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Original Article

Epidemiology of nontuberculous mycobacteria among patients with cystic fibrosis in Scandinavia

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Abstract

Background: Nontuberculous mycobacteria (NTM) are an emerging threat to cystic fibrosis (CF) patients but their epidemiology is not well described.
Methods: In this retrospective observational study we identified all Scandinavian CF patients with a positive NTM culture from airway secretions from 2000 to the end of 2012 and used national CF databases to describe microbiological and clinical characteristics.
Results: During the 13-year period 157 (11%) CF patients were culture positive for NTM at least once. *Mycobacterium abscessus* complex (MABSC) (45%) and *Mycobacterium avium* complex (MAC) (32%) were the predominant species with geographical differences in distribution. Younger patients were more prone to MABSC ($p < 0.01$). Despite treatment, less than one-third of MABSC patients with repeated positive cultures cleared their infection and a quarter had a lung transplant or died.
Conclusion: NTM are significant CF pathogens and are becoming more prevalent in Scandinavia. MABSC and MAC appear to target distinct patient groups. Having multiple positive cultures despite treatment conveys a poor outcome.

Keywords: *Mycobacterium abscessus*; *Mycobacterium avium*; Prevalence; Susceptibility

1. Introduction

The clinical significance of a nontuberculous mycobacteria (NTM) positive culture from airway secretions of cystic fibrosis (CF) patients remains uncertain [1]. For some, a positive NTM

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culture coincides with clinical deterioration, while for others, culture positivity seems to be transient and of no clinical importance [1]. If little is known about the significance of a positive culture [2], even less is known about patient susceptibility and risk factors for acquisition [3]. Understanding the risks associated with infection is particularly important due to the well-described adverse effects of current NTM treatment regimens [4,5]. In light of the recent attention NTM is receiving as a threat to CF patients [6], we examined the situation in Scandinavia. The objective of this retrospective multicenter study was to describe the scope and importance of NTM in the complete Scandinavian CF population. We thus report, for the first time, the prevalence of NTM among all CF patients in Scandinavia; geographical differences in species distribution; explore risk factors for acquisition; and describe outcomes including development of end-stage-lung-disease (ESLD).

2. Methods

2.1. Setting

Scandinavia consists of Denmark, Norway and Sweden and has a total population of 20.2 million people [7], with an estimated CF incidence of 1 in 4900 live births [8,9] and generally a high proportion of patients who are homozygous for the F508del mutation in the CF transmembrane conductance regulator (CFTR) gene (87%, 71%, 67% for Denmark, Norway, Sweden) [10]. All CF patients receive treatment at one of eight CF centers, where patients are seen on an outpatient basis on average eight times annually. Patients with less than 8 scheduled annual visits (Norway, Sweden), were seen additionally at local hospitals as part of shared care agreements, implemented to reduce long distance travel. With the exception of Denmark, patients were screened for NTM annually either by expectorated sputum, laryngeal suction or bronchoalveolar lavage (BAL), starting at age 6 to 10 years of age with some variability in screening policies over time and between centers. In Denmark, systematic annual screening was introduced in 2011; prior to this, patients were only cultured for NTM upon clinical suspicion. During visits, anthropometric data and forced expiratory volume in 1 s (FEV1) were recorded. Pulmonary function tests were performed according to international recommendations [11], measuring FEV1, expressed as a percentage of predicted values for sex and height, using reference equations from Wang or Hankinson [12,13].

2.2. NTM isolation

Depending on CF center, sputum and BAL samples were pretreated with SDS-NaOH, a cocktail of antibiotics (amphotericin B, carbenicillin, polymyxin B-sulfate and trimethoprim-lactate), or 5% oxalic acid. Samples were then cultured for mycobacteria on either Löwenstein–Jensen egg medium, Bactec 460™ culture system, MGIT™ (Mycobacteria Growth Indicator Tube) 960 system or *Burkholderia cepacia* selective agar [14]. In most centers, more than one method of decontamination and culture was used reflecting ongoing advances in methodology. Positive cultures were identified to species-level by 16-23S spacer array technique, sequencing of the *rpoB* gene, hybridization and/or growth ability on Löwenstein–Jensen slants with 5% NaCl. In some centers, the GenoType Mycobacterium CM and AS tests [15] and DNA sequencing of the *hsp65* gene [16] were used.

2.3. Prevalence study

In the first part of the study we aimed to describe the prevalence as well as geographical and species distribution of NTM in Scandinavia. CF registries and microbiological databases in Denmark, Norway and Sweden were queried for any patient with CF, who had at least one positive NTM airway culture from January 2000 to December 2012. The American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA)'s microbiological criteria were used to classify patients [17], dividing NTM patients into those with only a single positive sputum culture, and those with >1 positive sputum culture or at least one positive BAL.

2.4. Comparison with background Scandinavian CF population

In the second part of the study we aimed to describe the clinical characteristics of patients at time of first NTM positive culture. For comparison purposes, similar data from a recent clinical study of the Scandinavian CF population were captured [10], including sex, age, and CFTR mutation data. Prior Gram-negative infection, pancreatic insufficiency (PI), azithromycin and steroid maintenance treatment as well as CF-related diabetes mellitus (CFRD) diagnosed using previously published criteria [18], were all also included at time of first positive NTM culture for cases, and in the calendar year 2002 for the background population. We stratified the analysis according to NTM species to examine whether different NTM species were more common in CF patients with particular clinical characteristics.

2.5. Outcome study

The third part of the study aimed to describe the clinical impact of NTM disease. We therefore examined number of positive cultures, NTM treatment (yes, no), duration of infection, development of end stage lung disease (ESLD) and clearance of NTM, stratified by age group (<20 years vs. ≥ 20 years of age), gender, NTM species and ATS/IDSA criteria. ESLD was defined as lung transplantation or death, whichever came first. To distinguish patients where NTM involvement was judged to have played a role in the development of ESLD, data was further subdivided depending on clinical certainty of NTM involvement in death or lung transplantation. Time of NTM clearance was defined as the first calendar year without culture positivity, if the patient was off treatment.