Nontuberculous Mycobacterial Infections in Cystic Fibrosis

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KEYWORDS

• Cystic fibrosis • Nontuberculous mycobacteria • Atypical mycobacteria
• *Mycobacterium avium* complex • *Mycobacterium abscessus*

KEY POINTS

- Patients with cystic fibrosis (CF) are at a very high risk of acquiring nontuberculous mycobacteria (NTM).
- NTM disease in CF patients is associated with bacterial coinfections, making diagnosis and treatment more challenging.
- *Mycobacterium avium* complex (MAC) and the *M abscessus* complex (MABSC) are the most frequently encountered NTM respiratory pathogens in CF patients.
- Diagnosis of NTM lung disease in CF patients generally follows American Thoracic Society (ATS) guidelines, with an emphasis on evaluating and treating all known comorbidities.
- Initial therapy for NTM respiratory pathogens in CF patients should be directed by published guidelines.
- Optimal management of patients with CF and NTM lung disease requires carefully considered treatment of both conditions.

INTRODUCTION

Over the past 2 decades, NTM have emerged as important pathogens in the setting of CF lung disease.[1] CF affects 1 in 3200 non-Hispanic whites in the United States due to autosomal recessive mutations in the CF transmembrane conductance regulator (CFTR) gene on chromosome 7. The impaired transport of sodium and chloride across epithelial surfaces, which occurs due to severely reduced CFTR function, results in viscous respiratory and gastrointestinal secretions leading to multiorgan disease. The principal cause of morbidity and mortality is obstruction of the small and medium-sized airways with dehydrated mucous plugs, resulting in bronchiectasis, chronic airway infections, and progression toward respiratory failure. Although historically considered a fatal disease of childhood, improvements in therapy have resulted in a steady increase in expected lifespan, with a current projected median survival of 37 years.[2] Replacement of pancreatic enzymes and supplementation with fat-soluble vitamins can compensate for malabsorption that arises from reduced exocrine pancreatic function.[3] A variety of airway clearance techniques combined with hydrating agents, mucolytics, and bronchodilators can assist mucociliary function and reduce bronchial obstruction.[4,5] Inhaled antibiotics targeting *Pseudomonas aeruginosa* have proved effective in both eradicating initial infection[6]

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and in managing chronic infection.[5] More recently, the discovery of compounds that directly modulate the synthesis and/or function of CFTR protein have become available to a subgroup of CF patients based on their specific CFTR mutation.[7] As a result, the CF population is the oldest and healthiest in history.[2] But as the disease phenotype has changed in response to improved treatment, it seems that susceptibility to NTM has increased.[8–12]

Epidemiology

The ATS has identified the CF population as having both an especially high risk for NTM and posing unique challenges with regard to diagnosis and treatment.[13] Although the incidence of NTM disease in the general population of industrialized countries is approximately 1 in 100,000,[14] there is a 10,000-fold greater prevalence of these organisms in respiratory cultures from patients with CF. The reported prevalence of positive NTM cultures and/or NTM infection within various CF patient cohorts or at single centers varies dramatically,[15,16] but in the largest studies the overall the prevalence is 6% to 13%.[9,10,12,17–20] There is widespread agreement that the prevalence of NTM infection is increasing within the CF population,[1,8–12,21] as has been reported within the general population.[22,23] It is uncertain, however, to what extent improved culture techniques, increased physician awareness, and more frequent diagnosis of nonclassic forms of CF in adulthood may contribute to the apparent increase in NTM prevalence observed in this population.[24]

An overwhelming majority of NTM species recovered in CF samples in the United States are from either the MAC or the MABSC.[20] MAC has historically been the most common NTM isolated,[25–28] and in the largest US survey it was present in up to 72% of patients with NTM-positive sputum cultures.[9] The percentage of MABSC reported in CF patients with NTM-positive sputum cultures has ranged between 16% and 68%,[9,12,17,29] and it seems that the proportion of MABSC is increasing,[10,11,30] with some centers reporting a greater frequency than MAC. In part, this effect may be due to geographic factors, because MABSC seems especially prevalent in Europe,[1,12,17,29,30] and *M simiae* and MABSC are the most common species isolated in Israel.[31] Differences in relative prevalence of MAC and MABSC may also relate to the age of the cohorts studied, because MAC is more often associated with older CF patients and often diagnosed in adulthood, whereas MABSC is frequently seen in younger patients and those with more severe lung disease.[12,32] Less frequently isolated species include *M kansasii*[16,17,26,28] and *M fortuitum*.[8,17,27,33–35]

Risk Factors for Nontuberculous Mycobacteria in Cystic Fibrosis

Understanding of risk factors for NTM in CF patients is incomplete, because most reports have studied small cohorts from single centers or specific geographic areas, often leading to contradictory conclusions. The most worrisome trend from the largest population studies is that increased prevalence of NTM[9,11,18,27,30,31] and NTM disease[31,33] is strongly linked to older age and milder lung disease.[9] A high prevalence has been recorded in patients with an adult diagnosis,[25,36] which is typically associated with the nonclassic form of CF resulting from less severe mutations.[25,37] CFTR-related genotypes associated with partial CFTR function, such as D1152H, R75Q, and the 5T allele, have been specifically correlated with an increased frequency of NTM-positive cultures,[38,39] and in non-CF population, the presence of a single Q1352H allele has been linked to an increased prevalence of NTM disease.[40] The presence of *Aspergillus fumigatus*[11,31,41–43] has also been associated with increased risk for NTM, as has allergic bronchopulmonary aspergillosis (ABPA).[44,45] Coinfection with *P aeruginosa* has been associated with decreased prevalence of NTM.[9,28] Other studies, however, have reported the opposite conclusions, in particular that NTM is common in severe lung disease[18,31,33,46] and associated with higher rates of *P aeurginosa* coinfection.[31] These divergent findings may relate in part to differences in study methodology, because many reports have not distinguished between a positive NTM culture and the presence of NTM disease, and often culture data from MAC and MABSC are combined within both adult and pediatric populations.

Although increased survival may indirectly result in greater NTM prevalence through longer cumulative exposure,[47] a greater concern is the possibility that various medications and CF treatment strategies have contributed directly to the apparent increase in NTM prevalence. Although these reports are for the most part retrospective and their conclusions are not entirely consistent, they have served to heighten awareness of the potential for unforeseen consequences of many therapies in common use. In particular, administration of systemic steroids, often in the context of ABPA treatment, has been associated with increased prevalence of NTM[31,42,44,45] as well as high dose ibuprofen.[31] Other studies, however, have failed to see an increased in NTM-positive cultures with steroid use[18,31,48] or even an association with decreased NTM.[49] Azithromycin, an antibiotic with diverse anti-inflammatory properties, has also been associated