactamase	Antibiotic-degrading enzymes
Macolides	*erm(41) gene*	23S RNA methyltransferase	Target-modifying enzymes
	MAB_2297		
Several antibiotics	scattered in genome	ABC transporters. Mmpl. family	Efflux pumps

Note: Adapted from Nessar et al.[36]

Table 3 CLSI MIC Breakpoints for *MABc*

Antimicrobial	MIC for broth dilution (μg/mL)		
	Susceptible	Intermediate	Resistant
Amikacin	≤16	32	≥64
Cefoxitin	≤16	32–64	≥128
Clarithromycin	≤2	4	≥8
Ciprofloxacin	≤1	2	≥4
Doxycycline	≤1	2–8	≥16
Imipenem	≤4	8	≥16
Linezolid	≤8	16	≥32
Moxifloxacin	≤1	2	≥4
Trimethoprim-sulphamethoxazole	≤2/38	n/a	≥4/76
Tobramycin	≤4	8	≥16

Note: Adapted from National Committee for Clinical Laboratory Standards (CLSI). Susceptibility testing of mycobacteria, nocardiae, and other aerobic actinomycetes. Approved Standard. Wayne, PA: NCCLS; 2011. Document No. M24-A2.[45]

couple point mutations are needed in DNA gyrase subunits A and B to confer fluoroquinolone resistance (MICs > 8 mg/L).[48] This combined with the frequent use of fluoroquinolones for a variety of medical conditions, and almost ubiquitous use in agriculture, means that a sizeable proportion of MABc organisms are quinolone-resistant even if the patient has not received prior quinolone therapy for their mycobacterial disease.[49–51] Aminoglycoside resistance can also develop more easily than with other bacteria as MABc only possesses a single copy of the ribosomal RNA (rRNA) operon that aminoglycosides target.[36,52] This allows several single genetic mutations to cause high-level (MICs > 1,000 mg/L) drug resistance to aminoglycosides.[36,52] In addition to the inducible resistance mechanism to macrolides mentioned above, there is also the potential for a point mutation in the 23S rRNA peptidyl transferase region of MABc, which confers macrolide resistance (MICs > 4 mg/L), most commonly in the setting of prior macrolide monotherapy.[53]

Susceptibility Testing

The CLSI currently recommends the broth microdilution minimal inhibitory concentration (MIC) method for determining the susceptibility of MABc using a panel of 10 antimicrobials (►**Table 3**).[45] Agar tests, including the E-test, are not recommended because of inconsistency of results.[54] It is important to note that there is no proven clinical correlation between MICs and treatment outcome for pulmonary MABc.[1] There does appear to be a correlation between in vitro susceptibility and clinical response in skin and soft tissue infection, although this observation has not been prospectively confirmed.[1] In general, amikacin, cefoxitin, imipenem, clofazimine, and macrolides (the last only in MABc organisms without an active *erm* gene) have the most reliably low MICs suggesting the highest chance of clinical activity, although with no antibiotic is this reliable enough to dispense with MIC testing (►**Table 4**).[1,36]

Treatment Choice and Treatment Response

Because of a paucity of prospective, controlled, or randomized treatment studies, most treatment recommendations for MABc disease rely heavily on small retrospective or observational datasets, extrapolation from the treatment of other mycobacterial organisms, in vitro studies, and expert opinion.[1] In this context, individual patient response, treatment toxicity,

Table 4 Antibiotic susceptibility of *MABc* as defined by MIC (mg/L)

Antibiotic	Studies	Number of subjects	MIC range (mod) (mg/L)	Percent susceptible[a]
Clarithromycin	2	48–74	0.03–16 (0.03)	83–99
Cefoxitin	2	48–74	16–128 (32)	11–99
Imipenem	2	48–74	1–64 (8)	8–55
Ciprofloxacin	2	48–74	0.016–8 (2)	44–57
Levofloxacin	1	21	8–64 (32)	Not reported
Moxifloxacin	1	21	2–32 (16)	73
Doxycycline	1	20	2 - >128 (>128)	5
Minocycline	1	20	0.25 - >64 (>64)	5
Tigecycline	1	20	≤0.06 - 1 (0.12)	100
Linezolid	1	98	0.5 - 128 (32)	23
Sulfamethoxazole	2	48–74	4 - 256 (256)	1–12
Amikacin	2	48–117	0.25 - >128 (2 and 16)	87–94
Tobramycin	3	21–117	4 - >128 (8 and 16)	36–95
Clofazimine	1	117	0.25-1 (0.5)	99

Note: Adapted from Nessar et al.[36]
[a]**Susceptibility breakpoints as defined by Griffith et al[1] and Woods et al.[54]**

and overall goals of therapy are important considerations. That said, owing to the disease complexity and use of uncommon antimicrobials, expert recommendations and guidelines have an important role to play in management, a sobering concept given how infrequently even basic guidelines are followed for NTM disease.[1,55] Below we have attempted to outline treatment considerations and recommendations for pulmonary MABc as well as specific considerations for the various antibiotics most frequently used.[56] There are some general principles that should be followed, including prolonged therapy, an induction phase of therapy with a three- to four-drug regimen including one to two different active intravenous (IV) agents, and a suppressive phase which should involve at least two oral or inhaled antibiotics considered active based on drug susceptibilities, since most patients cannot tolerate 12 to 18 months of IV therapy.[1]

Pulmonary MABc disease is difficult to manage and treatment outcomes are generally poor.[1,4] There is a clear difference in treatment response based on subspecies with subsp *massiliense* having significantly better treatment outcomes than subsp *abscessus* (►**Table 5**). This is almost certainly due to the ability to use macrolide-based therapy for *massiliense*, which allows a more effective overall regimen and less treatment-related toxicity.[1,57,58] IV amikacin is generally the most active agent and is recommended as part of most treatment regimens if feasible from a renal and ototoxicity standpoint using three times per week (TIW) dosing.[1,4] Generally, an IV BL (either imipenem or cefoxitin) should be added for the initial phase of therapy as well.[1] Imipenem has a better toxicity profile than cefoxitin and older concerns about its efficacy have been somewhat refuted by newer in vitro data, so it is our preferred BL in most cases.[36,59] At least 4 to 8 weeks of dual IV induction therapy is recommended to give the best chance of prolonged clinical response.[1,15,58] In macrolide-susceptible isolates, an oral macrolide should be part of the treatment regimen, but even in nonsusceptible isolates, there may be a role for an oral macrolide given the benefits to airway inflammation and against other concurrent potential pathogens (see section Macrolides below). Clofazimine is often the only other oral antibiotic with a favorable susceptibility profile, although there are no rigorous clinical trials proving its efficacy.[60,61] However, in vitro data and small case series suggest it could be a useful agent to add instead of or along with a macrolide.[60,61] Given how difficult it is to obtain the recommended 12 months of negative sputum cultures for MABc lung disease, symptom and radiographic improvement are useful markers of treatment success.[1]

Because of the poor response to antibiotic treatment, in many cases surgical intervention in combination with antibiotic therapy holds the greatest chance of prolonged remission or cure, especially in cases where the areas of pulmonary infection are focal.[62,63] Although most NTM lung surgery data are in pulmonary MAC, the surgical technique is similar for MABc.[64,65] In pulmonary MAC, surgical intervention has been shown to be safe and effective, although there is not a large enough body of literature in MABc to prove it is equally safe.[64,65] If surgery is pursued, we recommend aggressive antimicrobial therapy in the 4 to 8 weeks before surgery to lower the bacterial burden and geographic extent of infection before lung resection. We also strongly recommend this take place at a center surgically experienced in NTM lung disease.

Specific Antimicrobials

One of the key components of MABc treatment is the use of three or more antimicrobials in most treatment regimens to increase efficacy and decrease the development of antibiotic resistance. Thus, the interplay between different antibiotics is an important dynamic with synergy or enhanced abilities to protect each other from the development of resistance as key theoretical components of more effective regimens.

Beta-lactams

Although BLs are a mainstay in the treatment of many gram-positive bacterial infections, most of the class has little utility against MABc because of its production of Bla_{MABc}, a broad-spectrum β-lactamase that inactivates most BLs.[66] Unfortunately, Bla_{MABc} is not effectively inhibited by the standard β-lactamase inhibitors clavulanate, tazobactam, and sulbactam.[66] Imipenem and cefoxitin are more slowly hydrolyzed than other BLs, allowing them to maintain activity against many MABc isolates.[66] Other carbapenems such as meropenem are not as active as imipenem, and in the treatment of MABc, imipenem is the carbapenem of choice.[67] In vitro studies suggest that imipenem has lower relative MICs than cefoxitin, although there can be difficulties around the lack of reliability of imipenem MICs.[1,59,68] Interestingly, in animal models, the new β-lactamase inhibitor, avibactam, effectively inhibits Bla_{MABc} potentially improving imipenem efficacy against these organisms and significantly reducing MICs against the new BL ceftaroline, although not enough to make ceftaroline useful in treatment.[69–71] There is potential intracellular synergy between imipenem and amikacin that is not present with cefoxitin and amikacin, another argument for imipenem over cefoxitin since both drugs are often used in combination with an aminoglycoside.[1,59,68] Although there are no comparative studies to date on the toxicity of imipenem versus cefoxitin, our experience has been that imipenem is also more tolerable over a prolonged treatment course. One nuance in using both antibiotics to treat MABc is that both are dosed every 12 hours in contrast to the every 8-hour or every 6-hour schedule on which they are dosed for most other infections. There does not appear to be utility to continuous infusion dosing with cefoxitin and it is impractical with imipenem because of drug stability.[72]

Intravenous Amikacin

IV amikacin is generally considered the most active antibiotic available for the treatment of MABc infections.[1,5,36] Microbial killing due to IV amikacin is believed to be linked to peak serum-to-MIC (C_{max}/MIC) ratios with the optimal ratio estimated as 3 to 5.[1,73] ATS treatment guidelines suggest a dose of 10 to 15 mg/kg, with the lower dose of 10 mg/kg recommended in the elderly or those on prolonged therapy (situations applying to most patients).[1,36] The concern with IV amikacin is drug toxicity with ototoxicity/vestibular and renal toxicity

Table 5 Studies of antibiotic treatment response in MABc subspecies abscessus and massiliense

Study, year, country	Study number and population	Study design	Study period	Treatment duration (wk)	Treatment regimen	Treatment success (%)[a]
Subsp *abscessus*						
Choi et al, 2017, South Korea[140]	12 patients with acquired macrolide resistance starting treatment	Retrospective review	2006–2016	Average: 96 (64–176)	IV amikacin + IV cefoxitin or imipenem + oral macrolide ± FQ/TCN/CFZ	0 (1 converted s/p surgery)
Yang et al, 2017, South Korea[61]	42 patients starting clofazimine for initial (36%) or salvage (64%) treatment	Retrospective review	2013–2015	Median: 48 (25–48)	Oral CFZ + oral macrolide (85% resistant) + IV amikacin (67%) and/or IV BL (67%)	24 (81 had improved sx)
Park et al, 2017, South Korea[57]	19 patients starting treatment after disease progression	Retrospective review	2006–2015	Median: 61 (29–116) • Amikacin: 16 (2–50) • Cefoxitin: 2 (0–6) • Imipenem:3 (0–5)	At least two IV agents (amikacin, imipenem, or cefoxitin) + oral macrolide	26 (surgery in 3 patients)
Koh et al, 2017, South Korea[58]	67 patients initiating therapy	Prospective observational cohort	2002–2012	All: 48 • All: Initial IV therapy 4 wk	IV agent (amikacin or cefoxitin) + macrolide ± quinolone ± doxycycline	42 (surgery in 6 responders and in 3 nonresponders)
Lyu et al, 2014, South Korea[141]	26 patients initiating therapy	Retrospective review	2006–2012	Average: 65 (SD ± 46) • IV therapy mean: 39 (SD ± 16)	IV amikacin ± IV imipenem or cefoxitin + oral macrolide	42 (surgery in 8 patients)
Kim et al, 2012, South Korea[15]	24 patients initiating therapy	Retrospective review	2004–2009	All: 96 • All: initial IV therapy 4 wk	IV amikacin and IV cefoxitin + oral clarithromycin + oral ciprofloxacin ± oral doxycycline	50 (33 had CT-based imaging improvement)
Subsp *massiliense*						
Park et al, 2017, South Korea[57]	17 patients starting treatment after disease progression (out of larger group of 56 patients)	Retrospective review	2006–2015	Median 97 (64–120) • Amikacin: 7 (2–30) • Cefoxitin: 3 (0–6) • Imipenem: 0 (0–4)	At least two IV agents (amikacin, imipenem, or cefoxitin) + oral macrolide	82 (surgery in 2 patients)
Koh et al, 2016, South Korea[142]	71 patients initiating therapy	Prospective observational cohort	2007–2012	Median 96 (92–97) for *2007–2010* • All: IV agent 4 wk **and** Median 61 (51–72) for *2010–2012* • All: IV agent 2 wk	IV amikacin and IV imipenem or cefoxitin + macrolide + quinolone (*if 2007–2010*)	98 (96 had symptom improvement)
Lyu et al, 2014, South Korea[141]	26 patients initiating therapy	Retrospective review	2006–2012	Average: 48 (SD ± 18) IV therapy mean: 19 (SD ± 10)	IV amikacin ± IV imipenem or cefoxitin + oral macrolide	96 (82 had symptom improvement, surgery in 1 patient)
Kim et al, 2012, South Korea[15]	34 patients initiating therapy	Retrospective review	2004–2009	All: 96 • All: initial IV therapy 4 wk	IV amikacin and IV cefoxitin + oral clarithromycin + oral ciprofloxacin ± oral doxycycline	100 (88 had CT-based imaging improvement)

Abbreviations: CFZ, clofazimine; CT, computed tomography; FQ, fluoroquinolones; IV, intravenous; s/p, status post; sx, symptoms; TCN, tetracycline.
[a]Treatment success defined as sustained sputum culture conversion.

being the primary considerations, although liver function testing abnormalities also occur. In general, ototoxicity seems to be irreversible and related to cumulative dose and higher trough levels, while renal toxicity is usually reversible with drug discontinuation/dose reduction and vestibular toxicity is often transient, regardless of dosing change.[74–77] Toxicity seems to increase with treatment courses longer than 8 to 12 weeks.[77] It is controversial whether daily versus TIW dosing is more efficacious and there are no good comparative data.[1] However, there are comparative data showing lower toxicity rates with TIW dosing, so this is generally our recommended strategy. There does not appear to be any benefit to dosing more than once a day as is done with many other bacterial infections, so we strongly recommend against this for MABc.[76] Given the toxicity, close monitoring is important, and we recommend baseline and monthly audiology testing as well as at least a complete metabolic panel and complete blood count every other week as well confirming correct amikacin dose via estimation of serum-to-MIC levels as above. In vitro data suggest that subinhibitory amikacin levels may be not just less effective but also harmful by causing physiologic changes to the organism that make it more robust and virulent.[78,79] Even more concerning, in vitro data suggest that MABc organisms with a functional *erm* gene may be able to induce amikacin resistance on macrolide exposure through a WhiB7-dependent network of resistance genes.[80] These data need additional confirmatory work and in vivo evaluation, but it is worrisome given the prevalence of both macrolides and amikacin in many regimens and raises the question of whether this contributes to the poor outcomes for subsp *abscessus* where a functional *erm* gene is frequently present and macrolides still often used.

Inhaled Amikacin

Since the most limiting feature of IV amikacin is drug toxicity, it is not surprising that there has been interest in whether an inhaled formulation of that drug has efficacy for treating MABc pulmonary infections. A retrospective study of 15 patients suggested that inhaled amikacin led to improved symptoms and culture responses in a notable minority of the cases, but that increasing toxicity limited doses higher than 250 mg/day.[81] Subsequent animal model work suggested a new liposomal form of inhaled amikacin might be effective for the treatment of MABc (as well as MAC).[82] This led to one of the few randomized controlled trials in this field using inhaled liposomal amikacin for NTM lung disease which showed improvement in the intervention arm, although only one-third of the 89 patients were MABc and their response was difficult to observe in the only 3-month-long study.[83] There is currently an ongoing open-label trial evaluating the liposomal formulation in subsp *abscessus* lung infection (NCT03038178), which may shed more light on this issue.

Macrolides

Antibiotics in the macrolide class (clarithromycin, azithromycin, erythromycin) have traditionally been the most important agents in the treatment of NTM infections. However, as mentioned above, their use in the treatment of MABc infections is much more complicated because of inducible macrolide resistance conferred by a functional *erm* gene. Selection of macrolide resistance is sometimes even less straightforward than presence or absence of a functional *erm* gene as certain subsp *abscessus* sequevars and subsp *bolletii* appear to have other mechanisms that cause macrolide nonsusceptibility.[84] Although, traditionally, clarithromycin (CLARI) has been the macrolide of choice, data suggest the newer macrolide azithromycin (AZI) is more active, easier to tolerate, and causes somewhat less activation of the inducible macrolide resistance mechanism.[85] AZI has the added benefit of fewer drug–drug interactions as well as daily dosing instead of twice-daily dosing with CLARI, and for these reasons, it should be considered the macrolide of choice for MABc.[86] As mentioned, there is concern about potential antagonism by macrolides and amikacin in MABc strains with an active *erm* gene, as well as with fluoroquinolones specifically in subsp *abscessus* (discussed in more detail in next section).[80] Interestingly, for subsp *massiliense*, there is possible in vitro synergy between macrolides (CLARI was macrolide studied) and the fluoroquinolone moxifloxacin as well as the tetracycline tigecycliane, another example of the different drug response phenotype of this subspecies.[87] One other difficulty created by macrolide and aminoglycoside combination therapy is that macrolides can rarely cause sensorineural ototoxicity, which in a small number of cases can be irreversible.[88] This effect can start after limited macrolide exposure and can make it difficult to know whether it is the aminoglycoside or the macrolide causing ototoxicity.[88] The anti-inflammatory properties that macrolides, particularly AZI, possess have been well documented as part of their benefit against airway exacerbations in many different lung diseases states including non-CF bronchiectasis.[89,90] It is possible as part of a long-term regimen that they benefit to MABc pulmonary infections in this way, but this has not been proven and, when used in this fashion, they should not be counted as an active MABc antibiotics, unless the organism is known to be macrolide susceptible.

Clofazimine

Clofazimine (CFZ) is an older antibiotic that has long been used in treatment of the mycobacterial infections caused by *Mycobacterium leprae* and more recently included in some new regimens for drug-resistant tuberculosis.[91,92] CFZ MICs to MABc are typically very low and make it the most reliably active in vitro oral antibiotic option available (►**Table 3**).[36,93] In the context of MABc therapy, CFZ also has the attractive property of in vitro synergy with amikacin, which seems to decrease MICs to both by four- to eightfold.[93–95] It also appears to have some synergy with macrolides.[95] These findings make CFZ a potentially useful agent in MABc therapy, and it is used off-label frequently.[1] Two recent studies, one retrospective cohort (15 patients for initial therapy and 27 patients for salvage therapy) and one prospective observational cohort (54 patients), used CFZ as part of a multidrug regimen for MABc pulmonary disease and showed promising symptom and culture-based outcomes with relatively minimal rates of treatment-limiting side effects.[60,61] Given these data, we recommend CFZ as an important part of many MABc treatment

regimens, especially when there are no other active oral agents. Although skin discoloration is the most well-known of CFZ side effects, the most common treatment-limiting side effects are gastrointestinal in nature.[60,61] CFZ has a very long half-life of roughly 50 to 75 days and a provider should assume it takes around 2 months before the drug reaches therapeutically active levels.[96,97] CFZ has not been available through traditional pharmaceutical distribution since 2004 and can only been obtained either via investigational new drug (IND) directly from the manufacturer (Novartis) or through individual IRB-approved IND to the Federal Drug Administration (FDA). There is an ongoing placebo-controlled trial funded by the FDA looking at the use of CFZ in MAC pulmonary disease, which should shed further light on the drug's use in pulmonary NTM disease (NCT02968212).

Fluoroquinolones

Fluoroquinolones (FQs) are an attractive option for MABc therapy because of their excellent oral bioavailability and good performance in the treatment of other mycobacterial infections, especially tuberculosis. However, there are a couple of in vitro considerations that somewhat mitigate this optimism for MABc as resistance to FQs has been shown to develop quickly during monotherapy, and there is evidence of antagonism between macrolides and FQs in many subsp *abscessus* isolates.[98–100] As previously mentioned, FQs are used in many other clinical diseases and ubiquitously in agriculture, and this may contribute to the fact that high percentage of isolates are FQ resistant, and thus the drug class should not be relied on without susceptibility testing on a recent isolate.[101] That said, FQs have been used as part of combination therapy in a couple of retrospective studies and there is probably a role for their use when MIC testing shows favorable results.[9,102] Given the concerning in vitro studies with FQ monotherapy and potential antagonism with macrolides for subsp *abscessus* (much more with CLARI than AZI), we strongly recommend against monotherapy or dual therapy with only CLARI as part of a treatment or suppressive regimen.[98–100] When used for gram-positive infections such as mycobacterial infections, moxifloxacin is generally the most active drug in the class and is the FQ we recommend if these drugs are to be used for MABc therapy. Since therapy is often prolonged and the patient population often receives intermittent steroids or other QT prolonging agents, care should be taken to monitor for both QT prolongation and arthropathies when using FQs for MABc therapy.

Tigecycline

The tetracycline (TCN) drug class has broad antibacterial activity including against some mycobacteria. The newer IV TCN, tigecycline, appears to have particular in vitro efficacy against rapid-growing mycobacteria including MABc compared with other TCNs and to its own activity against slow-growing mycobacteria.[103,104] Here again, synergy with other drugs is an important consideration, and in vitro data suggest that tigecycline may have synergy with macrolides, although it does not appear to have this benefit with aminoglycosides.[105] Clinical data are limited, but one study that used tigecycline as part of a salvage therapy regimen in 52 patients with MABc/*M. chelonae* infection (roughly 75% were MABc) showed clinical improvement in 62% of patients who received more than 1 month of therapy out of the subset of 36 patients who had clinically evaluated outcomes.[106] Adverse drug events were common, and although it is unclear which antibiotic in the treatment was the cause of the symptoms, many of these events were gastrointestinal in nature (nausea > vomiting > diarrhea > anorexia), side effects particularly common with tigecycline.[106] The side effect profile was more pronounced at higher doses and mitigated by preinfusion treatment with antiemetics; hence, in pulmonary disease we recommend dosing at 50 mg/day and using preinfusion antiemetics when the tigecycline is used.[106] When used in this manner, we recommend tigecycline as an alternative IV option if either amikacin or imipenem/cefoxitin is not possible based on susceptibility testing or other factors.

Oxazolidinones

The oxazolidinone drug class, which includes linezolid (LZD) and tedizolid (TZD), acts by inhibiting protein synthesis at the 50s ribosomal subunit and has the attractive properties of good oral bioavailability and tissue penetration.[107] LZD has been studied extensively for the treatment of tuberculosis and seems effective and more tolerable at doses of either 300 or 600 mg daily compared with the 600 mg twice daily dose used for nonmycobacterial infections.[108,109] Although the option of an active oral agent is appealing, clinical data for the oxazolidinones in the treatment of MABc are at the level of case reports, and MICs to a majority of MABc isolates are much higher than for TB, although good in vitro activity can be seen in a minority of isolates.[1,110,111] LZD appears to have in vitro synergy with amikacin and macrolides in a proportion of isolates, although it may have potential antagonism with both cefoxitin and moxifloxacin.[87,111] TZD may have better MABc activity than LZD with lower MICs on in vitro testing—however, interpretive breakpoints do not yet exist for TZD.[110] Unfortunately, toxicity with LZD appears to be common in prolonged treatment courses even at daily dosing and most individuals cannot tolerate treatment for more than 4 to 6 months.[112] Peripheral neuropathy, not mitigated by pyridoxine, is the most common side effect seen in roughly 25% of cases.[112] In general, we do not recommend the oxazolidinones as part of first-line regimens given the paucity of clinical data. However, they may have a role for periods of time when supported by favorable susceptibility testing.

Bedaquiline

Bedaquiline is a novel diarylquinoline antibiotic that potently inhibits ATP synthase in mycobacteria, has good bioavailability, and is now FDA approved for the treatment of drug-resistant tuberculosis.[113,114] It appears to have a broad range of in vitro activity against NTM isolates including members of the MABc.[115,116] Specifically, in this complex, roughly 70 to 80% of isolates appear to be susceptible based on in vitro testing and estimated, but not formally established, breakpoints.[115] Data for NTM disease are limited, but safety data can

probably be approximated from the tuberculosis literature and suggest that nausea, hepatotoxicity, and QT prolongation are the primary drug-related adverse events.[117] Clinical efficacy data are very limited, with the primary clinical study published to date (a 10-patient case series: 6 MAC lung disease and 4 MABc lung disease) using the 400 mg daily followed by 200 mg TIW dosing that has been used in the tuberculosis trials.[118] This study suggested some microbiologic response based on semiquantitative sputum cultures, although it also demonstrated high rates of nonsevere side effects.[118] Given these limited data, we recommend considering bedaquiline in alternative or salvage therapy regimens when other oral antibiotic options are limited, although ability to effectively utilize the medication will likely be constrained by cost and drug access in some cases.

Specific Disease State Treatment Considerations

Cystic Fibrosis

CF is an important underlying predisposition for pulmonary NTM infection and disease because of the significant bronchiectasis and impairment to pulmonary immune defenses that CF confers. As a result, a high percentage of individuals with CF have pulmonary colonization with an NTM, ranging from 5 to 30% depending on the case series.[18,26,119–121] MABc is the second most common NTM after MAC in this setting, but for reasons that are unclear its incidence is rising, unlike MAC incidence, which is flat. Most NTMs can cause invasive disease in CF, leading to more rapid decline in lung function and at times to NTM-related mortality, with MABc seeming to contribute to a more deleterious course than other NTMs.[121–123] Although there is concern for human transmission in MABc outbreaks at CF centers, the limited genetic diversity in the complex makes genetic clustering harder to use as an outbreak marker; therefore, while there is concern about this issue, it is generally considered an unresolved concern.[25,124] Despite the importance of MABc in CF, there are no randomized controlled trials or highly controlled studies looking at the effect of antimicrobial therapy versus no therapy or comparing different antimicrobial regimens in CF, and treatment guidance is limited to small, retrospective, single-center case series.[123]

One common practice in CF management, the use of prophylactic azithromycin to prevent pulmonary exacerbations, does appear to be protective against the development of incident NTM lung disease, although it is unclear if this applies to MABc, with some datasets suggesting lower MABc prevalence and others suggesting the NTM prevalence shifting toward MABc.[125,126] One concern given the antibiotic exposure in the CF population is that their MABc isolates may in general be more resistant than in non-CF cases, but this has not been clearly borne out by data.[127] Once MABc pulmonary disease develops, the same principles that apply to MABc treatment in the non-CF population should be applied.[1] Similar to the non-CF setting, the subsp *massiliense* appears to be associated with better treatment outcomes than subsp *abscessus*.[128] Given the young age of this patient population, repeated treatment courses or long-term suppression is more likely to be needed because of the many years of potential for reinfection and/or relapse. In the CF population, there are even more issues with concurrent pulmonary disease caused by other NTMs, especially MAC, as well as other respiratory pathogens such as *Staphylococcus aureus*, *Pseudomonas*, and *Aspergillus*.[28,123] Unfortunately, although surgery is an attractive option for difficult MABc lung disease cases in other patient populations, there may be additional risks to this intervention in the CF leading to less favorable outcomes.[30] Another difficulty is that for many more advanced CF cases, the only management strategy available is lung transplant, but as is discussed more in the subsequent section, at many centers lung transplant is not offered when there is concomitant MABc infection.

Treatment Considerations Specific to Lung Transplant Recipients

Lung transplant raises four unique and complicated considerations in relation to MABc infection: (1) pretransplant management, (2) viability of lung transplant in the setting of MABc lung disease, (3) risk of posttransplant MABc lung disease, and (4) management of posttransplant MABc lung disease.

In general, pretransplant management is the same as general MABc management mentioned above, although we favor the most aggressive possible antimicrobial therapy in the immediate pretransplant period. One important consideration for MABc lung disease is that many centers consider MABc infection a contraindication for lung transplant, which precludes CF patients with end-stage disease from having a transplant, which is the only curative management strategy for their CF disease.[129] This contraindication is largely based on expert opinion and the literature to support this practice is limited.[130,131] In fact, several more recent small retrospective series suggest that outcomes may not be worse in those with pretransplant pulmonary cultures showing MABc, although there seems to be a higher rate of treatable posttransplant surgical site infections with MABc in these hosts.[129,132–134]

Lung transplant is the solid organ transplant with the highest risk of posttransplant NTM lung disease.[135,136] There does seem to be a significant rate of transient and clinically insignificant colonization in the posttransplant period, so being post–lung transplant does not inherently change the dynamic that not all positive pulmonary NTM cultures require treatment and transient colonization does not seem to portend a worse posttransplant outcome.[137,138] MABc appears to be the most common posttransplant cause of NTM lung disease with a risk of infection highest in the first 3 years after transplant.[3,136] There seems to be a trend toward worse posttransplant survival in cases that develop NTM lung disease. However, it is not clear if this trend is further worsened in those whose lung disease is caused by members of MABc, and there is evidence suggesting that posttransplant MABc infection can be successfully managed with prolonged aggressive therapy.[3,129,132–134,136,139] Treatment is no different than in the nontransplant population, although regimen choice may be more difficult and closer toxicity monitoring needed because of potential drug interactions with transplant medications.[1] We recommend the same criteria for MABc disease in the posttransplant setting as the

nontransplant population but would initiate aggressive MABc therapy if a patient meets criteria for MABc disease without any period of observation off therapy. We recommend prolonged therapy along with multidrug IV induction therapy and would generally err on the side of treating longer than the nontransplant population because of the underlying immunodeficiencies. Finally, we would be more inclined to continue some form of chronic suppressive therapy in this population if there is an oral regimen with tolerable side effects and toxicities, although this is not needed in all cases.

Conclusion

The MABc organisms are increasingly recognized as a pulmonary pathogen that requires treatment in some individuals. Our belief is that most infected individuals eventually progress to disease, although natural history studies to definitively substantiate this are lacking. The MABc poses significant and unique treatment challenges because of its extensive drug resistance profile and propensity for persistence. The antibiotic regimens used for this disease involve both antibiotics less commonly used by pulmonary or infectious diseases practitioners and those that require prolonged use and careful monitoring. Response to therapy is highly dependent on MABc subspecies, and even with optimal therapy, some organisms in the MABc still have suboptimal antibiotic treatment outcomes. In settings of suboptimal response, lung-resection surgery is a consideration in management. While MABc disease is both more common and problematic in the unique populations of CF and lung transplant recipients, the organism can still be managed in these settings. Because of the complexity of this disease, expert consultation is a recommended part of management. Additional research is desperately needed to better understand disease pathogenesis, discover novel antibiotic therapies, and identify optimal treatment strategies, with one of the most important challenges being the identification whether in vitro susceptibility data predict clinical response.

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