Original Article

Outcomes of Pulmonary *Mycobacterium abscessus* Infection

William G. Flight[1], Natasha E. Hough[1], Stephen J. Chapman[1,2]

[1]Oxford Adult Cystic Fibrosis Centre, Oxford University Hospitals NHS Foundation Trust, [2]University of Oxford, Oxford, UK

Abstract

Background: Treatment of *Mycobacterium abscessus* pulmonary disease (PD) is challenging with frequent side effects and uncertain rates of success. **Methods:** We performed a retrospective review of all patients at our center with at least one respiratory sample positive for *M. abscessus* between 2014 and 2019. Electronic health records were reviewed to determine factors associated with *M. abscessus* infection and clinical outcomes. **Results:** Thirty-seven patients were identified including 24 with cystic fibrosis (CF), 10 with bronchiectasis, two with chronic obstructive PD (COPD), and one with asthma. American Thoracic Society/Infectious Diseases Society of America criteria for nontuberculous mycobacteria PD were met in 21/37 (56.8%) of cases. Evidence of *Aspergillus* lung disease was noted in 18 (75.0%) CF patients compared with 3 (23.1%) non-CF patients ($P = 0.005$). Induction therapy for *M. abscessus* was given to 22/37 (59.5%) patients (18/24 [75%] with CF and 4/13 [30.8%] without CF). Median duration of induction therapy was 6 weeks (range 3–12). Maintenance antibiotic therapy was prescribed to 17/22 (77.3%) of treated patients. Culture conversion was seen in 15/24 (62.5%) of CF patients compared with 3/13 (23.1%) in the non-CF group ($P = 0.034$). Culture conversion occurred in 10/22 (45.5%) of treated patients compared with 8/15 (53.3%) untreated patients. Three patients (8.1%) died during follow-up: one with CF and two with COPD. **Conclusions:** Culture conversion following isolation of *M. abscessus* from respiratory samples not only is more common in CF than in patients without CF but also frequently occurs spontaneously in both groups. Targeted treatment for *M. abscessus* did not clearly impact rates of culture conversion.

Keywords: Bronchiectasis, cystic fibrosis, *Mycobacterium abscessus*, nontuberculous *Mycobacterium*

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Introduction

Numerous studies have reported that the prevalence of pulmonary infection with nontuberculous mycobacteria (NTM) has been increasing over recent decades[1,2] and is associated with significant risk of mortality.[3] *Mycobacterium abscessus* complex is a group of rapidly-growing species of NTM with extensive, intrinsic resistance to antimicrobial therapy. *M. abscessus* accounts for up to 16% of cases in epidemiological studies of NTM-pulmonary disease (NTM-PD)[4] although the prevalence varies according to the geographical location and the particular characteristics of the cohorts studied. *M. abscessus* accounts for a much greater proportion of cases of pulmonary NTM infection among people with cystic fibrosis (CF), for example, with 39% of cases reported in the US CF Foundation Patient Registry found to be due to *M. abscessus*.[5]

Treatment of *M. abscessus* PD is extremely challenging with high rates of treatment failure and relapse.[6-8] Although national and international guidelines have been published on the diagnosis and management of NTM-PD,[9-11] there have been no randomized controlled trials to date of therapy for *M. abscessus* infection. As a result, the recommendations contained in the current guidelines are based on single-center case series and expert opinion. Treatment of *M. abscessus* typically involves an induction phase which includes a combination of intravenous antibiotics followed by a prolonged maintenance phase of multiple oral and nebulized antibiotics. Such treatment regimens are associated with considerable side effects and risk serious complications, such as ototoxicity and renal impairment.[10] A further significant challenge is that it is difficult to identify accurately whether a given patient isolating *M. abscessus* has active NTM-PD requiring therapy or alternatively has simple colonization which does not require treatment.[12]

Address for correspondence: Dr. William G. Flight, Oxford Universoty Hospitals NHS Foundation Trust, Oxford, OX3 9DU, England.
E-mail: william.flight@ouh.nhs.uk

ORCID:
https://orcid.org/0000-0003-3343-4211

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We reviewed cases of pulmonary infection with *M. abscessus* among patients attending our center to identify factors associated with successful culture conversion and clearance of *M. abscessus*. Some data from this study have previously been presented in the abstract form at a scientific conference.[13]

Methods

We performed a retrospective cohort study to determine outcomes following *M. abscessus* pulmonary infection. Patients attending our center were included if they provided at least one respiratory sample which was culture positive for *M. abscessus* between January 2014 and July 2019. Demographic, clinical, and microbiological data were obtained from patients' electronic health records.

Culture conversion was defined according to the British Thoracic Society NTM Guidelines (i.e., three consecutive negative mycobacterial sputum cultures collected over a minimum of 3 months, with the time of conversion being the date of the first of the three negative mycobacterial cultures).[10] Clearance of *M. abscessus* was defined as ≥6 negative sputum samples over a period of ≥12 months off treatment, or ≥1 negative bronchoalveolar lavage (BAL) sample after at least 12 months off treatment.

The study was registered with the Clinical Governance Department at our institution. Formal research ethics committee approval was not sought as the project was deemed primarily to be a service evaluation to inform future patient care.

Data are presented as mean (standard deviation) or median (range) as appropriate. Categorical variables were compared using Fisher's exact test while continuous variables were analyzed using the Mann–Whitney U-test. Statistical analysis was conducted using GraphPad Prism v. 8 (GraphPad Software, San Diego, USA).

Results

Thirty-seven patients were identified. All patients had a history of underlying lung disease with 24 (64.9%) having CF, 10 (27.0%) bronchiectasis, 2 (5.4%) chronic obstructive PD (COPD), and 1 (2.7%) asthma. Within the CF group, one patient first isolated *M. abscessus* following lung transplantation. Baseline demographics of the cohort separated into patients with and without CF are shown in Table 1.

American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria for NTM-PD were met in 21/37 (56.8%) of cases. Twenty-nine patients (78.4%) had a thoracic computed tomography scan at baseline, and a summary of the reported radiological features in the cohort is shown in Table 2. Six patients (16.2%) had a single isolate of *M. abscessus* only. Initial isolates were smear-positive in 21/37 cases (56.8%) including 13/24 (54.2%) CF patients and 8/13 (61.5%) in the non-CF group. Thirty patients (81.1%) had positive sputum samples only, 3 (8.1%) had both positive sputum and BAL samples, while 4 (10.8%) had positive BAL samples only. Coinfection with other NTM species was common with 13/37 (35.1%) of patients isolating ≥1 NTM other than *M. abscessus* during the study period *(Mycobacterium avium* complex, *n* = 10; *Mycobacterium fortuitum*, *n* = 2; *Mycobacterium gordonae*, *n* = 2; and *Mycobacterium triplex*, *n* = 1). A history of isolating NTM other than *M. abscessus* was more common in patients with CF, affecting 11/24 (45.8%) compared with 2/13 (15.4%) in the non-CF cohort.

Table 1: Baseline demographics

	CF	Non-CF	*P*
Number of patients	24	13	-
Age at first isolate of *Mycobacterium abscessus*, median (range)	21 (13-56)	70 (56-89)	-
Female: male	9:15	8:5	0.19
Smear positive at baseline, *n* (%)	13 (54.2)	8 (61.5)	0.74
History of other NTM isolates, *n* (%)	11 (45.8)	2 (15.4)	0.08
ATS/IDSA NTM-PD criteria met, *n* (%)	15 (62.5)	6 (46.2)	0.49
History of *Aspergillus* lung disease, *n* (%)	18 (75.0)	3 (23.1)	0.005

CF: Cystic fibrosis, NTM: Nontuberculous *Mycobacterium*, ATS: American Thoracic Society, IDSA: Infectious Diseases Society of America, PD: Pulmonary disease

Table 2: Radiological features on baseline thoracic computed tomography scans

	CF	Non-CF	Overall
Number of patients with scan	15	13	28
Pulmonary nodules	6 (40.0)	9 (69.2)	15 (53.6)
Tree-in-bud nodularity	12 (80.0)	10 (76.9)	22 (78.6)
Bronchiectasis	15 (100.0)	9 (69.2)	24 (85.7)
Consolidation	6 (40.0)	7 (53.9)	13 (46.4)
Cavitation	2 (13.3)	4 (30.8)	6 (21.4)
Emphysema	0 (0.0)	5 (38.5)	5 (17.9)

CF: Cystic fibrosis

In vitro antimicrobial susceptibility testing of initial isolates revealed that amikacin had the lowest rates of resistance of the agents tested with 58.6% sensitive, 27.6% intermediately sensitive, and 13.8% resistant. Equivalent values for clarithromycin were 20.0%, 10.0%, and 70.0%. Sensitivity rates for the full panel of antibiotics tested are shown in Figure 1.

Twenty-two patients (59.5%) received treatment for *M. abscessus* infection including 18 patients with CF and four patients with other diagnoses. Of the treated patients overall, 19/22 (86.4%) met the ATS/IDSA criteria for NTM-PD. Treated patients received initial induction therapy with a median of two (range 2–3) intravenous antibiotics for a median duration of 6 weeks (range 3–12). Details of induction intravenous antibiotic therapy are given in Table 3. An oral macrolide was included alongside intravenous antibiotics in 14/22 cases (azithromycin in 10 and clarithromycin in 4 patients). Maintenance therapy was prescribed in

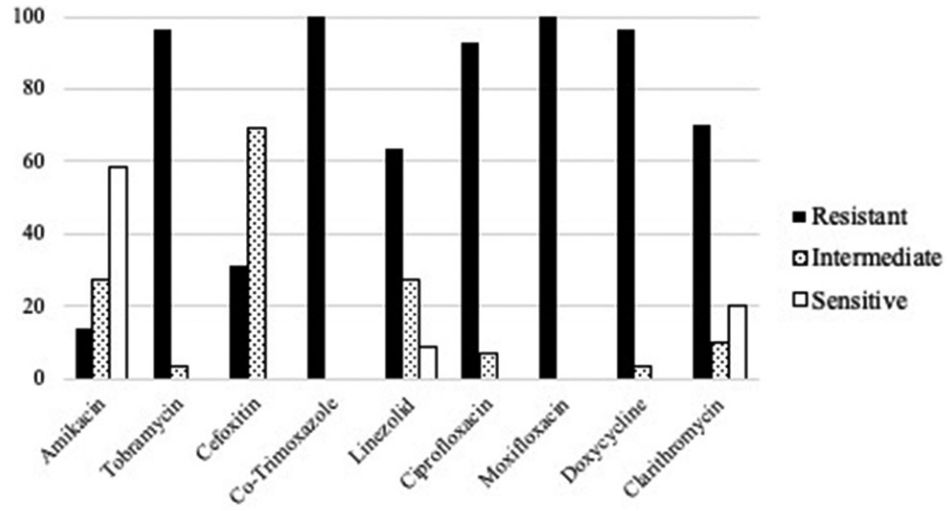

Figure 1: *In vitro* antimicrobial sensitivity test results for initial isolates of *Mycobacterium abscessus*

Table 3: Frequency of use of various antibiotic agents in initial induction therapy regimens

Antibiotic	*n* (%)
Amikacin	19 (95)
Cefoxitin	14 (70)
Imipenem	7 (35)
Tigecycline	5 (25)
Meropenem	2 (10)
Azithromycin	10 (50)
Clarithromycin	4 (20)

17/22 (77.3%) of the patients who received induction treatment. Nebulized amikacin as part of maintenance therapy was poorly tolerated and was continued in only 8/22 (36.4%) patients.

Overall, 18/37 (48.6%) of the patients achieved culture conversion with a median of 15 (range 4–54) negative respiratory samples. Culture conversion was seen in 15/24 (62.5%) CF patients compared with 3/13 (23.1%) in the non-CF group (P = 0.034). Confirmed clearance of *M. abscessus* was seen in 9/24 (37.5%) in the CF group and 3/13 (23.1%) of non-CF patients (P = 0.48). Culture conversion and confirmed clearance were seen in 10/22 (45.5%) and 6/22 (27.3%) of the patients who received treatment for *M. abscessus* compared with 8/15 (53.3%) and 6/15 (40%) among untreated patients. There was no significant difference in time from first *M. abscessus* isolate to initiation of treatment among those with culture conversion compared with those patients failing to convert (median of 88.5 days [range 14–946] versus 69 days [49–979], respectively; P = 0.60).

During the follow-up period, three (8.1%) patients died at a median of 29 months (range 11–41) following first isolation of *M. abscessus*. Of the patients that died, one had CF and two had COPD.

Discussion

M. abscessus infection continues to pose a considerable challenge in the management of CF, bronchiectasis, and other chronic lung diseases. Our data add to the currently very limited literature and further highlight the difficulty in making informed treatment decisions when faced with new *M. abscessus* infection. We have identified significant differences in the demographics and outcomes between patients with CF and *M. abscessus* infection compared to those with bronchiectasis or obstructive airway disease. As with a number of other case series, we found that spontaneous clearance of *M. abscessus* was common which raises important questions as to when combination therapy is needed.[14,15]

In our cohort, patients with CF were significantly more likely to have coexisting *Aspergillus* lung disease than patients without CF. A link between NTM infection and *Aspergillus* lung disease including allergic bronchopulmonary aspergillosis (ABPA) has been noted in previous studies although the pathophysiology of this connection is poorly understood.[16-19] Whether the risk of *Aspergillus*-NTM coinfection is truly increased in CF compared to non-CF bronchiectasis, a group also at risk of ABPA, requires further investigation. Similarly, the tendency we have observed for patients with CF and *M. abscessus* infection to have cultured other species of NTM is not currently explained. This finding suggests that there is a particular phenotype of CF that predisposes to mycobacterial infection. Potential factors contributing to this may include non-CFTR modifier genes, environmental exposures, and maintenance therapies for CF. Additional work in larger cohorts is required to unravel these associations.

A further important finding from our study is the high rates of spontaneous culture conversion and subsequent clearance of *M. abscessus* infection. There was no significant difference in the proportion of patients clearing *M. abscessus* or reaching culture conversion among those receiving antibiotic treatment

compared with the untreated patients. This mirrors findings from other cohorts of *M. abscessus* infection, for instance, the work of Tippett *et al*. which found that over two-thirds of cases cleared *M. abscessus* spontaneously.[14] Jhun *et al*. also found that the initiation of antimicrobial therapy in NTM-PD had no significant impact on prognosis.[3] A novel finding in our study is that culture conversion was significantly more likely among patients with CF than in the non-CF group. It is also of interest that of the four non-CF patients in our cohort who received treatment, none reached culture conversion despite aggressive therapy. One possible explanation for this observation is a degree of selection bias with only those patients with more severe disease or rapid progression offered active treatment and therefore having a lower chance of clearance of *M. abscessus*.

Although the international guidelines have been published on the management of NTM-PD,[9-11] there have been no randomized controlled trials of initial antibiotic treatment for *M. abscessus* infection. Recommendations from the CF Foundation and European CF Society for the treatment of *M. abscessus* in CF are largely drawn from single-center case series in Asia and the United States in non-CF cohorts.[6-8] It is unclear how applicable these studies truly are to the CF population specifically and more generally to people with *M. abscessus* infection in a UK or European setting. The use of population-based registries, already well developed in the field of CF and more recently introduced in non-CF bronchiectasis,[20] represents a promising means of enriching the quality of the NTM-PD literature with regard to outcomes.

In addition to considering the likelihood of successful treatment, the current NTM-PD guidelines recommend that the decision on whether and when to initiate treatment should take into account of a variety of additional factors.[10] Important considerations include patient-specific factors such as severity and rate of disease progression as well as the presence of any significant comorbidities. Additional factors of importance include the radiological appearances as well as microbiological factors, such as the frequency of positive cultures and smear positivity. An additional important consideration, especially in the context CF, is the likelihood of future lung transplantation. Although recent guidelines are at pains to state that a history of NTM-PD should not preclude assessment for lung transplantation,[9,10] a considerable number of studies have reported adverse outcomes following transplantation in patients with preexisting *M. abscessus* infection.[21-24] As a result, our practice has been to adopt a lower threshold for starting *M. abscessus* treatment in people with CF in whom lung transplantation is likely to be an option in future in the hope of early eradication of the infection. This is likely to explain why not all patients receiving targeted treatment for *M. abscessus* in our cohort fully met the ATS-IDSA criteria for NTM-PD. Whether such a strategy is justified given the high rate of spontaneous clearance of *M. abscessus* we have observed remains unclear, particularly as two recent small case series from the USA have reported equivalent posttransplant outcomes in patients with *M. abscessus* infection to those without.[25,26]

Our study is subject to all the usual limitations of retrospective analyses. Although it is larger than many case series of *M. abscessus* infection, our cohort remains small and is drawn from a single center which may limit its applicability to other settings. In addition, the study covered a period in which our clinical service was in transition from paper-based medical notes to an electronic health record. As a result, the data available electronically were incomplete, particularly with regard to lung function and height, so it was not possible to include reliable data on forced expiratory volume in 1 s percentage-predicted or body mass index. Despite these limitations, our study adds important data to a field with a paucity of clinical information to guide treatment decisions.

Conclusion

We have shown that in patients with *M. abscessus* infection, there are important differences between patients with and without CF. We have shown that spontaneous culture conversion is common and that targeted antibiotic treatment of *M. abscessus* at our center was not clearly associated with improved outcomes. There is a pressing need for future large-scale randomized controlled trials and registry studies to determine the true efficacy and costs of *M. abscessus* therapy.

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Conflicts of interest

There are no conflicts of interest.

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