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# Nontuberculous mycobacteria: the changing epidemiology and treatment challenges in cystic fibrosis

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## Abstract

**Purpose of Review.—**Although patients with cystic fibrosis (CF) face numerous infectious pathogens over the course of their lifespan, increasing attention has recently been paid to nontuberculous mycobacteria (NTM). As reported prevalence rates rise across many countries such as the United States, the ability to recognize disease caused by NTM and subsequently treat such disease has become increasingly important. This review summarizes new observations on the epidemiology of NTM in CF as well as key elements to consider during the treatment phase.

**Recent Findings.—**While overall rates of NTM isolation appear to be increasing, particular concern has focused on the emerging predominance of *Mycobacterium abscessus*. New data suggesting that chronic macrolide therapy now part of routine CF care has contributed to this rise, however, have yet to be confirmed prospectively. Transmission of *M. abscessus* between CF patients has also now been described through the use of genome sequencing. While the greater virulence of *M. abscessus* makes it a challenging species to treat, identification of the subspecies type can now determine the presence of inducible macrolide resistance, thereby helping to guide treatment.

**Summary.—**Given increasing prevalence rates, clinicians should maintain a high level of suspicion for NTM as disease-causing organisms in CF, particularly for *M. abscessus*. New knowledge regarding this species, however, can help to tailor appropriate therapy.

### Keywords

cystic fibrosis; *Mycobacterium abscessus*; *Mycobacterium avium* complex; nontuberculous mycobacteria

## Introduction

The impaired ability of cystic fibrosis (CF) patients to clear respiratory secretions often leads to long-term airway damage and permanent bronchiectasis. In large part, these changes are driven by a variety of infectious pathogens, first by *Staphylococcus aureus* and *Haemophilus influenzae* in early childhood followed by *Pseudomonas aeruginosa* in

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adolescence.[1-5] As CF patients age, the microbiology of the lungs changes and bacteria such as *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Burkholderia cepacia* complex are increasingly found in rates of 14.0%, 6.2%, and 2.6% of CF patients, respectively.[5] Recently, the emerging specter of disease caused by nontuberculous mycobacteria (NTM) has provided additional problems for CF patients and providers alike. To begin with, the reported prevalence of NTM appears to have increased since its initial description in CF in 1980[6-8] and it is likely that increasing numbers of CF patients will ultimately be afflicted by NTM as their overall survival improves.[5,9,10] Furthermore, how to interpret and manage NTM-positive cultures in this population is far from clear. For some CF patients, the discovery of NTM is a harbinger of progressive respiratory decline and functional impairment yet for others merely an incidental finding with no particular short-term clinical significance. Separating the former group from the latter, however, is imperative as the decision to treat NTM must be weighed against the significant toxicity burden that anti-mycobacterial therapy can often carry. Indeed, with the current antibiotics available for the treatment of NTM, treatment courses can be lengthy, arduous, and often not curative, particularly for more resilient organisms such as *Mycobacterium abscessus*. In this review, we describe the emergence of NTM as significant pulmonary pathogens for patients with CF, emphasizing the need for clinicians to maintain high vigilance for these organisms as prevalence rates continue to increase. In addition, we describe the particular treatment challenges posed by NTM and offer an algorithm for management.

## The Changing Epidemiology of NTM

After the first report of NTM in CF by Boxerbaum in 1980, initial estimates of the prevalence of NTM in this population were low, around 1.3% in a study by Smith et al in 1984.[7] By the 1990s, reported prevalence rates were notably increasing with 6.6%,[11] 7.0%,[12] 9.3%,[13] 12.5%,[14] and 19.5%[15] of CF patients found to have NTM-positive cultures in various studies. Since then, the percentage of CF patients with positive cultures has been reported to be as high as 32.7%.[8] The largest studies, however, performed in 986, 1,216, and 1,582 CF patients, have demonstrated prevalence rates of 13.0%,[16] 13.7%,[17] and 6.6%,[18] respectively. Since 2010, the CF Foundation Patient Registry has tracked NTM prevalence with estimates of 10.1% in 2010 and 10.8% in 2011.[5] One interpretation of these increasing numbers is that the true prevalence of NTM is rising in the CF population.[19,20] On the other hand, heightened surveillance practices in conjunction with laboratory techniques that have substantially improved the recovery of NTM organisms could potentially confound this hypothesis. Surveillance protocols that now call for multiple rather than single culture specimens and the implementation of “double-processing” of sputum samples to prevent bacterial overgrowth have enhanced our ability to detect NTM in CF patients.[16,21]

Regardless the reason, the rising numbers have forced clinicians to consider the pathogenic potential of NTM. Distinguishing disease from innocuous chronic infection upon the return of positive cultures can be difficult in CF patients, though. The estimation of NTM disease in this population is thus fraught with challenges. If the strict criteria employed by the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) to define NTM disease (consisting of repeated positive sputum cultures, clinical symptoms, and radiographic evidence of bronchiectasis and nodules)[22] are applied to the CF population, the

reported prevalence of disease among patients with positive sputum cultures lies somewhere between 20 and 59%.[8,16,18,23-26] However, these criteria may be non-specific for the detection of NTM disease as radiologic findings may be indistinguishable from baseline CF lung damage. Moreover, competing pathogens such as *P. aeruginosa* or *B. cepacia* can precipitate the same clinical symptoms as NTM, thereby making the identification of a culprit organism particularly challenging. Still, meeting ATS/IDSA criteria in these patients has been associated with other signs of disease progression, such as positive sputum smears and quantitative sputum burden,[23,25] as well as the progression of high-resolution chest computed tomographic (CT) findings such as cysts, cavities, subsegmental parenchymal consolidation, nodules, and tree-in-bud opacities.[27] At this time, standard guidelines for defining disease specifically in NTM-positive CF patients have yet to be implemented in clinical practice.

Determining which CF patients are at highest risk for acquiring NTM has been the subject of a number of case-control analyses. Age appears to be one such risk factor with multiple studies demonstrating that affected individuals are older than unaffected individuals.[14,16,18] In one study by Pierre-Audigier et al, the peak prevalence of NTM in a French pediatric population was in the 15 to 19 year age range (16.0% compared to 5.7% in the 1–4 year age range).[24] Further approximations suggest that NTM patients are on average 4 to 5 years older than culture-negative patients.[16,25] Prolonged exposure to mycobacteria that are commonly found in the environment[28] may account for this age discrepancy.

Beyond age, however, other risk factors thought to be associated with NTM have not consistently demonstrated clear links. Higher lung function as measured by forced expiratory volume in 1 second ($FEV_1$), for instance, has been shown to be either negatively,[16] positively,[25] or inconsequentially[29] associated with the development of NTM in different studies. Co-infection with other organisms has similarly provided few definite associations. While NTM patients may have higher rates of *Aspergillus fumigatus*[17,25,30] and allergic bronchopulmonary aspergillosis[26,31] compared to NTM-negative controls, this is likely the only co-pathogen felt to confer greater risk. Conversely, the presence of *P. aeruginosa* appears to found at both higher[25] and lower[16,17] rates in NTM patients compared to NTM-negative control subjects. No clear association also exists for *S. aureus* and *S. maltophilia*.[16,17,25,32]

The role that antibiotic exposure may play in precipitating NTM disease has recently garnered considerable attention. In particular, the use of chronic macrolides, felt to improve respiratory function[33-35] and widely recommended for patients older than six years,[36] has been put forth as a possible explanation as to why NTM rates have been increasing. In 2011, Renna et al reported a simultaneous rise in the use of chronic azithromycin and colonization and infection rates with NTM, particularly *M. abscessus*.[37] Mouse models in this study further supported this association by demonstrating that azithromycin could impair autophagic and phagosomic degradation, thereby inhibiting the intracellular killing of mycobacteria in macrophages. Such findings have since prompted a number of retrospective analyses designed to quantify the risk of developing NTM after chronic macrolide use. The most recent case-control analyses, however, have not established any association with maintenance azithromycin use in patients with *M. abscessus* disease compared to non-

infected controls,[32,38,39] echoing previous studies also suggesting no greater risk.[29,40] Until further prospective studies are carried out, the link between chronic macrolide use and NTM remains indeterminate.

Because of the particular virulence demonstrated by *M. abscessus*,[41-45] its growing proportion among recovered NTM species has raised concern in recent years. While *Mycobacterium avium* complex (MAC) remains the most common species isolated (found in up to 72% of patients with NTM-positive sputum cultures[8,13,15,16,23,40,46,47]), rates of *M. abscessus* have increased and in certain centers have even surpassed those of MAC.[5,17,18,24] Reported rates of *M. abscessus* in patients with NTM-positive sputum cultures range between 16 and 52%[16,31] Less frequently isolated species include *Mycobacterium kansasii*[13,23,31,46,48] and *Mycobacterium fortuitum*.[7,11,12,14,15,31,40,47] The proportion of each species does vary by geography, however. For instance, *Mycobacterium simiae* and *M. abscessus* are the most common species isolated in Israel,[25] whereas estimates in France suggest that *M. abscessus* species are more commonly isolated compared with MAC.[24,31]. Pertinent characteristics of MAC, *M. abscessus*, and *M. kansasii* can be found in Table 1.

Although NTM is generally not considered to be a transmissible disease,[22,49,50] recent evidence forged through genome sequencing has brought to light the possibility that *M. abscessus* can in fact be spread through CF populations. This was first reported by Aitken et al after an outbreak of *M. abscessus* ss *massiliense* occurred in five CF patients at the University of Washington.[51] All five cases had identical isolates as demonstrated by repetitive unit-sequence-based polymerase chain reaction patterns and pulsed-field gel electrophoresis analyses. Exposure of four of the patients to the index case, who was noted to have a high mycobacterial burden on multiple sputum smears, occurred through overlapping clinic visits. Since that initial report, whole genome sequencing of *M. abscessus* ss *massiliense* has supported between-patient transmission in two outbreaks at a CF center in the United Kingdom.[52] Nearly identical isolates were found in patient clusters, reflecting less genetic variation than seen within single individuals. Moreover, transmission of mutations conferring antibiotic resistance appeared to occur as patients with no known antibiotic exposures exhibited the same resistance patterns as other individuals. Patients affected by the isolates found in the clustered outbreaks were more likely to have been exposed to the CF inpatient wards and outpatient clinics compared to unclustered cases. Whether transmission is a phenomenon solely of this particular subspecies of *M. abscessus* is unknown, but the availability of new sequencing techniques may soon shed light on transmission patterns and dispel the prevailing notion that NTM are not communicable organisms. Infection control measures may ultimately need to be altered based on these new observations.

## Treatment Challenges

The treatment of NTM disease in CF patients can often be a difficult and unsatisfactory endeavor thanks to the natural resilience of the organisms and the less-than-optimal therapeutic options available at the present time. Patients may face toxic effects of the drug regimens employed without any promise of cure.[53] Therefore, the decision to treat should be reserved for those patients with objective evidence of disease progression such as repeatedly

positive sputum cultures, the presence of progressive radiographic signs such as cavities, nodules, and tree-in-bud opacities, and ongoing clinical decline despite the treatment of other common CF pathogens. For more virulent species such as *M. abscessus*, a lower threshold to treat may be appropriate,[17,45] especially if such patients are to be considered for lung transplantation in the future.[44,54,55] Even if *M. abscessus* is ultimately eradicated, chronic suppressive therapy may be warranted.

It should also be remembered that no randomized controlled trials exist for the treatment of NTM in CF, therefore the 2007 ATS/IDSA guidelines for NTM treatment in the general population are often used in lieu of CF-specific guidelines.[56] Standard therapy for NTM based on these guidelines includes the concurrent use of three or more drugs to prevent the development of drug resistance and the continuation of therapy for one year of consistently negative sputum cultures after conversion from culture positivity.[19,22] A joint US/European committee sponsored by the US CF Foundation and the European CF Society has recently drafted guidelines for the diagnosis and management of NTM infections in the setting of CF. These draft guidelines were presented at the 2013 European CF Society conference in Lisbon and excerpts of the treatment recommendations for specific NTM species were incorporated into Table 1. It should be noted that the evidence to support many of these recommendations is scant and they are meant to serve as a consensus starting point with hopes that future clinical studies will be forthcoming to provide future evidence based treatment regimens.

The response of CF patients to antimycobacterial therapy can be variable. While cures have certainly been reported,[15,23,46,47,57-61] so too have treatment failures.[7,26,62,63] Assessment of treatment success should include clinical evaluation, repeated sputum cultures, spirometry, and chest imaging. The failure to improve, however, should prompt clinicians to consider several important factors in CF patients. First, the special physiology of CF patients with their larger volume of distribution, increased renal clearance, and insufficient oral absorption distinguishes them from NTM patients in the general population and often requires higher doses of antibiotics.[64-67] Insufficient dosing could lead to subtherapeutic drug levels, ultimately leading to treatment failure. The use of drug level monitoring, however, could potentially expose such problems and has been routinely applied for aminoglycosides used against *P. aeruginosa*.[68] An analysis of serum drug concentrations in nine CF patients being treated for NTM by Gilljam et al found subtherapeutic levels in seven of the patients, with one patient having clinical improvement once dose adjustments were made.[69]

Secondly, antimicrobial resistance should be taken into account in patients who fail to improve with drug therapy. While there is often poor correlation between in vitro drug susceptibility testing and clinical response for most antimycobacterial drugs, one exception to this is the macrolide class of antibiotics.[22] This is particularly true for certain subspecies of *M. abscessus*. The new classification of *M. abscessus* into three distinct subspecies,[70-72] while taxonomically controversial and likely to change, has brought to light the importance of an inducible erythromycin ribosome methyltransferase (*erm*) gene in distinguishing *M. abscessus* ss *massiliense* from *M. abscessus* ss *abscessus* and *M. abscessus* ss *bolletii*.[73] A deletion in the *erm* gene of *M. abscessus* ss *massiliense* is now known to confer clarithromycin susceptibility in this subspecies compared to the inducible resistance seen in

*M. abscessus* ss *abscessus* and *M. abscessus* ss *bolletii*.[73-75] Clinical observations have supported this distinction in macrolide sensitivity, with a number of studies reporting greater radiologic improvement and smear negativity in patients with the *massiliense* subspecies.[76,77] Macrolide sensitivity testing and the identification of the exact subspecies of *M. abscessus* isolated may therefore provide useful information for tailoring the drug regimen of the patient.

For treatment-refractory cases, consideration can also be given to newer alternative drugs with the caveat that prospective trials in CF patients for these drugs are still lacking. Anecdotal evidence, however, has supported the use of linezolid which has been shown to have *in vitro* activity against NTM.[78-80] Clofazimine, once developed for the treatment of *Mycobacterium leprae*, *Mycobacterium lepromatosis*, and *Mycobacterium tuberculosis*,[81] has also been used to achieve negative sputum cultures.[46] Its use in the United States is currently restricted by the US Food and Drug Administration but may be permitted with an investigational new drug application under an institutional review board approved protocol. Finally, aerosolized amikacin, thought to confer antimycobacterial activity without the same degree of nephrotoxicity, ototoxicity, and vestibular toxicity as intravenous amikacin, has also been shown to eradicate both MAC and *M. abscessus*.[58,59,82] In one case series, six patients with treatment-refractory MAC achieved clinical improvement with aerosolized amikacin, with only one later experiencing a recurrence of disease.[82] Similarly, a patient with *M. abscessus* who had previously failed to maintain a sustained response to standard therapy was able to achieve eradication after starting on aerosolized amikacin. Ten years later, eradication had been sustained with chronic suppressive therapy using alternating monthly clarithromycin and aerosolized amikacin.[59]

Surgical resection of diseased lung, while a relatively successful operation in non-CF patients with refractory focal infections,[83-86] is more rarely performed in CF where infections and airway damage are often more diffuse. However, the results of surgical resections performed for other reasons such as atelectasis and localized bronchiectasis suggest that lobectomies and segmentectomies may in fact be well-tolerated in CF.[87-90] Even pneumonectomies have been reported to have successful outcomes.[89,91] For CF patients with drug refractory infections, surgical resection could be considered a therapeutic option if disease is localized and if preoperative $FEV_1$ exceeds 30% predicted.[92]

## Conclusion

The increasing lifespan of CF patients has prolonged their exposure to NTM that are otherwise ubiquitous in the environment. As a result, with growing numbers of CF patients now being found to harbor NTM, clinicians have been forced to recognize mycobacteria as potentially harmful disease-causing organisms. Thus, the ability to distinguish disease from mere colonization has become imperative. In cases of progressive clinical and radiographic decline, a high degree of suspicion for causative NTM organisms may yield a treatable etiology; therefore, a low threshold for sputum microbiology testing should always be maintained. While treatment of these organisms can be challenging, new knowledge of resistance patterns and alternative drugs may provide additional guidance in choosing the

appropriate drug regimen. For particularly resilient organisms such as *M. abscessus*, which may be affecting increasing numbers of CF patients, such a strategy may be beneficial.

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**Key Points**

1. With rising numbers of CF patients testing positive for nontuberculous mycobacteria, particularly *Mycobacterium abscessus*, clinicians should maintain a high level of suspicion for disease caused by these organisms.
2. The growing proportion of CF patients with *M. abscessus* isolates may be related to the advent of chronic macrolide therapy, but further studies are warranted to clarify the association.
3. Recognition of inducible macrolide resistance conferred by expression of a novel *erm* gene in certain subspecies of *M. abscessus* may help to tailor antibiotic regimens

**Table 1:**

Characteristics of Specific Nontuberculous Mycobacteria Species

| ***Mycobacterium* Species** | **Prevalence Among NTM Positive Sputum Cultures** | **Microbiologic Characteristics** | **General Treatment Options** | **Treatment Duration** |
|---|---|---|---|---|
| *Mycobacterium avium* complex | Up to 72% | -Made up of *M. avium, M. intracellulare, M. chimaera,* and *M. colombiense*<br>-Slow growing organisms<br>-Recommended media broth for culturing: Middlebrook 7H10 and 7H11 agar and BACTEC 12B broth | **1** Clarithromycin 15-30 mg/kg/day by mouth (max 1,000 mg) or Azithromycin 250-500 mg by mouth daily<br>**2** Rifampin 10 mg/kg by mouth daily (max 600 mg)<br>**3** Ethambutol 15 mg/kg by mouth daily<br>**4** For cavitary disease: amikacin 10-15 mg/kg dosed once daily and adjusted to maintain peaks in the 20-30 ug/ml range for initial 2 months | 1 year following culture conversion defined as 3 consecutive negative cultures with the time of conversion set as the date of the 1st of the 3 negative cultures, and no positive cultures during the 12-month period |
| *Mycobacterium abscessus* group | 16-52% | -Rapidly growing organisms<br>-Recommended media broth for culturing: Middlebrook 7H10 or 7H11 agar and BACTEC 12B broth | Intensive phase (3-12 weeks determined by severity of infection, response to treatment, and tolerability of regimen)<br>**1** Azithromycin 250-500 mg by mouth daily<br>**2** Amikacin 10-15 mg/kg dosed once daily and adjusted to maintain peaks in the 20-30 ug/ml range<br>**3** One or more of the following guided but not dictated by in vitro susceptibility testing:<br>**a.** Imipenem 1-2 g intravenous daily in divided doses<br>**b.** Cefoxitin 200 mg/kg daily intravenous in divided doses (max 12 g)<br>**c.** Tigecycline 25-50 mg intravenous daily<br>Continuation phase<br>**1** Azithromycin 250-500 mg by mouth daily<br>**2** Amikacin (dilute in 3 mL normal saline) 250 mg inhaled daily to 500 mg twice daily<br>**3** Two or more of the following guided but not dictated by in vitro susceptibility testing<br>**a.** Clofazimine 100 mg by mouth daily to thrice weekly (requires IRB approved protocol and individual use IND from FDA)<br>**b.** Linezolid 300-600 mg by mouth daily + pyridoxine 50 mg by mouth daily<br>**c.** Moxifloxacin 400 mg by mouth daily<br>**d.** Minocycline 2mg/kg (max dose 100mg) twice daily by mouth | 1 year following culture conversion. Individuals who fail to culture convert and post lung transplant patients may benefit from long-term suppressive antibiotic treatment |

| *Mycobacterium* Species | Prevalence Among NTM Positive Sputum Cultures | Microbiologic Characteristics | General Treatment Options | | Treatment Duration |
|---|---|---|---|---|---|
| *Mycobacterium kansasii* | Up to 5% | -Slow growing organisms<br>-Recommended media broth for culturing: BACTEC 12B broth, Middlebrook 7H10 agar and Lowenstein-Jensen agar | **1**<br>**2**<br>**3** | Isoniazid 5 mg/kg by mouth daily<br>Rifampin 10 mg/kg by mouth daily<br>Ethambutol 15 mg/kg by mouth daily | 1 year following culture conversion |