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Nontuberculous Mycobacteria in Cystic Fibrosis and Non–Cystic Fibrosis Bronchiectasis

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Abstract

Increasing numbers of cystic fibrosis (CF) and non-CF bronchiectasis patients are affected by pulmonary nontuberculous mycobacteria (NTM) infection worldwide. Two species of NTM account for up to 95% of the pulmonary NTM infections: *Mycobacterium avium* complex (MAC) and *Mycobacterium abscessus* complex (MABSC). Diagnosis of pulmonary NTM infection is based on criteria specified in the 2007 AmericanThoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines. While many initial positive cultures do not progress to active NTM disease, even a single positive NTM sputum culture obtained from higher risk groups such as classic CF or older women with bronchiectasis and very low body mass index should be closely monitored for progressive disease. Macrolides remain the most effective agents available against MAC and MABSC. Infection with MABSC may be associated with worse clinical out-comes, as more than half of MABSC isolates have inducible macrolide resistance conferred by an active *erm(41)* gene. Of growing concern in CF is that MABSC is becoming more common than MAC, seems to target younger patients with classic CF, and is more difficult to manage, often requiring prolonged courses of intravenous antibiotics. Recurrence rates of NTM after initial successful treatment remain high, likely due to nonmodifiable risk factors raising the question of whether secondary prophylaxis is feasible. More rapid and readily available methods for detecting inducible macrolide resistance and better in vitro susceptibility testing methods for other drugs that correlate with clinical responses are needed. This is crucial to identify more effective regimens of existing drugs and for development of novel drugs for NTM infection.

Keywords

nontuberculous mycobacteria; mycobacterium avium complex; mycobacterium abscessus; cystic fibrosis; bronchiectasis

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Bronchiectasis in CF and Non-CF Patients

Bronchiectasis, an irreversible dilatation of the medium sized airways with chronic infl ammation,[1] has different clinical features between cystic fibrosis (CF) and non-CF patients. Recent studies, however, are recognizing that dysregulation in immune response plays an important role in the pathogenesis of bronchiectasis in both CF and non-CF patients.[2,3]

Among CF patients, bronchiectasis can appear even during infancy. A retrospective cohort study on 76 children diagnosed with CF at birth revealed that bronchiectasis is persistent and occurs in higher prevalence with increasing age: 29% at 3 months of age to 61% at 3 years of age.[2] The strongest risk factor for bronchiectasis the authors identified was the high level of free neutrophil elastase activity in bronchoalveolar lavage fluid, suggesting overactivation of the neutrophil-induced immune response and resulting tissue destruction as a major pathogenic factor of bronchiectasis in CF patients. Bacterial infection, especially by *Pseudomonas aeruginosa,* was an independent risk factor for bronchiectasis in CF patients, but less significant than neutrophil elastase activity.[2]

Bronchiectasis in non-CF patients is a growing concern with increasing prevalence. Analysis on 5% of the Medicare beneficiaries during 2000–2007 demonstrated that the prevalence of bronchiectasis during the 8-year period was 1,106 cases per 100,000 people with annual increase of 8.5%.[4] One study that evaluated 150 non-CF patients with bronchiectasis to identify any underlying factors revealed previous lung infections as the most common finding (29%), but other underlying conditions such as allergic bronchopulmonary aspergillosis, primary humoral immune defects, rheumatoid arthritis, and aspiration were also identified. However, it should be noted that 53% of the patients in this study did not have any identifiable causative factors.[5] A recent study done in the United States that analyzed 106 patients with non-CF bronchiectasis reported that the majority of the cases (63.2%) had an immune dysregulation as an underlying cause.[3]

Epidemiology of Nontuberculous Mycobacteria Pulmonary Infection

There has been a remarkable increase in the incidence of nontuberculous mycobacteria (NTM) infection worldwide for the past two decades. Part of this increase could be due to improved microbiology techniques that have enhanced the isolation and identification of NTM in respiratory samples, but these organisms have become serious emerging pathogens affecting CF patients and susceptible non-CF patients.

CF patients:

The first large-scale multicenter study that evaluated the prevalence of NTM infection in CF patients in the United States published a prevalence of 13% in 2003. Of the NTM isolated, 72% were *Mycobacterium avium* complex (MAC), while 16% belonged to *Mycobacterium abscessus* complex (MABSC).[6] Subsequent large-scale epidemiologic studies from Israel, France, United Kingdom, and Scandinavian countries noted a NTM prevalence in CF patients ranging from 3.3 to 22.6%.[7–10] Older CF patients (i.e., 15 years of age and older) were found to be more susceptible to NTM infection.[6,7,11]

In addition, there have been reports of recent outbreaks that occurred in major CF centers in the United States and in the United Kingdom by highly virulent strains of *Mycobacterium massiliense*, a subspecies of MABSC. Whole genome sequencing and genotyping of the strains revealed that each outbreak was caused by a clonal strain, making person-to-person transmission in nosocomial settings a strong possibility.[12,13] Moreover, close genomic relatedness among the *M. massiliense* strains that caused the outbreaks in different areas of the world has been reported.[14]

Non-CF patients:

There are relatively fewer epidemiologic data on NTM infection in non-CF patients in the literature. The largest study available to this date is the one by Prevots and her colleagues published in 2010.[15] Their study population comprised 4.1 million beneficiaries from four different integrated health systems located in different geographical areas in the United States from which 7,940 patients had a myco-bacterial culture collected from any site.[15] The site-specific annual prevalence of NTM pulmonary infection ranged between 1.4 and 6.7 per 100,000 in the study population. MAC was the most common pathogen recovered from 80% of definite cases. The most striking observation in this study was that the prevalence of NTM pulmonary infection was increasing at an alarming rate: 2.6% per year among women and 2.9% per year among men. A recent study performed at the University of Illinois Medical Center evaluated 182 non-CF patients with bronchiectasis. They reported that NTM infection was present in 37% of the patients. The predominant species was MAC accounting for 81% of the isolates.[16] A study from Korea that evaluated the correlation between the computed tomographic (CT) findings of diffuse bronchiectasis and bronchiolitis and NTM infection in 105 patients showed that the prevalence of NTM infection among those who had the above CT findings was 34%. Again, MAC was the leading pathogen (50% of the isolates) followed by MABSC (39%).[17] Thus, prevalence is significantly higher when the study population denominator is patients with established bronchiectasis compared with a general, non-disease-selected population.

Pathophysiology

NTM infection and bronchiectasis are very closely linked.[18] Seitz and her colleagues who analyzed a 5% sample of the Medicare beneficiaries in the United States showed that patients with a reported diagnosis of bronchiectasis were 50 to 75 times more likely to have NTM infection compared with those without bronchiectasis.[4]

NTM adhere to damaged areas of the respiratory mucosal surface. It has been suggested that fibronectin attachment protein from NTM binds to the fibronectin in the extracellular matrix that is exposed only in the damaged respiratory mucosa and thus NTM are not able to adhere to the intact mucosal suface.[19,20] Also, stagnant mucus may facilitate NTM infection in both CF and non-CF patients, as peripheral mucus plugging was more pronounced on the high-resolution CT (HRCT) scans of NTM-infected patients.[21]

Despite a clear association between bronchiectasis and NTM infection, the question of NTM infection being a cause or a consequence (or both) of bronchiectasis has not been clearly answered,[18] especially for non-CF patients. Bronchiectasis without NTM infection has been

observed at higher percentages in CF patients compared with non-CF patients, which implies NTM infection could be more of a consequence of bronchiectasis at least in CF patients.

NTM are ubiquitous in our environment and commonly found in our water systems, especially in biofilms formed on household plumbing fixtures such as a showerhead.[22] A study by Falkinham demonstrated that the same strain of NTM collected from a patient sputum sample was also found on showerheads or other plumbing fixtures in 19% of the NTM patients' households.[23] These results suggest that water systems may be a prominent reservoir of the NTM that infect susceptible humans. However, it is not well understood how exposure to the water system leads to infection and if any preventive measure to reduce the exposure would be effective or even feasible.

Diagnosis

Currently, the diagnosis of pulmonary NTM infection in both CF and non-CF patients is based on the criteria specified in the 2007 American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) guidelines.[24] Both clinical and microbiological criteria must be met. Clinically, the presence of symptoms (respiratory ± constitutional) and abnormal radiological findings consistent with NTM infection should be established. Microbiologically, two or more positive cultures from expectorated sputum samples or one positive culture from bronchial lavage or a lung biopsy (with the appropriate histological findings) are required to make a diagnosis of pulmonary NTM infection.[24]

Clinical Features

In both CF and non-CF patients with bronchiectasis, the symptoms from NTM infection are nonspecific. Almost all of them present with chronic respiratory symptoms including cough, wheezing, dyspnea, and increased sputum production. Some also develop chronic constitutional symptoms including fever, malaise, and weight loss, which may be associated with more advanced NTM infection.[24] However, clinicians should be aware that bronchiectasis itself can have exacerbations producing similar symptoms which may be attributable to other bacterial infections associated with bronchiectasis.[18]

Some features on the HRCT images may be more specific to NTM infection. Abnormal findings on HRCT of mostly non-cavitary, multifocal bronchiectasis with scattered clusters of small nodules are suggestive of NTM infection. When NTM infection causes cavitary lesions, they tend to be thin-walled cavities that spread contiguously and often involve the pleura.[24]

CF patients:

A multicenter cohort study in the United States that followed 60 CF patients for 15 months who had at least one positive NTM culture demonstrated that worsening HRCT finding is a valid predictor of progression to NTM disease, but not serial FEV_1 (forced expiratory volume in 1 second) measurements. The study also reported that 87% of the patients who had two or less positive NTM cultures during the 15-month period did not develop clinically

significant NTM infection, but those who had three or more positive cultures all progressed to clinically significant NTM disease.[25] A recent retrospective study on 96 patients at the Colorado CF center during 2000–2010 also confirmed that a majority of the patients who had transient NTM-positive cultures did not progress to NTM infection. Unlike the former, this study observed that the patients who eventually developed NTM infection had lower baseline FEV_1 at the time of first positive culture and higher rates of decline in FEV_1 during the year before and subsequent years after the first positive culture.[26] The results from these two studies indicate that the CF patients who have two or more persistent positive NTM cultures will need closer evaluation/monitoring that includes serial HRCT as well as FEV_1 measurements.

Non-CF patients:

As for NTM infection in non-CF patients with bronchiectasis, it has been shown in multiple studies that certain preexisting physical features are associated with NTM infection. These features are as follows: being taller and leaner (hence low body mass index [BMI]), female gender, pectus excavatum, scoliosis, and mitral valve prolapse.[27–29] These preexisting phenotypic features are important clues that suggest the existence of genetic predisposition for NTM infection. However, the findings have been observed mostly in white patients so far. There has been one recent study from Korea that looked into the preexisting phenotypic features in Korean pulmonary NTM patients. It was a prospective study that analyzed non-CF patients with bronchiectasis with established NTM infection ($n = 84$) and without NTM infection ($n = 47$). Their results also showed that lower BMI was a significant clinical feature associated with NTM infection as well as existence of scoliosis, but not older age or female gender.[30] Association with lower BMI found in this Korean study needs to be carefully interpreted, as there was no significant height difference and active NTM infection itself may cause significant weight loss. Association with scoliosis, on the other hand, is more suggestive of possible similar genetic predispositions in pulmonary NTM patients with Asian ethnicity.

Challenges in Treating NTM Pulmonary Infection

Importance of species identification:

Although there are more than 150 species of NTM identified in the environments, only a handful of them are known to cause pulmonary infection in humans. By far, MAC and MABSC are responsible for the majority (70–95%) of the NTM infections in both CF and non-CF patients worldwide. There are other NTM species capable of infecting the human lung, including *M. kansasii, M. chelonae, M. fortuitum, M. xenopi, M. peregrinum, M. immunogenum, M. lentiflavum, M. malmoense, M. terre,* and *M. simiae.* However, the prevalence of pulmonary infection by these “other” NTM species is much lower than that of MAC or MABSC.[6,8–10,17,30] Before initiating any NTM treatment, its species needs to determined and for MABSC, the subspecies delineation is necessary because of the different inherent macrolide resistance patterns among the subspecies. Nowadays multilocus genotyping techniques can reliably identify the MABSC group to its subspecies level.[31,32]

Once the patient and the clinician have decided on treating the NTM infection, it is recommended to base the therapy on the species-specific treatment regimen provided in the 2007 ATS/IDSA guidelines[24] for both CF and non-CF patients. Joint US CF Foundation and European CF Society guidelines for the diagnosis and management of NTM in CF have been drafted and are being submitted for publication.

Management of bronchiectasis:

Because bronchiectasis and NTM infection are closely related disease entities,[18] clinicians taking care of patients with NTM pulmonary infection should be aware that evaluation/management of the patient's bronchiectasis must be an important part of the patient care. If exacerbation of bronchiectasis is suspected (often due to other bacterial infections or bronchospasm), it needs to be treated or ruled out before modifying treatment for NTM infection. Routine use of airway clearance measures such as hypertonic saline or oscillating positive pressure devices in stable bronchiectasis patients are recommended by most of the experts.[33] Airway clearance measures have been associated with improved quality of life among bronchiectasis patients.[34] Regular aerobic exercise in particular was shown to reduce the frequency of exacerbation in a recent randomized clinical trial.[35]

Treatment for MAC:

The first-line treatment regimen for MAC pulmonary infection consists of a macrolide (either clarithromycin or azithromycin), rifampin, and ethambutol. The macrolide is the most important component of the regimen and the clinical outcome is quite poor if a macrolide is not included in the regimen or the pathogen develops macrolide resistance.[36] The macrolide resistance in MAC is caused by acquisition of certain single-base mutations in the 23S rRNA gene, usually selected due to macrolide monotherapy. It is found in up to 4% of MAC clinical isolates.[36,37]

The multidrug treatment for MAC infection should be continued until the patient has persistently negative sputum cultures for 12 months while on the treatment.[24] Although it is a challenging task for both the patient and the clinician, the outcome seems favorable when the recommended treatment regimen and duration have been fulfilled. A recent study from University of Texas Health Science Center at Tyler reported that the rate of treatment success (negative sputum cultures for 12 months while on therapy) was 87% among the 180 non-CF patients who adhered to the recommended treatment. No patient developed macrolide resistance during the study. One concerning finding in their study was that, among the patients who had initial treatment success, 48% of them had recurrence of two or more positive sputum cultures with MAC after being off any treatment. Genotyping of the recurrent MAC isolates showed that 75% of them were different from the original MAC strain, while 25% were the original strain.[38] More investigation to identify risk factors for recurrence of MAC after the first successful treatment is warranted, as the reported recurrence rate is unacceptably high. For some patients, recurrence might be unavoidable due to the existence of an inherited host susceptibility or disruption of airway clearance related to the severity of their bronchiectasis. If so, effectiveness/feasibility of secondary prophylaxis can be considered. The potential benefits of using agents such as macrolides or inhaled amikacin, which are effective for treatment as part of a multidrug regimen, as

monotherapy for prophylaxis, would need to be balanced with the potential for precipitating drug resistance if recurrent infection occurred while on these drugs.[39–41]

Treatment for MABSC:

As for MABSC pulmonary infection in non-CF patients with bronchiectasis, the mortality rate directly related to this infection was reported as high as 20%.[42] MABSC is naturally resistant to most of the oral antimycobacterial agents. The 2007 ATS/IDSA guidelines were not able to specify a firm, evidence-based treatment regimen for MABSC pulmonary infection. Instead they suggested periodic multidrug therapy that includes a macrolide and a parenteral agent (amikacin plus cefoxitin or imipenem) for several months at a time with the aim of symptomatic improvement and slowing down of the disease progression.[24]

Lyu and her colleagues conducted a retrospective outcome analysis on 41 MABSC-infected non-CF patients who were treated with an oral macrolide combined with 2 to 20 months (median, 7.6 months) of parenteral amikacin ± 0.8 to 9.6 months (median, 2.8 months) of cefoxitin or imipenem.[43] The outcomes measured after 1 year of the treatment showed a success rate of 80.5% (success defined as sputum conversion, clinical improvement, and having received at least 6 months of treatment) with a 10% relapse rate. They did not observe a significant difference in the success rate between the groups who received one parenteral agent (amikacin) and two parenteral agents (amikacin plus cefoxitin or imipenem).[43] Although it was a small study, their finding implies that a long-term parenteral amikacin ± cefoxitin or imipenem combined with a macrolide could be highly effective against MABSC, achieving more than just symptomatic relief. However, a major limitation in their study was that no subspeciation was done to distinguish between *M. abscessus* sensu stricto and *M. massiliense.* Also the analysis of *erm(41)* and inducible macrolide resistance was not performed. Among the MABSC subspecies, about two-thirds of *M. abscessus* sensu stricto and all *M. bolletii* isolates have an intact *erm (41)* gene (full length with T at position 28) that results in inducible resistance to macrolides, but it is not observed in *M. massiliense* that has a truncated *erm(41)*.[44,45] The possibility that most of their isolates did not have intact *erm(41)* gene (i.e., belonging to *M. massiliense* or having C at position 28) leading to the better treatment outcome cannot be ignored.

Studies indicate that MABSC pulmonary infection in CF patients is associated with much poorer clinical outcomes than MAC infection. Another observation is that recent studies from Europe and the United States report that the prevalence of MABSC infection is higher than that of MAC infection in CF patients.[8–10,46]

One retrospective study from Scandinavian countries included a limited outcome analysis on 125 CF patients who had more than one positive NTM sputum culture. Compared with MAC, they observed MABSC infection was more frequently found in younger CF patients and was associated with more devastating outcomes: one-fourth of the MABSC-infected patients who had persistently positive sputum cultures in the study had lung transplantation or died.[10] A French study on 50 MABSC-infected and 23 MAC-infected CF patients confirmed the higher prevalence of MABSC infection in younger patients (average age of 17.4 years for MABSC vs. 23.1 years for MAC). By performing a nested case-control analysis, they observed the tendency of MABSC to be associated with patients with more

manifestations of CF (i.e., those with AF508/AF508 genotype, lower FEV_1, use of pancreatic enzymes, and longer hospital stays).[47] Because of the higher risk of MABSC infection leading to catastrophic outcome in CF patients, a single MABSC-positive sputum obtained at a routine follow-up should alert the clinician to obtain subsequent sputum cultures without delay along with close monitoring for changes in HRCT and lung function. If the subsequent cultures are persistently positive (i.e., three or more), the likelihood of developing progressive MABSC pulmonary infection in CF patients has been reported to be quite high.[25] Initiating treatment for MABSC infection should be strongly considered in these patients.[48]

Emerging threats from MABSC:

MABSC pulmonary infection is associated with worse clinical outcomes than MAC infection in both CF and non-CF patients. The most obvious explanation is that antibiotic choices are extremely limited against MABSC because of its natural resistance to most of oral, better-tolerated antimycobacterial agents.

In line with the treatment for MAC infection, macrolides are likely the most effective agents currently available against MABSC. The problem is that resistance to macrolides is much more commonly encountered in MABSC pulmonary infection, mainly due to the natural inducible resistance by the intact *erm(41)* gene found in the two subspecies of MABSC (accounting for more than half of the recovered clinical isolates).[46,49] In addition, the acquired 23S rRNA mutations that confer a high degree of resistance to macrolides[37] are also found in MABSC at similar rates as in MAC clinical isolates (2–4%).[36,50] One study from Korea demonstrated the clinical significance of the inducible macrolide resistance in MABSC infection in non-CF patients. They compared the treatment outcomes between 24 *M. abscessus* sensu stricto and 33 *M. massiliense* infected patients. All of the *M. abscessus* sensu stricto isolates developed in vitro inducible clarithro-mycin resistance by 14 days of incubation and were found to have the full length of *erm(41).* On the contrary, none of the *M. massiliense* isolates developed inducible resistance, as they all had a truncated *erm(41*). The patients received clarithro-mycin-containing multidrug regimen for a minimum of 12 months in addition to the initial 4 weeks of parental amikacin plus cefoxitin or imipenem. The treatment success rate (sputum conversion to negative without relapse during follow-up) was 88% for *M. massiliense,* while it was 25% for *M. abscessus* sensu stricto.[51] Similar results were also observed among CF patients who were treated with clarithromycin-containing regimen.[49]

Several studies have reported that the rough colony morphotype of MABSC could be associated with more severe infection and poor outcomes. The switch from the smooth to the rough morphotype occurs due to a mutation in the genes involved in the synthesis of glycopeptidolipid, a major class of glycolipids located in the outer cell wall of MABSC.[52–55] Kreutzfeldt and his colleagues in their MABSC serial clinical isolates showed there is a clear adaptive trend for the pathogen to switch from the smooth to the rough morphotype in the human lung as the infection becomes more prolonged which correlated with an increase in severity of symptoms in some cases.[56] A recent in vivo study infecting Zebra fish embryos showed that MABSC with the rough morphotype were able to form thick cords in

the extracellular space impairing phagocytosis by host macrophages leading to abscess formation.[55] However, the significance of cording in the human lung infection is entirely unknown.

Besides the pathogen factors mentioned earlier, the mechanism of establishing and maintaining infection in the human host could be quite different between MABSC and MAC, which may explain the worse outcomes observed with MABSC infection. The tendency of MABSC to infect younger and more severe form of CF patients supports this possibility. To answer this question, we will need to understand the interaction among pathogenic NTM, damaged or bronchiectatic respiratory mucosa, and stagnant mucus from the molecular levels. Establishing an animal model where this complex interaction can be induced and observed will be critical.

Additional measures for refractory NTM infections:

For limited cases of NTM pulmonary infections, surgical resection can be considered, especially when the major burden of the infection is localized to a specific lobe/area. A study from University of Colorado at Denver reported favorable out-comes in 110 non-CF patients with localized disease in the right middle lobe or lingula who had thoracoscopic resections combined with the antibiotic treatment. They observed 84% conversion to negative sputum culture postoperatively with relapse rate of 8.7%.[57] It should be noted that preoperative nutritional status and cardiopulmonary function are important factors in determining who can be a surgical candidate.

With such a limited choices of oral drugs available for NTM infection, clofazimine and linezolid have been added to the treatment regimen for refractory MAC or MABSC infection. There have been in vitro susceptibility results showing the possible efficacy of these drugs, often in synergy with other drugs (i.e., clofazimine and amikacin, linezolid and a macro-lide).[58,59] Unfortunately, in vitro susceptibility results for NTM are notoriously inconsistent with actual clinical responses (with the exception of clarithromycin susceptibility). The efficacy and actual clinical benefit of adding clofazimine or linezolid against MAC or MABSC infection remain uncertain until more data on relevant clinical outcomes become available.

A small single-center study from Canada tested the effectiveness of the three-drug regimen including clofazimine (in lieu of rifampin), ethambutol, and a macrolide in 30 non-CF patients infected with MAC. None of the patient isolates were resistant to clarithromycin. Of these, 87% of patients were able to complete the treatment, maintaining negative sputum cultures for at least 6 months while on the therapy with the relapse rate of 19%.[60] These results are comparable to those from the traditional treatment regimen. Although the study did not prove actual added benefit of clofazimine, it suggested that clofazimine could be an alternative to rifampin when the patient is unable to continue rifampin due to its hepatotoxicity or drug interaction issues.

Amikacin remains as an important drug for treatment of MABSC and severe/refractory MAC infections.[24] Parental amikacin, however, is associated with irreversible hearing loss due to ototoxicity, requiring frequent monitoring of its serum levels and audiology exams.

Inhaled amikacin at least in small studies showed that ototoxicity was much less of an issue and showed favorable outcomes.[40,41] A recent multisite clinical trial of liposomal amikacin for inhalation targeting treatment refractory patients with *M. avium* complex or *M. abscessus* has been completed. The inhaled route may prove to be a safer and more effective way of delivering longterm amikacin treatment.

Need for in vitro susceptibility tests that correlate to clinical responses:

Perhaps one of the most frustrating aspects in treating NTM infections is the inconsistency between in vitro susceptibility results and actual clinical responses. We do not understand why this inconsistency occurs with NTM, but not with *M. tuberculosis.*[24] One plausible hypothesis is that the environment where we test the susceptibilities could be quite different from the lung environment where the NTM thrives. Global metabolic shifts that can affect NTM's tolerance to various antibiotics could be occurring more rapidly in NTM than in *M. tuberculosis* once taken outside the human lung and cultured in standard growth media. Developing in vitro testing conditions that closely mimic the patient's lung environment could be a starting point in tackling this issue.

Summary and Suggestions for Future Investigation

Increasing numbers of CF and non-CF bronchiectasis patients are affected by pulmonary NTM infection worldwide. Two NTM species account for up to 95% of the pulmonary NTM infections: MAC and MABSC. NTM infection is up to 75 times more frequent in those with bronchiectasis. Therefore, evaluating and treating exacerbations of bronchiectasis (often not directly related to NTM infection) is an important part of managing NTM infection.

Macrolides are the most effective medications available against MAC and MABSC. Accordingly, the pathogen's susceptibility to macrolides is an important prognostic factor. In both CF and non-CF patients, MABSC infection is associated with worse clinical outcome than MAC infection. A major part of this observation may be attributable to the fact that more than half of MABSC isolates have inherent inducible macro-lide resistance by *erm(41).* On the other hand, MAC does not have an *erm* gene and becomes resistant to macrolides only by acquired mutations, which is encountered in 4% of MAC isolates and mostly preventable by avoiding macrolide monotherapy.

A growing concern among CF patients is that the prevalence of MABSC infection is now higher than that of MAC. MABSC seems to target younger CF patients with a more severe form of CF, becoming a serious threat to this group of population. This finding supports the possibility that MABSC and MAC could have quite different ways of interacting with the host environment.

There are three immediate obstacles that need to be over-come to improve the treatment outcomes of pulmonary NTM infection. One is the inducible resistance by *erm(41)* in MABSC. Faster and more widely available diagnostic methods to detect its presence as well as investigations on ways to suppress its induction in the presence of macrolides are called for. The other obstacle is the high reinfection rate after successful treatment. Further identification of modifiable risk factors for repeated infection and the potential utility of

long-term secondary prophylaxis can be explored. Finally, we urgently need new in vitro susceptibility testing methods that correlate with clinical responses. This is crucial, not only to find more effective, synergistic treatment regimens with existing drugs but also in development of novel drugs for NTM infection.

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