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%

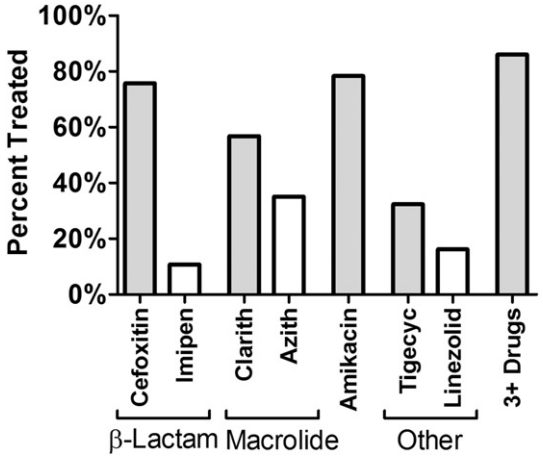

Fig. 1. Treatment antibiotics. Percent of patients treated with various antibiotics. Imipen = Imipenem; Clarith = Clarithromycin; Azith = Azithromycin; Tigecy = Tigecycline.

study, with 6/10 patients who started treatment in 2013 or later having resistant isolates, compared to only 2/22 treated prior to 2013.

30 patients received continuation therapy after the intensive phase using a macrolide plus up to 3 other antibiotics. The median duration of treatment for the continuation phase was 15.5 weeks, with a range of 3 weeks to 3 years.

3.2. Lung function

Of the 33 patients who could perform spirometry, 25 had at least three post treatment lung function values within the year following treatment initiation to allow longitudinal analysis. The pre-treatment FEV_1 was obtained −7.2 ± 12.4 days prior to treatment start, and the average times of FEV_1 measurement for the 30, 60, 90, 180, and 365 day intervals were 22.9 ± 4.1, 46.3 ± 8.4, 82.3 ± 13.1, 147.1 ± 19.4, 319 ± 43.7 days respectively. We observed statistically significant improvement at 30 and 60 days post treatment (Fig. 2A), although lung function measured at later time points (90, 180, or 365 days) was not significantly improved from baseline values. There was no overall trend towards improvement over the year post treatment, though values were not significantly worse either. Changes in lung function were inversely related to pre-treatment FEV_1 (Fig. 2B). Using all lung function data from the year before and the year after treatment, we also examined whether change in lung function over time was altered after initiating treatment. We did not detect any significant change (−5.3% ± 13.1% per year pre-treatment vs. -3.0% ± 12.9% per year post-treatment, p = 0.45), though this analysis was limited by the large variability in the dataset.

3.3. Bacterial clearance

Of the 26 patients who had at least 3 acid fast bacillus cultures following initiation of treatment, 10 patients achieved bacterial clearance defined as at least three negative cultures with no subsequent positives. Patients who cleared did not differ from those who did not in age, pre-treatment FEV_1, treatment duration, or number of antibiotics used. No patients with macrolide resistant *M. abscessus* isolates cleared infection (n = 8), though this did not differ significantly from sensitive strains (p = 0.10). Of note, 3 of 8 (37.5%) patients with excellent pre-treatment lung function (% predicted FEV_1 > 100%) cleared *M. abscessus*, which did not differ from the 6 of 17 (35.3%) rate of clearance of those with lower lung function.

3.4. Influence of antibiotic choices

We explored the influence of antibiotic choices through examination of changes in lung function or bacterial clearance with different antibiotic regimens, with a focus on antibiotics utilized within a traditional regimen of amikacin, a beta-lactam (imipenem or cefoxitin), and a macrolide (clarithromycin or azithromycin). Comparing antibiotics within classes (or amikacin to no amikacin), we did not observe differences in lung function changes with any treatment regimen except for a trend towards more improvement with a traditional regimen (Fig. 3A). For bacterial clearance, patients treated with clarithromycin had higher rates of clearance than those treated with azithromycin (Fig. 3B), though there were no changes for any other antibiotic

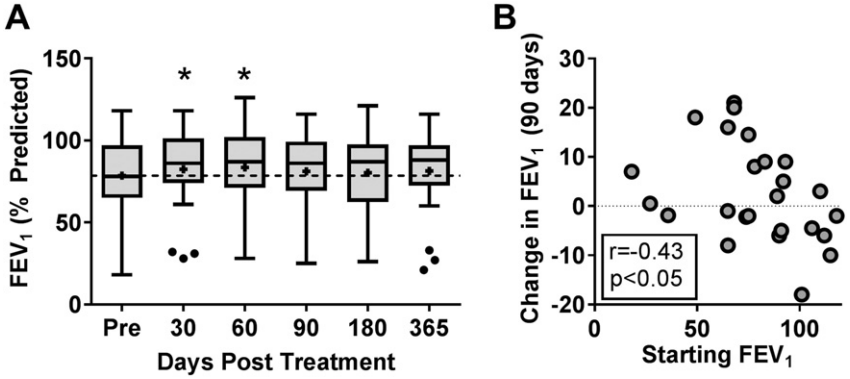

Fig. 2. Lung function changes after treatment of *M. abscessus*. A) Percent predicted FEV_1 was significantly elevated 30 and 60 days after starting treatment ($p < 0.05$ by repeated measure ANOVA, Dunnett's multiple comparisons test), but not at later time points. B) Change in % predicted FEV_1 at 90 days was inversely related to starting % predicted FEV_1.

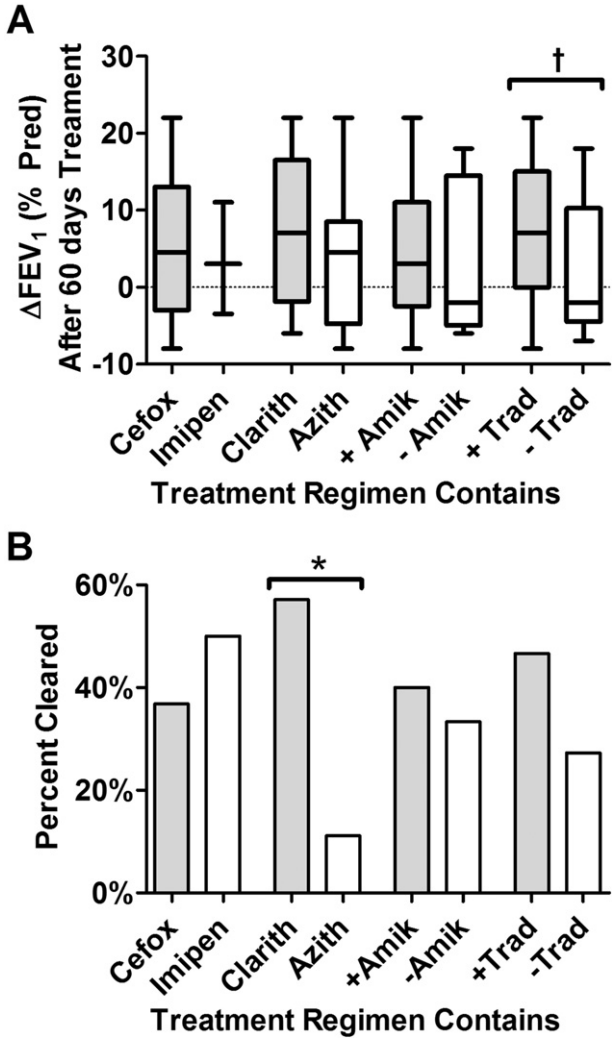

Fig. 3. Antibiotic related changes. The impact of various antibiotic choices on differences in percent predicted FEV_1 (pretreatment vs. 60 days of treatment) (A) or bacterial clearance (B) were examined, focusing on the beta-lactams, macrolides, and amikacin that traditionally recommended for treatment of *M. abscessus* pulmonary infection in CF. A) No differences in changes in % predicted FEV_1 were noted for the different beta-lactams or macrolides, or in regimens that included amikacin vs. those that did not. There was a trend towards more improvement in % predicted FEV_1 in regimens that included all of the elements of a traditional regiment (beta-lactam, macrolide, amikacin) vs. those that did not ($p = 0.08$). B). Patients treated with regimens that included clarithromycin cleared *M. abscessus* more often that those treated with regiments that included azithromycin ($p < 0.05$). No differences in clearance were observed for any other comparisons. Cefox = Cefoxitin; Imipen = Imipenem; Clarith = Clarithromycin; Azith = Azithromycin; Trad = Traditional.

comparisons. We did not observe any significant differences in FEV_1 or the change in FEV_1 before or after treatment in those who cleared relative to those who did not clear infection.

4. Discussion

4.1. In CF patients treated for M. abscessus respiratory infection

In CF patients treated for *M. abscessus* respiratory infection, we observed a significant short term improvement in lung function after the intensive phase of treatment. Although average improvement was modest and within the range of normal variation, many subjects did have more substantial improvement, though this was more common in those with lower pre-treatment FEV_1. These findings are generally consistent with previous studies that have shown improvement in other outcome measures including symptom scores, radiographic measures, and sputum clearance after treatment [9–13], although this study represents one of the first evaluations using lung function as an objective measure. Although we did not see any significant improvement in FEV_1 in the group as a whole after a year, we also did not observe any significant decline, suggesting the possibility that treatment prevented further worsening of lung disease. However, this cannot be validated without a control group of patients with *M. abscessus* disease who do not receive treatment, which would not be ethically appropriate.

These findings suggest that treatment of *M. abscessus* may not improve lung function in patients who have infection despite good lung function at baseline. However, we recognize that FEV_1 is only one measure of efficacy, and our study was not designed to determine whether patients may have received other clinical benefit, such as improvement in symptoms. Furthermore, treatment may prevent declines in FEV_1 even in patients with good lung function, which would be difficult to demonstrate in our study. Prospective studies are needed to better capture other measures of the clinical efficacy of NTM treatment in CF.

The low rate of sustained sputum conversion seen in this study is consistent with previous studies [10,11,13] and suggests that clearance of *M. abscessus* from cultures is often not an achievable goal. Patients who cleared *M. abscessus* from sputum cultures did not differ in age, lung function, or intensity of treatment regimen, suggesting that other factors influence bacterial clearance. In light of evidence that CF patients with chronic NTM infection have worse outcomes than those with more transient infection [6,17,18] there may be benefits to clearing *M. abscessus* from sputum cultures that were not measured in this study.

The high degree of variability in drugs used makes it difficult to draw meaningful conclusions about the superiority of certain drug regimens compared to others. Those treated with clarithromycin appeared to clear infection more often, though this could reflect several factors. For example, macrolide resistance was more common in later years of the study, which coincides with greater use of azithromycin. The relative efficacy of clarithromycin vs. azithromycin will be important to investigate in future studies, as the most recent guidelines favor azithromycin over clarithromycin for treatment of *M. abscessus* [7] and there is conflicting data on the rates of inducible resistance evoked by clarithromycin compared to azithromycin [19,20].

Although this study is limited by being retrospective and including patients from only a single center, it is the first attempt to correlate treatment of *M. abscessus* with lung function outcomes in patients with CF. We recognize that there are many other important factors that we did not account for, such as the antibiotics utilized in the continuation phase of treatment as well as other respiratory pathogens. Larger scale studies that utilize protocol-driven approaches to diagnosis and treatment such as the PREDICT and PATIENCE trials [21] are needed to be able to

effectively measure treatment-related clinical outcomes while controlling for these confounding factors [22].

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