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Original Article

Outcomes associated with antibiotic regimens for treatment of *Mycobacterium abscessus* in cystic fibrosis patients

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Abstract

Background: Mycobacterium abscessus infection is associated with declining lung function in cystic fibrosis (CF), but there is little evidence on clinical efficacy to guide treatment.
Methods: Retrospective review of 37 CF patients treated for *M. abscessus* respiratory infection at a single center from 2006 to 2014. Outcomes included change in FEV_1 at 30, 60, 90, 180, and 365 days after treatment and clearance of *M. abscessus* from sputum cultures.
Results: Lung function was significantly improved after 30 and 60 days of treatment, but not at later time points. Gains were inversely related to starting lung function. Antibiotic choices did not influence outcomes except for greater clearance with clarithromycin.
Conclusions: Treatment of *M. abscessus* resulted in short term improvement in lung function that is inversely related to pre-treatment FEV_1.

Keywords: Mycobacterium abscessus; Nontuberculous mycobacterium; Cystic fibrosis

1. Background

1.1. Nontuberculous mycobacteria (NTM)

Nontuberculous mycobacteria (NTM)[1] have been increasingly isolated from the lungs of patients with cystic fibrosis (CF) [1,2]. NTM are ubiquitous in the environment, but infection appears more common in coastal geographic areas that have a higher air vapor pressure [3]. Diagnosis of NTM lung infection requires clinical pulmonary symptoms, positive cultures from at least two separate expectorated sputum samples or one bronchial wash/lavage sample, and exclusion of other possible diagnoses [4].

NTM can be divided into rapidly growing and slower growing groups. The rapidly growing mycobacteria belonging to the *M. abscessus* complex (hereafter referred to simply as *M. abscessus*) appear to be more virulent than more slowly growing mycobacteria [5], and CF patients with *M. abscessus* respiratory infection have significantly worse decline in FEV_1 over time compared to those who do not have NTM [6]. Recommended treatment regimens for *M. abscessus* are complex, including a 3 to 12 week intensive phase with multiple agents including amikacin, cefoxitin, imipenem, and a macrolide (clarithromycin or azithromycin), followed by a consolidation phase of oral and inhaled medications. A recommendation has been made for azithromycin as the macrolide of choice in both phases [7].

Despite the clinical significance of *M. abscessus* respiratory infection in CF, there is relatively little evidence on treatment efficacy. Recently published guidelines on NTM respiratory

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[1] Abbreviations: NTM, Nontuberculous mycobacteria; AFB, Acid fast bacilli; Cefox, Cefoxitin; Imipen, Imipenem; Clarith, Clarithromycin; Azith, Azithromycin; Trad, Traditional.

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infection in CF [7] had to base treatment recommendations largely on small case studies [8] or studies that include a large number of non-CF patients and/or non-respiratory infections [9–13]. In fact, a 2014 Cochrane Review was unable to offer any recommendations due to the lack of randomized controlled studies comparing treatment regimens or comparing treatment to no treatment in patients with CF [14].

A substantial fraction of CF patients in our center have NTM respiratory infection, with rates of M. abscessus infection between 6 and 8% [6,15,16]. Because we have treated *M. abscessus* respiratory infection in a relatively large number of CF patients, we reasoned that a retrospective review could reveal treatment outcomes specific to this respiratory infection in CF. Due to the complexity of treatment regimens in this retrospective dataset, we elected to focus on relatively short term outcomes in the intensive phase of treatment.

2. Methods

2.1. Study design

This study was a single-center, retrospective, longitudinal cohort analysis that included pediatric patients with CF who had at least one positive culture for *M. abscessus* and were treated for this bacteria between 2006 and 2014. Patients were excluded if they received only oral antibiotics for initial treatment of *M. abscessus* or if they received a lung transplantation during or before treatment for *M. abscessus*. This study was approved by the Office of Human Research Ethics at the University of North Carolina at Chapel Hill (IRB 14-3272).

2.2. Data collection

Data were obtained through chart review from patient medical records as well as from the PortCF database, including patient age at time of treatment, anti-mycobacterial drugs received, medication route of administration, start and stop dates of drug therapy, and all FEV_1 measurements during the year prior to *M. abscessus* treatment and for one year following the start of treatment. % predicted FEV_1 values were recorded for the intervals 8–30 days, 31–60 days, 61–90 days, 91–180 days, and 181–365 days. If more than one lung function value was available within an interval, the latest one was chosen. If no lung function value was available in an interval, we extrapolated the missing value as the average of the values from the intervals before and after the missing value, which occurred for 8, 5, 11, 2, and 0 subjects respectively. On average, imputed % predicted FEV_1 values were 1.2 + 1.1% different from surrounding intervals. Patients missing values from two or more consecutive intervals or with fewer than three post-treatment lung function values were excluded from analysis. Pre-treatment FEV1 was defined as the most recent value obtained before day 3 of treatment. Changes in FEV_1 over the year before and after treatment were calculated using linear regression of all values available within those intervals. Mycobacterial culture data, including cultures specific for acid fast bacilli (AFB cultures), and presence of *M. abscessus*, were collected from a database maintained by the microbiology laboratory.

2.3. Definitions

Clearance of *M. abscessus* from sputum cultures was defined as having at least three AFB sputum cultures negative for *M. abscessus* during or subsequent to treatment with no subsequent positive cultures within 12 months.

2.4. Statistical analysis

Descriptive statistics were used to describe the demographics of the study population, the drugs used for treatment of *M. abscessus*, and the percentage of patients who achieved sputum culture clearance. The data passed a test of normality and a linear mixed effects model with Kenward-Roger approximation was used to compare pre-treatment and post-treatment FEV_1 at various time points. Changes in FEV_1 post treatment were not normally distributed, so non-parametric statistics were utilized for analyses (Spearman correlation, Mann–Whitney).

3. Results

3.1. Patients and treatment

41 patients met the initial inclusion criteria for this study, with three patients excluded due to lung transplant and one patient due to use of oral therapy only during the intensive phase, resulting in 37 patients for data analysis (Table 1). For patients with more than one intensive phase treatment in the study period, only the first course of therapy targeted against *M. abscessus* was included. However, three patients were treated prior to study period. All but three patients met ATS microbiological criteria for disease [4], and two of the three who did not meet microbiological criteria had evidence of NTM disease on CT scan.

The most commonly used drug for treatment of *M. abscessus* during the intensive phase was amikacin, though it was used as intravenous in 25/37 (68%) and inhaled amikacin in 4/37 (11%) (Fig. 1). Of the beta-lactams, cefoxitin was utilized most frequently in 28/37 (76%). The macrolide clarithromycin was used in 21/37 (57%) of courses, with azithromycin in 13/37 (35%). Newer antibiotics used less frequently included tigecycline in 12/37 (32%) and oral linezolid in 6/37 (16%). The majority of patients received three or more drugs, and a "traditional" regimen including a beta-lactam, macrolide, and amikacin was used in 22/37 (59%). Macrolide sensitivity was determined in 32/37 isolated, of which 24 were sensitive and 8 had evidence of resistance. Resistant isolates were encountered more frequently in the later years of the

Table 1
Baseline characteristics of the study population.

Characteristics	Mean ± S.D.
Age (years)	14.5 ± 4.2
Days of intravenous antibiotics	36.4 ± 18.6
Pre-treatment FEV_1 (% predicted)	80.8 ± 24.9%
Change in % predicted FEV_1 over the year prior to treatment	−2.3 ± 17.0%