Original Article

Mycobacterium abscessus Complex: Natural History and Treatment Outcomes at a Tertiary Adult Cystic Fibrosis Center

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Abstract

Background: *Mycobacterium abscessus* complex (MAbsC) is a significant management dilemma when taking care of patients with cystic fibrosis (CF). **Methods:** We undertook a retrospective cohort analysis of all CF patients in whom MAbsC was isolated from 2005 to 2014. The natural history of MAbsC was determined and clinical factors examined in an attempt to predict transient compared to persistent colonization. **Results:** No correlation was found between recurrent MAbsC isolation and clinical factors such as body mass index, respiratory function, or age. Over two-thirds of our cohort cleared MAbsC colonization with no intervention and no consistent effect on lung function was identified. Four CF patients were initiated on treatment with only one successful outcome. **Conclusion:** This analysis demonstrates there are no clear predictors of those CF patients who will become persistently colonized with MAbsC and that a significant proportion will spontaneously clear carriage. As treatment success rate is poor, more work is urgently required in improving patient outcomes.

Keywords: Atypical mycobacterium, cystic fibrosis, *Mycobacterium abscessus*, nontuberculous mycobacterium

Introduction

Mycobacterium abscessus complex (MAbsC), an acid-fast, rapidly-growing atypical mycobacterium, is an opportunistic respiratory pathogen which presents significant management challenges in patients with cystic fibrosis (CF). The impact of pulmonary colonization may range from asymptomatic carriage to progressive, fulminant lung disease.[1] Treatment commits a patient to a multi-antibiotic regimen, including parenteral agents, over months to years and puts the patient at risk of significant, potentially life-threatening side effects with low chance of successful clearance.[2,3] In the CF population, determining whether MAbsC is contributing to lung disease is clouded by the presence of multiple pulmonary microbes and significant underlying CF-related bronchiectatic lung disease making radiological assessment difficult and the decision to treat imprecise. Previous isolation of MAbsC is a relative contraindication to lung transplantation which has major implications for CF patients with declining lung function.

As MAbsC infection is a relatively uncommon condition, it is not surprising that little is known about the pathogenesis, natural history of infection and optimal treatment regimens. *In vitro* antibiotic sensitivities do not correlate well with *in vivo* responses,[1,4] except potentially clarithromycin resistance at 14 days,[5] and clinical practice guidelines have generally been inferred from more common atypical mycobacteria such as *Mycobacterium avium* complex. Furthermore, the population most at risk of infection with MAbsC, the CF population, has rarely been examined in isolation. The most recent and specific guidelines for atypical mycobacteria in CF, published by the European Cystic Fibrosis Society and the US Cystic Fibrosis Foundation, acknowledges that evidence regarding management and treatment of MAbsC is severely lacking.[3] Several recent reports have suggested interpersonal and nosocomial transmission of MAbsC[6-9] as well as high-level resistance to hospital-grade biocides,[10] which has significant implications for infection control policies regarding patients with MAbsC.

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This study was conducted at a tertiary hospital with one of the largest cohorts of adult CF patients under its care. We reviewed all CF patients with MAbsC-positive cultures isolated between 2005 and 2014. The questions asked were; what is the natural history of MAbsC colonization in patients with CF; are there differences in patient attributes that may contribute with spontaneous clearance of colonization; and finally, what were the treatment outcomes and complications of those in whom MAbsC treatment has been undertaken?

Methods

Cases were identified for this retrospective cohort study by searching the microbiology database for all positive acid–fast bacilli isolates between 2005 and 2014. Recommended practice at the Alfred Hospital for management of CF patients is to routinely test sputum samples from patients with chronic pulmonary disease on a yearly basis for mycobacterial microscopy and culture in keeping with the 2016 consensus recommendations.[3] The medical history of each patient with a positive isolate was examined for further detail.

Patients were categorized based on the number of positive samples as follows: (a) single isolate followed by multiple negative tests (arbitrarily assigned 1 day of being culture positive), (b) multiple isolates with spontaneous clearance, and (c) persistent colonization, in an attempt to identify factors that may predispose to clearance versus persistence. Patients were deemed to have cleared MAbsC colonization if there were at least two negative sputum samples over a 6-month period. If the patient did not have repeat testing following the initial positive sample, they were excluded from analysis (n = 6). Information regarding patient demographics, pulmonary function, CF disease comorbidities, concurrent prophylactic antibiotic use, and other microbial isolates was collated. Finally, the clinical outcomes for patients in whom the decision to treat was made were reviewed in greater detail.

Differences between the groups were tested using GraphPad Prism 6.0 (Graft Pad Software, La Jolla, California, USA). using the nonparametric one-way ANOVA (Kruskal–Wallis) for numerical data and Fischer's exact Chi-squared test for categorical values. Statistical significance was considered $P < 0.05$. This study was conducted under Ethics Approval (project number 591/13). Informed consent was obtained due to the retrospective nature of this study.

Results

Demographics

From January 2005 to December 2014, MAbsC was isolated from specimens from 45 individual patients [Table 1], the majority of whom had underlying lung disease such as CF (n = 26), chronic obstructive pulmonary disease (n = 6), or idiopathic bronchiectasis (n = 4). As MAbsC is of particular concern to those patients with CF, this cohort is the focus of further analysis.

The major characteristics of those patients with CF, in whom MAbsC was isolated were collated [Table 2]. The median age of CF patients with MAbsC was 33.5 years (range 21–66) with a heavy male predominance of 19 of the 26 patients. The median forced expiratory volume in 1 s (FEV_1) at time of the first isolate was 73% of normal (range 20%–100%). Subtyping was not available for the majority of isolates and was reported simply as MAbsC. Of the 12 isolates further subtyped, four were *Mycobacterium massiliense* and eight *M. abscessus* ssp. *abscessus*. Isolation of other nontuberculous mycobacterium was common. One death was reported in this CF cohort over the period studied.

Risk factors of persistent *Mycobacterium abscessus* complex colonization

Patients were then classified into those in whom MAbsC was isolated only once, those in whom it was isolated multiple times and then subsequently spontaneously cleared, and in those with persistent colonization or progressing to treatment to assess for any factors that may protect against persistent colonization or contribute to spontaneous clearance. The factors examined

Table 1: Demographics of all patients from whom *Mycobacterium abscessus* complex has been isolated between January 2006 and December 2014

	n	Age median (range)	Male, *n* (%)	Multiple isolates, *n* (%)	FEV_1% median (range)
All	45	36 (19-77)	33 (73)	25 (55)	73 (20-108)
Cystic fibrosis	26	28 (18-48)	19 (73)	14 (53)	73 (20-100)
COPD	6	62 (57-78)	3 (50)	4 (66)	66 (49-75)
Other lung dx	9	60 (32-70)	5 (83)	3 (33)	
Asthma	1	39	1 (100)	0	95
Interstitial lung disease	2	54 (49-70)	2 (66)	2 (66)	65 (40-90)
Bronchiectasis	4	53 (32-64)	3 (75)	2 (50)	79 (61-97)
Tuberculosis	1	34	1 (100)	1 (100)	-
Immunosuppressed	2	60 (43-77)	2 (100)	1 (50)	
CVID	1	80	1 (100)	1 (100)	88
AML	1	44	1 (100)	0	108
Nil	2	28 (25-32)	1 (50)	2 (100)	-

COPD: Chronic obstructive pulmonary disease, CVID: Common variable immunodeficiency, AML: Acute myeloid leukemia, Nil: No significant past medical history, FEV_1: Forced expiratory volume in 1 s

Table 2: Specific characteristics of individuals with cystic fibrosis in whom *Mycobacterium abscessus* complex was isolated

Patient number	Genotype	Age	Sex	Duration of testing (years)	Positive samples/total samples	Weeks negative (negative tests)	Subspecies	Other NTB isolate	FEV_1 (%)
Single MAbsC isolates									
7	ΔF508/c. (1585-1G>A)	34	Female	7.4	1/13	434 (12)	Complex	-	89
8	ΔF508/ΔF508	34	Male	6.3	1/5	415 (4)	Complex	-	73
15	ΔF508/ R1162X	26	Male	6.7	1/20	317 (18)	Complex	MAC	82
29	ΔF508/ΔF508	43	Male	6.7	1/13	163 (6)	Abscessus	-	36
35	ΔF508/ΔF508	44	Female	4.9	1/22	126 (14)	Massiliense	-	73
38	ΔF508/G551D	25	Male	1.8	1/5	151 (3)	Complex		92
41	ΔF508/ΔF508	21	Male	1.0	1/7	118 (5)	Massiliense	MAC	40
44	ΔF508/R117H	48	Female	11.2	1/16	42 (5)	Complex	MAC	96
Multiple MAbsC isolates - spontaneous clearance									
1	ΔF508/ G1061R	32	Female	8.4	4/27	517 (22)	Complex	-	49
2	ΔF508/ΔF508	37	Male	8.9	2/19	560 (16)	Complex	-	73
3	ΔF508/ΔF508	49	Female	5.0	3/11	140 (7)	Complex	Gordonae	31
5	ΔF508/UK	36	Male	8.1	3/26	352 (22)	Massiliense	-	100
20	ΔF508/UK	33	Male	9.0	3/25	211 (5)	Complex	MAC, Gordonae	89
37	ΔF508/ΔF508	23	Male	3.7	2/21	114 (19)	Abscessus	Interjectum	47
Multiple MAbsC isolates - persistent colonization or treatment									
11	ΔF508/R117H	47	Female	4.0	19/30	0	Complex	-	41
14	ΔF508/G551D	44	Male	4.7	42/53	0	Massiliense	-	73
18	Unknown	23	Male	4.4	2/27	212 (21)	Complex	-	20
26	Unknown	22	Male	3.9	4/9	0	Abscessus	-	93
27	ΔF508/ΔF508	27	Male	6.1	10/26	0	Abscessus	Szulgai	90
28	ΔF508/ΔF508	39	Male	5.6	10/23	0	Abscessus	MAC	27
32	Unknown	36	Male	9.8	16/75	0	Abscessus	-	58
Excluded due to insufficient sampling									
10	Unknown	26	Male	0.0	1/1	N/A	Complex	-	-
19	ΔF508/ΔF508	28	Male	0.2	1/2	N/A	Complex	-	58
25	G551D/UK	30	Male	5.9	1/5	N/A	Complex	-	85
33	ΔF508/c. 489 + 1G>T	22	Female	1.3	1/2	N/A	Abscessus	-	92
36	G551D/UK	66	Male	1.0	1/4	N/A	Abscessus	-	74

Information collated includes age, gender, duration of which the patients have been tested for acid–fast bacilli, the proportion of samples that were MAbsC positive, *M. abscessus* subtype (if available), other nontuberculous isolates and FEV_1 at time of first isolation. NTB: Nontuberculous mycobacterium, FEV1: Forced expiratory volume in 1 s, MAC: *Mycobacterium avium* complex, MAbsC: *Mycobacterium abscessus* complex, *M. abscessus: Mycobacterium abscessus*, N/A: Not available

included the duration from first positive specimen to the last, lung function at the time of first MAbsC isolation and nutritional status (body mass index) [Table 3]. CF-related issues were also examined such as the presence of insulin-dependent diabetes mellitus, pancreatic insufficiency, the use of inhaled and systemic steroids, and the use of prophylactic antibiotics oral azithromycin or inhaled tobramycin [Table 3]. Finally, other microbial isolates were also assessed [Table 4].

On average, MAbsC was isolated for approximately 1 year before becoming culture negative in those patients who spontaneously cleared MAbsC [Figure 1]. Those in whom only a single specimen was positive for MAbsC had better lung function than those who had prolonged MAbsC isolation ($P < 0.01$) [Table 3]. However, the group with the lowest FEV_1 was able to clear MAbsC. There was no difference in nutritional status, the proportion of patients with insulin-dependent diabetes mellitus or pancreatic insufficiency. Inhaled steroids did not appear to be a risk factor for prolonged isolation of MAbsC. Similarly, the use of prophylactic antibiotics did not appear to be protective [Table 3]. Examination of other microbial isolates found in CF patients with MAbsC demonstrated similar rates of *Pseudomonas* spp., *Staphylococcus aureus*, and *Aspergillus* spp. [Table 4].

Table 3: Characteristics of cystic fibrosis patients stratified by those with a single isolate, multiple isolates followed by spontaneous clearance, and those with persistent *Mycobacterium abscessus* complex colonization

Patient number	Gender	Age	Cystic fibrosis genotype	Duration MAbsC positive (days)	FEV_1 (%)	BMI	IDDM	Pancreatic enzymes	Inhaled steroids	Systemic steroids	Azithromycin	Inhaled tobramycin
Single MAbsC isolates												
7	Female	34	ΔF508/c. (1585-1G>A)	1	89	23.0	No	Yes	Sporadic	No	No	Yes
8	Male	34	ΔF508/ΔF508	1	73	22.8	Yes	Yes	No	No	No	No
15	Male	26	ΔF508/R1162X	1	82	22	No	Yes	No	No	Yes	No
29	Male	43	ΔF508/ΔF508	1	36	16.9	Yes	Yes	No	Yes	Yes	Yes
35	Female	44	ΔF508/ΔF508	1	73	20.7	Yes	Yes	Yes	No	Yes	Yes
36	Male	66	G551D/UK	1	74	27.2	No	Yes	Yes	No	No	No
44	Female	48	ΔF508/R117H	1	96	25.1	No	Yes	No	No	No	Yes
Median	3/7	43.0		1	74.0	22.8	3/7	7	3/7	1/7	3/7	4/7
Multiple MAbsC isolates - spontaneous clearance												
1	Female	32	ΔF508/G1061R	467	49	19.0	No	Yes	Yes	No	No	Yes
2	Male	37	ΔF508/ΔF508	91	73	27.4	No	Yes	No	No	No	Yes
3	Female	49	ΔF508/ΔF508	846	31	21.0	Yes	Yes	No	No	No	No
5	Male	36	ΔF508/UK	1005	100	24.4	Yes	Yes	No	No	No	Yes
20	Male	33	ΔF508/UK	287	20	23	No	No	No	No	No	No
37	Male	23	ΔF508/ΔF508	219	47	18.4	No	Yes	Yes	No	No	Yes
Median	2/7	34.5		377	48.0	22.0	2/6	5/6	2/6	0/6	0/6	4/6
Multiple MAbsC isolates - persistent colonization or treatment												
11	Female	47	ΔF508/R117H	557	41	22.6	No	No	No	Sporadic	No	Yes
14	Male	44	ΔF508/G551D	1701	73	28.9	No	Yes	No	No	No	Yes
18	Male	23	UK	2	20	16.6	Yes	Yes	No	No	No	No
26	Male	22	UK	827	93	23.6	No	No	No	No	Yes	No
27	Male	27	ΔF508/ΔF508	459	90	22.2	Yes	No	No	No	Yes	No
28	Male	39	ΔF508/ΔF508	686	27	20.1	No	Yes	Yes	No	Yes	Yes
32	Male	36	UK	523	58	20.8	Yes	Yes	No	Yes	Yes	No
Median	1/7	36.0		557	58.0	22.2	3/7	4/7	1/7	2/7	4/7	3/7
P	0.5	0.97			<0.01	0.97	0.34	0.16	0.38	0.37	0.07	0.68

FEV_1: Forced expiratory volume in 1 s, BMI: Body mass index, IDDM: Insulin-dependent diabetes mellitus, UK: Unknown, MAbsC: *Mycobacterium abscessus* complex

Mycobacterium abscessus complex colonization versus disease

We also examined the effect of MAbsC colonization on FEV_1 preceding and following MAbsC isolation [Figure 2]. While being nonquantitative, there appeared no clear impact of MAbsC colonization on FEV_1 for any of the groups, and in fact, those with persistent colonisations often had stable FEV_1 during the period of being culture positive compared to the time before becoming culture positive.

Mycobacterium abscessus complex treatment outcomes

We further examined the treatment outcomes in those patients with CF in whom the decision to treat was made [Table 5]. Of the 26 patients with CF in whom MAbsC was isolated, the decision to treat was made in four, with three (patients 11, 14, and 32) being treated on two or more separate occasions. Indications for treatment included in preparation for lung transplant and posttransplant surgical site infection. The treatment backbone invariably included amikacin plus a macrolide and tigecycline or a second- or third-generation cephalosporin.

Treatment outcomes were poor with significant side effects including fulminant hepatitis, thought to be due to tigecycline in setting of CF cirrhosis, and permanent severe senineurol hearing loss. The only patient who was successfully treated (patient 18) had only recently become colonized with MAbsC and treatment was supplemented with surgical resection and lung transplantation. It is interesting to note the positive outcome in this patient given MAbsC colonization is a relative contraindication to lung transplant. Patient 14 underwent treatment with novel CFTR potentiator (ivacaftor) did not clear MAbsC carriage despite a significant improvement in pulmonary function tests. The final patient, patient 32, was not known to be colonized with MAbsC before lung transplant. Following lung transplant, he was found to have multiple surgical site infections, including within the pulmonary vein anastomosis. He is currently

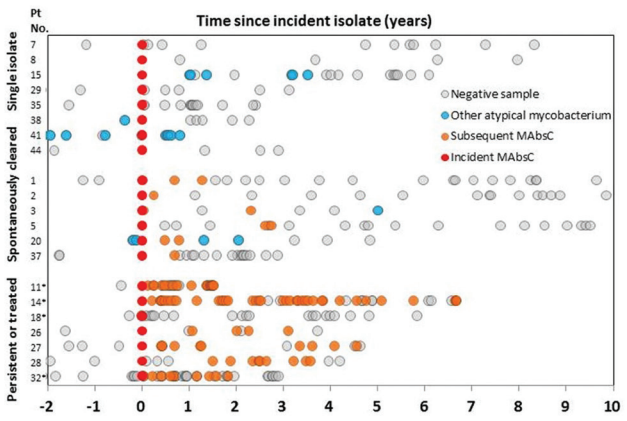

Figure 1: Acid–fast bacilli testing within cohort. Cystic fibrosis patients were classified into three groups: top; single *Mycobacterium abscessus* complex specimen, middle; multiple *Mycobacterium abscessus* complex isolates then spontaneous clearance, and bottom; persistent *Mycobacterium abscessus* complex isolation. All acid–fast bacilli testing is plotted against time (years) relative to the initial *Mycobacterium abscessus* complex positive culture (solid red dots). Subsequent *Mycobacterium abscessus* complex isolates are represented with orange dots and other Mycobacterium isolates with solid blue dots. Open dots represent negative acid–fast bacilli culture. *Patients who underwent treatment

undergoing treatment which has been supplemented with surgical resection of infected tissues.

Discussion

In this retrospective cohort study conducted at a large tertiary hospital with an adult CF unit, we examined all patients in whom MAbsC had been isolated over a 10-year period from between 2005 and 2014. As expected, MAbsC was predominantly found to be an opportunistic respiratory pathogen in patients with underlying pulmonary or immunological disease with patients with CF comprising the largest proportion. Our major findings in patients with CF include a relatively high rate of spontaneous clearance following prolonged isolation, no major clinical features determining those patients at risk of persistent colonization and no evidence of the contribution of MAbsC to significant progression of lung disease.

Within our cohort, a high proportion cleared MAbsC with no intervention; approximately one-third cultured MAbsC on only one occasion, one-third was positive for MAbsC for on average of 1 year before spontaneous clearance, and one-third was persistently colonized. The questionable significance of a single MAbsC isolated has been previously reported,[11] however,

Table 4: Other microbial isolates detected in sputum of cystic fibrosis patients in whom *Mycobacterium abscessus* complex has been isolated

Patient number	Microbe				
Single MAbsC isolates					
7	*Pseudomonas*	-	*Aspergillus*		
8	*Pseudomonas*	*S. aureus*	-	-	-
15	*Pseudomonas*	-	*Aspergillus*	-	*M. avium*
29	*Pseudomonas*	*S. aureus*	-	-	-
35	*Pseudomonas*	-	-	-	-
36	-	*S. aureus*	-	*Stenotrophomonas*	-
44	*Pseudomonas*	-	-	*Stenotrophomonas*	*M. avium*
Number Positive/Total	6/7	3/7	2/7	2/7	2/7
Multiple MAbsC isolates - spontaneous clearance					
1	*Pseudomonas*	-	-	-	-
2	*Pseudomonas*	*S. aureus*	*Aspergillus*	-	-
3	*Pseudomonas*	-	*Aspergillus*	-	*M. gordonae*
5	*Pseudomonas*	*S. aureus*	-	-	-
20	-	*S. aureus*	-	-	*M. avium, M. gorgonae*
37	*Pseudomonas*	-	-	*Stenotrophomonas*	*M. interjectum*
Number Positive/Total	5/6	3/6	2/6	1/6	2/6
Multiple MAbsC isolates - persistent colonization or treatment					
11	*Pseudomonas*	*S. aureus*	*Aspergillus*	-	-
14	*Pseudomonas*	-	*Aspergillus*	*Scedosporium*	-
18	*Pseudomonas*	-	-	-	-
26	*Pseudomonas*	*S. aureus*	*Aspergillus*	-	-
27	*Pseudomonas*	-	-	*Burkholderia*	*M. szulgai*
28	*Pseudomonas*	-	*Aspergillus*	-	*M. avium*
32	*Pseudomonas*	-	*Aspergillus*	-	-
Number Positive/Total	7/7	2/7	5/7	2/7	1/7

M. avium: Mycobacterium avium, M. gordonae: Mycobacterium gordonae, M. interjectum: Mycobacterium interjectum, M. szulgai: Mycobacterium szulgai, MAbsC: *Mycobacterium abscessus* complex, *S. aureus*: *Staphylococcus aureus*

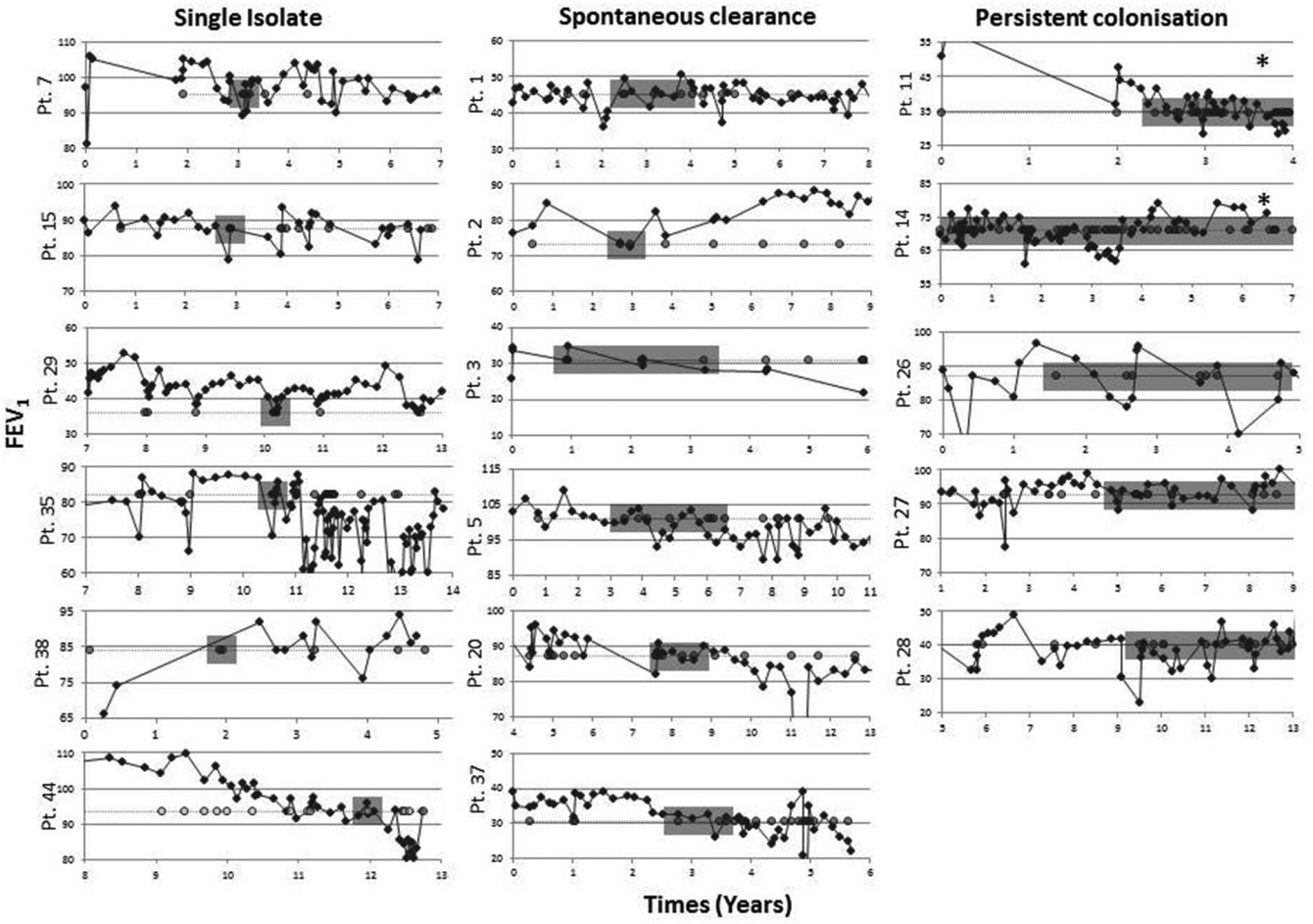

Figure 2: The effect of *Mycobacterium abscessus* colonization on pulmonary function. The effect of *Mycobacterium abscessus* colonization on pulmonary function was assessed by comparing the forced expiratory volume in 1 s (FEV_1) of every respiratory function test (solid line) over time (years, note variable axis) during the period for which the patient was tested for *Mycobacterium abscessus* complex. The period during which the patient was positive for *Mycobacterium abscessus* complex is represented as transparent gray bars. Duration of *Mycobacterium abscessus* complex testing is represented by dashed line with gray circles representing each acid–fast bacilli test. Patients who underwent lung transplant or did not undergo a sufficient duration of pulmonary function tests are not presented here. *Patients who underwent treatment

to the best of our knowledge, this is the first description of a substantial proportion of CF patients spontaneously clearing MAbsC following prolonged colonization. These findings have implications on our understanding of the natural history of MAbsC colonization and the need to intervene with treatment. Furthermore, the interpretation of therapeutic studies needs to consider these findings given a significant proportion of patients will clear carriage irrespective of treatment. Examination of clinical factors including nutritional status, steroid use, and prophylactic antibiotics did not help predict those who are more likely to remain persistently colonized compared to those in whom colonization spontaneously resolves.[12,13] Examination of larger cohorts of patients may uncover subtle trends not demonstrated within our relatively small sample size.

The effect of MAbsC on pulmonary function has previously been shown to cause a subtle acceleration in decline in FEV_1 of <1% per year.[14] Gross examination within our cohort on the effect of MAbsC colonization or clearance on FEV_1 did not demonstrate any obvious patterns of exacerbations of pulmonary disease in the presence of MAbsC colonization or, alternatively, improvement in pulmonary function following clearance. Furthermore, several patients with persistent MAbsC colonization maintained stable lung function over many years suggesting that MAbsC may, in fact, be benign in some people.

Here, we observe treatment outcomes in the CF population are poor, with cure occurring in only one patient in whom treatment was supplemented with lung transplantation. In another patient, while the prognosis was poor, treatment directly contributed to hastening the patient's death. These examples highlight the importance of balancing the risks of treatment with the likely failure to cure MAbsC in CF patients. While inherently resistant to antimicrobial therapies, current evidence suggests that MAbsC demonstrates the greatest sensitivity to amikacin, cefoxitin, and clarithromycin.[15,16] *In vitro* antibiotic sensitivities have proved to be unreliable in directing antibiotic regimens and the description of the inducible macrolide resistance gene *Erm* found in *M. abscessus* spp. *abscessus* further complicates treatment decisions[17] as this accounts for a

Table 5: Treatment regimens and outcome of patients who underwent *Mycobacterium abscessus* treatment

Patient number	Indication for treatment	Regime	Surgery	Duration (weeks)	Adverse events	Outcome
11	Unclear	Amikacin Ceftazidime Clarithromycin	-	28	-	Failed
	Lung function deterioration. In preparation for lung transplant	Amikacin Clarithromycin Clofazimine Tigecycline	-	3	Fulminant hepatitis	Deceased
14	Recurrent MAbsC isolation. Stable lung function	Amikacin Clarithromycin Ceftazidime	-	12	Ototoxicity	Failed
18	In preparation for lung transplant	Amikacin Clarithromycin Ceftazidime Tigecycline	Lung transplant	8	-	Successful
32	Presumed infective endocarditis	Amikacin →Tigecycline Azithromycin Cefoxitin		12	Acute kidney injury, parotid swelling	Relapsed
	Pulmonary artery anastomosis infection. Focal pleural, bone, and chest wall infection	Cefoxitin for 6 weeks Amikacin Tigecycline Azithromycin	Right pulmonary artery reconstruction, bone, and soft-tissue resection	Aiming 52		Under treatment

Factors assessed included indication for treatment, antibiotic regimen used, supplemental surgery, duration of treatment, adverse events, and treatment outcome. MAbsC: *Mycobacterium abscessus* complex, →: changed to

significant proportion of isolates found in Australia.[18] As there are both regional difference of MAbsC burden and CF, treatment may need to be tailored to the local situation.[19,20] New drug regimens for the treatment of MAbsC are sorely needed. Recent *in vitro* research suggests newer agents warranting further investigation include carbapenem/rifampicin combinations,[21] inhaled antibiotics,[22-25] tigecycline,[26,27] and *Mycobacterium leprae* drug clofazimine.[28-30] The novel MAbsC animal models recently described hold potential to improve our knowledge regarding antibiotic response of MAbsC.[26,31,32]

Conclusion

For the clinician, patients in whom MAbsC is isolated are often a management dilemma. Differentiation between MAbsC colonization and disease involves some modalities including the patient's clinical status and radiological evidence of pathology. In the setting of CF, teasing out the contribution of MAbsC to pulmonary function decline given multiple microbial isolates and inherent radiological changes is highly challenging. Given a significant proportion of patients will either spontaneously clear carriage or have a benign course, careful watchful waiting is a feasible management plan, saving patients from the potential toxicities associated with treatment. To date, clinical outcomes following decision to treat are disappointing with only weak evidence for the currently accepted antibiotic regimens.[1,33] Given that some studies report differing pathogenicity and response to treatment between *M. abscessus* ssp. *abscessus* and *M. massiliense*[16,34-37] further research into clinical outcomes of MAbsC is required with delineation of subspecies. Clinical trials comparing antibiotic regimens would greatly improve evidence, however, are technically difficult given the relatively infrequent commitment to treat and the heterogeneity of the patient population. Furthermore, our data show interpretation of studies demonstrating "cure" following treatment should be carefully assessed given the natural history in this patient population demonstrating high rates of spontaneous clearance over time. Given the low rate of success with our current regimen, the decision to treat a CF patient with MAbsC is one that should be carefully balanced and further research to improve treatment outcomes is desperately needed.

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E.T. collated and analyzed patient data, prepared the manuscript, and takes responsibility for the integrity of the data and accuracy of the data analysis. D.S. and T.K. were instrumental in study design, data interpretation, and manuscript preparation. J.W. was involved in data interpretation and manuscript preparation. S.E. was responsible for review and scoring of radiological chest imaging (data not included).

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Conflicts of interest

There are no conflicts of interest.

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