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Peer reviewed

Clinical Significance of Respiratory Isolates for *Mycobacterium abscessus complex* From Pediatric Patients

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Summary. *Mycobacterium abscessus complex* is the most virulent of rapidly growing mycobacteria causing invasive lung disease. To better delineate clinical pediatric experience and outcomes with *M. abscessus complex*, we retrospectively gathered 5-year data on *M. abscessus complex* infection and outcomes in a large, hospital-based pediatric pulmonary center. Patients were selected from the database of the microbiology department at Miller Children's Hospital in Long Beach, CA. Patients had at least one positive pulmonary isolate for *M. abscessus complex* from February 2006 to May 2011. Treatment modality data were collected and successful therapy of disease was determined as clearance of *M. abscessus complex* infection after antibiotics proven by culture negative respiratory isolate within at least 12 months of therapy initiation. Two cystic fibrosis patients with *M. abscessus complex* were identified, one with failed therapy and the other with stable pulmonary status despite persistent isolation. One primary ciliary dyskinesia patient had successful clearance of *M. abscessus complex*, however is now growing *M. avium intracellulare*. A patient with no prior medical history was successfully treated with antimycobacterial therapy. Eleven patients with neuromuscular disorders had tracheal aspirates positive for *M. abscessus complex*. None were treated due to stable lung status and all but two had spontaneous clearance of the mycobacteria. The two remaining persist with sporadic isolation of *M. abscessus complex* without clinical significance. We concluded that patients with tracheostomy associated *M. abscessus complex* infections do not appear to require treatment and often have spontaneous resolution. Cystic fibrosis or primary ciliary dyskinesia patients may have clinical disease warranting treatment, but current antimycobacterial therapy has not proven to be completely successful. As *M. abscessus complex* gains prevalence, standardized guidelines for diagnosis and therapy are needed in the pediatric population. Multicenter cohort analysis is necessary to achieve such guidelines.

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Key words: nontuberculous; tracheostomy; cystic fibrosis; primary ciliary dyskinesia.

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INTRODUCTION

Nontuberculous mycobacteria (NTM) are a common clinical pathogen.¹ *Mycobacterium abscessus complex* is the most virulent and chemotherapy resistant rapidly growing mycobacteria subgroup,^{2,3} however the true prevalence has not been fully elaborated.⁴ Pulmonary disease was first described in male smokers with emphysema.⁵ The majority of NTM infections are pulmonary in origin and rapidly growing mycobacteria such as *M. abscessus complex* are the second most common cause behind *Mycobacterium avium intracellulare* (MAI).⁶ Manifestations beyond lung disease include skin and soft tissue infections.⁷ Infected cystic fibrosis patients in particular note a progressive decline in lung function.⁸

M. abscessus complex clinical treatment guidelines are available from the American Thoracic Society and Infectious Disease Society of America (ATS/IDSA)

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with nonclinical trial evidence-based support from adult studies. Recommendations for treatment modalities in children are less specific.⁹ To better delineate pediatric experience and outcomes with *M. abscessus complex*, we retrospectively analyzed 5-year data on *M. abscessus complex* infection and outcomes in a large, hospital-based pediatric pulmonary center.

METHODS

Approval from the Institutional Review Board was obtained for the medical review of the patients' history. Patients were selected from the database of the microbiology department at Miller Children's Hospital in Long Beach, CA. Patients had at least one positive pulmonary isolate for *M. abscessus complex* from February 2006 to May 2011. Pulmonary isolates were defined as a culture from the sputum, tracheal aspirate, or bronchoalveolar lavage (BAL). Decontamination of samples was done with equal volume 4% sodium hydroxide. Acid-fast bacilli (AFB) stains were obtained on each isolate with standard Kinyoun technique (Remel, Lenexa, KS). Positive AFB were cultured in Lowenstein-Jensen medium (Bay Bioanalytical Laboratory, Inc., Hercules, CA) and rapidly growing mycobacteria were identified as appearance of mature, grossly visible colonies in less than 7 days of culture and a positive arylsulfatase test (Remel). Further differentiation of rapidly growing for species identification utilized biochemical techniques. *M. abscessus complex* identification was confirmed by a negative nitrate reduction (Remel), negative iron uptake (Remel), and positive 5% sodium chloride tolerance test (Bay Bioanalytical Laboratory, Inc.). Antimicrobial sensitivities were utilized if requested by the clinician and sent to Associated Regional and University Pathologist laboratory (Salt Lake City, UT). Once identified, patient charts were reviewed for medical history, source of *M. abscessus complex* isolation, body mass index (BMI), preceding chronic macrolide therapy, allergic bronchopulmonary aspergillosis (ABPA), concurrent infections of other NTM, fungi or bacteria, previous computed tomography (CT) scans of the chest, and radiologic evidence of bronchiectasis. Treatment modality data were collected (antibiotic course, respiratory therapy, and duration). Successful clearance of disease was determined as eradication of *M. abscessus complex* infection after therapy proven by culture negative respiratory isolate within at least 12 months of therapy initiation.

RESULTS

Miller Children's Hospital in Long Beach, CA has a pediatric pulmonology service with approximately 3,500 patients that includes 165 cystic fibrosis patients, 5 primary ciliary dyskinesia patients, and 218 patients with tracheostomy tubes of which 57 of them require

chronic mechanical ventilation. From February 2006 to May 2011 there were 3,804 negative respiratory AFB cultures and 150 positive respiratory cultures for NTM at the Miller Children's Hospital microbiology department. A total of 16 patients had a positive sputum, tracheal aspirate, or BAL isolate of *M. abscessus complex* during this time period. One patient was excluded due to lack of readily available clinical data. Fifteen remaining patients were evaluated with primary pulmonary diseases: two cystic fibrosis,² one primary ciliary dyskinesia,¹ one with no prior medical history,¹ and eleven tracheostomy dependency¹⁰ (Tables 1 and 2). All patients had BMI between the 25th and 75th percentiles for age without significant change regardless of management course. All the patients, except for the primary ciliary dyskinesia patient, had a diagnosis of gastroesophageal reflux disease by a gastroenterology subspecialist either clinically, by endoscopy, or by pH probe study. None of the patients were found to have a diagnosis of ABPA. Five patients met the ATS/IDSA diagnostic criteria for NTM pulmonary disease, but only three were treated.

Cystic Fibrosis and Primary Ciliary Dyskinesia

Two patients had a history of cystic fibrosis, an 8-year-old female and 10-year-old male. Both met the ATS/IDSA diagnostic criteria for NTM clinical pulmonary disease. The 8-year-old female initially isolated both *Mycobacterium avium intracellulare* (MAI) and *M. abscessus complex* from her sputum. Prior to this finding she had previously been treated with chronic azithromycin therapy. Her CT of the chest demonstrated minimal bronchiectasis and mild bibasilar atelectasis. Tiny scattered pulmonary nodules including a 2 mm nodule in right upper lobe were present. A bronchoalveolar lavage (BAL) revealed MAI. Multidrug regimen treatment against MAI with oral (PO) rifampin, PO ethambutol, and PO azithromycin was initiated for 4 months. Her repeat CT scan showed continued cylindrical bronchiectasis of the bilateral apices and the right lower lobe. Repeat BAL again resulted in MAI isolation as well as *M. abscessus complex*. Further antimycobacterial drug regimen was recommenced for treatment of both MAI and *M. abscessus complex* with PO rifampin, PO ethambutol, IV amikacin, and PO clarithromycin (Table 3). She had also been on IV cefoxitin which was discontinued after 1 month due to an adverse reaction. Bronchoscopy was performed one month later growing only *M. abscessus complex*. She continued to grow *M. abscessus complex* on repeat sputum cultures despite continued use of the described antimicrobial therapy for 12 more months. At the completion therapy, her CT of the chest remained unchanged and repeat BAL again grew *M. abscessus complex*. Prior to her initial mycobacteria culture her forced expiratory volume in one

TABLE 1—Descriptive Results of the 15 Analyzed Patients

Patient number	Age (years)	Pulmonary condition	Tracheostomy/ventilator dependent	ATS/IDSA clinical disease	Date of first + MAB culture and first BAL + MAB ¹ (month/year)	Total No. of +/- cultures after initial + MAB ¹	Clinical course	CT chest	Treatment outcome
1	8	Cystic fibrosis	No/no	Yes	4/2008 (S)	B = 2/1	Declining pulmonary function	Bronchiectasis with centrilobular nodularities, no tree-in-bud	Treatment failure
2	10	Cystic fibrosis	No/no	Yes	5/2008 (B) 5/2010 (B)	S = 5/23 T = 0/0 B = 1/0	Stable pulmonary function	Micronodular infiltrates with LLL bronchiectasis, no tree-in-bud	Not treated
3	13	Primary ciliary dyskinesia	No/no	Yes	9/2009 (S)	S = 2/8 T = 0/0 B = 2/3	Clearance of MAB	RLL bronchiectasis with scattered tiny nodular densities, no tree-in-bud	Successful treatment of MAB, however remains on MAI therapy
4	15	Cerebral palsy, mental retardation	Yes/no	No	8/2010 (B) 7/2009 (T)	S = 2/1 T = 0/0 B = 0/0	Spontaneous MAB clearance	None	Not treated
5	18	Rett syndrome	Yes/yes	No	11/2009 (T)	S = 0/0 T = 4/11 B = 0/4	Spontaneous MAB clearance	Bilateral apical infiltrates, no tree-in-bud or nodules	Not treated
6	1	Myotonic dystrophy	Yes/yes	No	8/2008 (T)	S = 0/0 T = 1/4 B = 0/1 S = 0/0 T = 2/7 B = 0/1	Sporadic MAB culture	None	Not treated
7	10	Cerebral palsy, severe kyphoscoliosis	Yes/no	No	10/2008 (T)		Spontaneous MAB clearance	Diffuse bronchial wall thickening with linear atelectasis, no tree-in-bud or nodules	Not treated
8	16	Batten Syndrome	Yes/no	No	10/2009 (T)	S = 0/0 T = 4/7 B = 0/0	Spontaneous MAB clearance	Mild LLL bronchiectasis, no tree-in-bud or nodules	Not treated
						S = 0/0 T = 1/6			

(Continued)

TABLE 1—(Continued)

Patient number	Age (years)	Pulmonary condition	Tracheostomy/ventilator dependent	ATS/IDSA clinical disease	Date of first + MAB culture and first BAL + MAB ¹ (month/year)	Total No. of +/– cultures after initial + MAB ¹	Clinical course	CT chest	Treatment outcome
9	5	Mitochondrial myopathy, cerebral palsy	Yes/no	No	5/2008 (T)	B = 0/1	Spontaneous MAB clearance	None	Not treated
10	3	Cerebral palsy, mental retardation	Yes/yes	No	9/2008 (T)	S = 0/0 T = 5/11 B = 0/0	Spontaneous MAB clearance	None	Not treated
11	5	Chromosome 4q deletion, cerebral palsy	Yes/yes	Yes	10/2008 (T)	S = 0/0 T = 2/5 B = 1/2	Sporadic MAB culture	Moderate LLL infiltrates with 5 mm nodule, mediastinal adenopathy, no tree-in-bud	Not treated
12	10	Cerebral palsy, mental retardation	Yes/yes	No	2/2011 (B) 2/2010 (T)	S = 0/0 T = 5/2 B = 0/1	Spontaneous MAB clearance	None	Not treated
13	13	Cerebral palsy, mental retardation	Yes/yes	No	3/2009 (T)	S = 0 T = 1/6 B = 0/1	Spontaneous MAB clearance	None	Not treated
14	6	Holoprosencephaly, cerebral palsy	Yes/no	No	7/2010 (T)	S = 0/0 T = 2/4 B = 0/0	Sporadic MAB culture	Bilateral lower lobe ground glass opacities, no tree-in-bud or nodules	Not treated
15	6 (months)	No prior history, evaluating for IFN-γ receptor deficiency	No/no	Yes	12/2007 (B)	S = 0 T = 3/5 B = 1/1	Chronic RLL infiltrate but clearance of MAB	Extensive right lung consolidation with scattered nodular densities, no tree-in-bud	Successful treatment
						S = 0/2 T = 0/0			

MAB, *Mycobacterium abscessus* complex; RLL, right lower lobe; LLL, left lower lobe.¹B = bronchoalveolar lavage, S = sputum, T = tracheal aspirate.

TABLE 2—Characteristics of the 15 Patients

Characteristics	Patients (n)	n = 15%
History		
Cystic fibrosis	2	13.3
Primary ciliary dyskinesia	1	6.6
Neuromuscular disorders	11	73
No prior disease	1	6.6
Other history		
Tracheostomy dependent	11	73
Ventilator dependent	6	40
Source of MAB		
Sputum	3	20
BAL	5	33
Tracheal aspirate	11	73
Other NTM cultured		
<i>M. avium intracellulare</i>	2	13.3
<i>M. chelonae complex</i>	9	60
<i>M. fortuitum complex</i>	5	33
<i>M. fortuitum</i>	1	6.6
Fungi cultured		
<i>Aspergillus fumigatus</i>	3	20
<i>C. albicans</i>	5	33
<i>C. parapsilosis</i>	5	33
<i>C. glabrata</i>	1	6.6
Yeast (unspecified)	3	20
Bacteria cultured		
<i>Pseudomonas aeruginosa</i>	8	53
Methicillin resistant <i>S. aureus</i>	4	26.7
<i>Achromobacter xylosoxidans</i>	4	26.7
<i>Stenotrophomonas maltophilia</i>	3	20
<i>Serratia marcescens</i>	6	40
<i>Acinetobacter baumannii complex</i>	1	6.6
<i>Klebsiella oxytoca</i>	1	6.6
<i>Burkholderia cepacia</i>	1	6.6
CT scan		
Obtained	7	46.7
Not obtained	8	53
Bronchiectasis	3	20
Treatment		
Treated with success	1	6.6
Treated with failure	1	6.6
Undergoing treatment	1	6.6
Not treated	12	80

MAB, *Mycobacterium abscessus*; BAL, bronchoalveolar lavage.

second (FEV₁) was 99% predicted and 6 months after therapy it had decreased to 90% predicted. No further intervention of her mycobacterial infection has been conducted and since then her FEV₁ has declined to 70% predicted 18 months later. Routine sputum cultures every 3–4 months continue to isolate *M. abscessus complex*.

The 10-year-old male with cystic fibrosis grew *M. abscessus complex* from a routine surveillance bronchoscopy. He had no prior macrolide therapy. CT of the chest showed nodular bronchiectasis of the left lower lobe and micronodular infiltrates in the bilateral apices and right lower lobe. His FEV₁ was 90% predicted and treatment was not initiated. Fourteen months after

his initial culture, repeat BAL was again grew *M. abscessus complex*. CT scan of the chest showed improved left lower lobe infiltrates, though continued mild bronchiectasis. His FEV₁ increased to 99% predicted and he remains under careful observation. Routine sputum culture every three months continues to grow *M. abscessus complex*.

A 13-year-old female with primary ciliary dyskinesia had an initial culture of MAI from a BAL. This finding was preceded by chronic azithromycin therapy. She continued to grow MAI from repeated sputum culture and 5 months later her sputum cultures grew *M. abscessus complex* instead of MAI. Her CT chest had shown extensive right middle lobe bronchiectasis and infiltrates 1 year prior to her initial mycobacteria isolation and the repeat CT afterwards demonstrated continued moderate right middle lobe bronchiectasis. She has since continued to culture *M. abscessus complex* from her sputum and BAL. Antimicrobial therapy with IV amikacin, IV meropenem, and PO azithromycin was initiated about 18 months after her first isolation and she presently continues on the same treatment regimen. Two bronchoscopies after 3 months of therapy yielded no evidence of NTM after which her FEV₁ was 95% predicted. A bronchoscopy at 8 months into therapy yielded a positive MAI culture, however no *M. abscessus complex*. BAL after 12 months of therapy resulted in a negative culture for NTM. Though she has had 12 months negative cultures for *M. abscessus complex*, she will remain on therapy for approximately 6 more months due to the presence of MAI on her repeat BAL.

Tracheostomy Patients

Of the 11 tracheostomy dependent patients 6 required at least nocturnal mechanical ventilation or full day ventilatory support. All the patients have some form of neuromuscular disorder including cerebral palsy, developmental delay, myotonic dystrophy, Batten syndrome, Rett syndrome, mitochondrial myopathy, chromosomal deletions, and holoprosencephaly. Their ages of initial culture range from 1 to 18 years of age. Tracheal aspirates were obtained for bacterial, fungi, and mycobacteria culture as routine for clinic visits two to three times a year. Positive NTM cultures led to increased testing frequency every 2–3 months. None of the patients had been on chronic macrolide therapy. All but two patients ceased to culture further *M. abscessus complex* on repeated tracheal aspirate cultures obtained routinely two to three times a year. The two patients continue to have culture positive tracheal aspirates at sporadic intervals. None of the tracheostomy patients were treated with antimycobacterial therapy. All the patients remained clinically stable despite isolation of *M. abscessus*

TABLE 3—Antibiotic Therapy for *M. abscessus* complex, Culture Sensitivities, and Positive and Negative Culture Dates of the Treated Subjects

Patient number	Patient data	Antibiotic and dosage	Length of therapy	Antibiotic sensitivities (antibiotic/MIC/resistance)	Positive MAB (months after therapy initiation)	Negative MAB (months after therapy initiation)
1 ²	8-year old with cystic fibrosis	Rifampin PO 600 mg TIW Ethambutol PO 400 mg TIW Amikacin IV 240 mg daily Clarithromycin 250 mg BID Cefoxitin 1 g QID	12 months (Cefoxitin only used for 1 month)	Amikacin 16.00 S Cefoxitin 32.00 I Clarithromycin 1.00 S Ciprofloxacin ≥8.00 R Doxycycline ≥32.00 R Linezolid 32.00 R Minocycline ≥16.00 Moxifloxacin ≥16.00 TMP/SMX ≥320.00 R Amikacin 16.00 S	12, 14, 19	2, 3, 4, 5, 7, 9, 13
3	13-year old with primary ciliary dyskinesia	Amikacin IV 350 mg daily Meropenem IV 2 g TID Azithromycin PO 250 mg daily	12 months (continued therapy for MAI)	Cefoxitin 32.00 I Clarithromycin 1.00 S Ciprofloxacin ≥8.00 R Doxycycline ≥32.00 R Linezolid 32.00 R Minocycline ≥16.00 Moxifloxacin ≥16.00 TMP/SMX ≥320.00 R Amikacin 32.00 I	0	5, 6, ¹ 8, ¹ 12
15	6-month old with no prior medical history	Cefoxitin IV 40 mg QID Meropenem IV 60 mg TID Amikacin IV 90 mg daily Clarithromycin PO 45 mg BID	3 months	Cefoxitin 32.00 I Clarithromycin 0.25 S Ciprofloxacin ≥32.00 R Gatifloxacin ≥16.00 Linezolid 32.00 R Minocycline 8.00 I TMP/SMX ≥320.00 R	0	5, 12, 26

TIW, three times weekly; BID, twice daily; TID, three times daily; QID, four times daily; TMP/SMX, trimethoprim/sulfamethoxazole; S, sensitive; I, intermediate; R, resistant; MIC, minimum inhibitory concentration.

¹Positive culture for MAI.

²From initiation of second antibiotic course.

complex as defined by no increase in hospitalization, antibiotic use, or ventilatory requirements if they were on a ventilator (Table 4).

CT scans of the chests were obtained on four patients. An 18-year-old female with Rett syndrome had a CT with both apical and lower lobe infiltrates without bronchiectasis. She only grew *M. abscessus complex* once without a positive culture since. A 10-year-old male with severe kyphoscoliosis and cerebral palsy grew *M. abscessus complex* on several tracheal aspirates over the course of 18 months. CT scan showed only bronchial wall thickening with scattered linear atelectasis but no bronchiectasis. He has been culture negative for the past 12 months. A 5-year-old female with chromosome 4q deletion had a CT demonstrating left lower lobe infiltrates without bronchiectasis. She has continued to grow *M. abscessus complex* from tracheal aspirates and BAL over the last 2 years without clearance. Resolution of her left lower lobe infiltrates on CT scan was seen, though she did develop a 5 mm left lower lobe nodule of unclear clinical significance. A 6-year-old female with holoprosencephaly had a CT scan done 2 years prior to her initial colonization of *M. abscessus complex* showing bilateral lower lobe ground glass opacities without bronchiectasis. Repeat CT was not done and she had three negative cultures of *M. abscessus complex* after 5 months.

Patient with no Prior Medical History

A 4-month-old born full term without known prior medical history was found to have pneumonia requiring bronchoscopic evaluation. CT of the chest demonstrated right upper lobe and bilateral lower lobe nodular densities. BAL revealed *M. abscessus complex*. Patient was started on antimicrobial therapy with IV cefoxitin, IV

meropenem, IV amikacin, and PO clarithromycin after placement of a Broviac catheter. He was continued on therapy for 3 months and repeat BAL did not culture any mycobacteria. Long-term follow up had residual right upper lobe consolidation without bronchiectasis nearly 2 years later despite continued negative BAL. He had other episodes of bacterial pneumonia diagnosed clinically and radiologically without direct microbial analysis since then. He is in the process of evaluation for possible IFN γ receptor deficiency.

DISCUSSION

M. abscessus complex is the most virulent of rapidly growing mycobacteria causing invasive lung disease.³ The name *abscessus* was first designated due to a report of human knee infection with deep abscess-like lesions.¹¹ Initially it was grouped under the *Mycobacterium fortuitum complex*¹⁰ but has been differentiated from *Mycobacterium chelonae*.¹² In addition to pulmonary disease *M. abscessus complex* causes skin, soft tissue, meningitic, and disseminated infections.¹³ NTM pulmonary disease in general has been shown to decrease a patient's quality of life.¹⁴ *M. abscessus complex* has shown to decrease lung function in cystic fibrosis patients.⁸

Pathogenesis

M. abscessus complex has two main variants, a rough and smooth morphology. The smooth variant is characterized by the ability to form biofilms and sliding motility while the rough variant acquires the ability to replicate in human macrophages and stimulate macrophage toll receptor 2 (TLR-2).¹⁵ The conversion from smooth to rough morphology has been associated with severe and fatal pulmonary infections.^{16–18} The rough

TABLE 4—Specific Clinical Information for Tracheostomy Patients

Patient number	Patient information	Respiratory hospitalizations (before 1st culture/after 1st culture)	Respiratory antibiotic therapies (before 1st culture/after 1st culture)	Ventilator changes (before 1st culture/after 1st culture)
4	15-year old with MRCP	1/1	1/1	N/A
5	18-year old with Rett Syndrome	2/3	3/3	0/0
6	1-year old with myotonic dystrophy	5/4	5/4	1/1
7	10-year old with CP, severe kyphoscoliosis	1/0	1/0	N/A
8	16-year old with Batten syndrome	0/1	0/1	N/A
9	5-year old with mitochondrial myopathy and CP	1/1	1/1	N/A
10	3-year old with MRCP	0/1	1/1	2/1
11	5-year old with chromosome 4 deletion	1/0	2/1	1/1
12	10-year old with MRCP	2/0	2/1	0/1
13	13-year old with MRCP	1/2	1/2	0/0
14	6-year old with holoprosencephaly and CP	1/1	1/1	N/A

MRCP, combined cerebral palsy and mental retardation; CP, cerebral palsy; N/A, not applicable.

B = bronchoalveolar lavage, T = tracheal aspirate, S = sputum culture.

variants are also known to cause rapid death in mice after IV administration¹⁹ and persistent infections with caseous lesions.²⁰ The transformation has been shown to correlate with the loss of the mycobacterial glycopeptidolipid which helps mask underlying cell wall phosphatidyl-myo-inositol mannosides.²¹ Glycopeptidolipids therefore limit the interaction with TLR-2 and decreases the induction of human macrophage interferon gamma (IFN γ).²¹

Deficiencies of the immune system or therapeutic immunosuppression allow NTM infections to present themselves as seen in cases of HIV infection, hyperimmunoglobulin E syndrome, anti-TNF α therapy, and immune suppression therapy in transplant patients.^{22–26} Indeed NTM infection in lung transplant patients is common.²⁷ While NTM infection, including *M. abscessus complex* can be treated successfully in lung transplant patients^{27,28} infections may be a cause for morbidity and mortality.^{29–32} Chernenko et al.³³ performed an international multicenter survey showing that in 5,200 patients among 31 centers 0.33% were found to have *M. abscessus complex* infections with two mortalities.

M. abscessus complex has a variety of manifestations for cystic fibrosis patients. Given *M. abscessus complex* has been shown to affect similar bronchiectatic diseases such as primary ciliary dyskinesia⁵ there may exist structural causes for infection. Analysis of the pathogenesis of NTM pulmonary infections in general help to offer data as to the mechanism to which *M. abscessus complex* causes disease. Previous studies have shown that while *Mycobacterium tuberculosis* can attach to healthy mucosa, NTM is only capable of attaching to damaged mucosa.³⁴ Indeed MAI has a virulence factor called fibronectin attachment protein that can adhere to fibronectin within exposed extracellular matrix on damaged mucosal surfaces.³⁵ Mucus plugging is a factor for NTM in noncystic fibrosis patients.³⁶ However it has also been postulated that cystic fibrosis patients have a defect of β -defensins that predispose them to tuberculous or NTM infections.³⁷ Cystic fibrosis transmembrane conductance regulator (CFTR) defects in themselves may allow vulnerability to mycobacteria as evidence by the data showing that a study group reported that 50% of patients with identified NTM infections were either heterozygous or homozygous for pathological CFTR mutations, even though only 20% met the diagnostic criteria for cystic fibrosis.³⁸

Huang et al.³⁹ performed a study involving chronic ventilator dependent patients in hospital long-term respiratory care wards in central Taiwan. Of the 38 patients from which tracheal aspirates were obtained, 23 were found positive isolates for *M. abscessus complex* and 15 were diagnosed with clinical disease

based on ATS/IDSA criteria. Five of those patients were placed on antimycobacterial therapy. Studies have not been done on tracheostomy patients without ventilator dependency. Airway mucosal damage may also specify the pathogenesis of *M. abscessus complex* infection in tracheostomy patients. The manner in which these patients develop damage may be secondary primary aspiration, secondary aspiration from gastroesophageal reflux disease or damage from tracheal suctioning. Contaminated water sources also remain a possibility. The chronic airway mucosal damage seen in tracheostomy and bronchiectatic patients may present the manner in which co-infection with other NTM may occur.

Diagnosis

While clinical isolation of mycobacteria in pulmonary cultures is a necessary step in diagnosing the presence of the organism, it does not delineate the difference between infection and colonization. Common findings on CT scans of the chest are bilateral small nodules, cylindrical bronchiectasis, cavity formation and branching centrilobular nodules.^{40,41} Chung et al.⁴² reported a considerable overlap in MAI and *M. abscessus complex* findings, however lobar volume loss, nodules, airspace consolidation, and thin-walled cavities were more common on MAI than *M. abscessus complex*. The difficulty in analyzing radiologic evidence for NTM pulmonary infections stems from differentiation from prior lung disease. Specifically, CF lung disease classically reveals progressive bronchiectasis regardless of NTM disease.

Treatment

M. abscessus complex is characterized as drug resistant requiring multimodal therapy.^{3,5} Clarithromycin is the most useful drug in its treatment.⁴³ Those patients with macrolide-resistant strains are much more difficult to treat and maintain a poor prognosis.⁹ Chopra et al.⁴⁴ evaluated 1,040 FDA approved drugs against *M. abscessus complex* in vitro and found that only metronidazole, morfloxacine, resorcinol, praziquantel, doxycycline, natamycin, and puromycin had significant antimicrobial activity. Current recommendations from ATS/IDSA involve the combination treatment with clarithromycin or azithromycin with amikacin plus cefoxitin or imipenem.⁹ *M. abscessus complex*, however is uniformly resistant to all standard antituberculous agents.⁹ Chihara et al.⁴⁵ showed *M. abscessus complex* is generally resistant to carbapenems though Miyasaka et al.⁴⁶ found imipenem had good synergistic effect. Jeon et al.⁴⁷ used clarithromycin, ciprofloxacin, and doxycycline with an initial regimen of amikacin and cefoxitin for the first 4 weeks yielding treatment

response rate of 83% for symptoms and 74% for high-resolution CT. Rates were much lower for those that were clarithromycin resistant.⁴⁷ Lyu et al.⁴⁸ performed a retrospective study on 41 patients with *M. abscessus complex* treated with a macrolide and amikacin in addition to either cefoxitin or imipenem giving an 80.5% successful treatment rate. Linezolid has shown some activity against several NTM⁴⁹ and evidence suggests it is synergistic with clarithromycin.⁴³ Overall, however, treatment of *M. abscessus complex* has yielded limited results.⁵⁰ Greendyke and Byrd⁵¹ showed even if minimum inhibitory concentrations indicate sensitivity to amikacin, clarithromycin and cefoxitin, the minimal bactericidal concentrations for these drugs were much higher than could be achieved at serum levels.

Given the limitations in antimicrobial therapy, surgical options have been utilized. Jarand et al.⁵² evaluated 107 patients from 2001 to 2008 who were treated with multidrug regimen with surgical resection or antibiotics alone demonstrating similar clinical outcomes. Mitchell et al.⁵³ looked at 236 patients who underwent lung resection for NTM yielding a mortality rate of 2.6% and morbidity rate of 11.7%. Much higher mortality of 23% was seen in other studies⁵⁴ and complication rates as high as 35%.⁵⁵

Alternative therapies include anti-oxidants such as MnTE-2-PyP which has shown to reduce intracellular growth of *M. abscessus complex*.⁵⁶ N-acetyl-L-cysteine has also been able to inhibit its growth⁵⁷ and is not an uncommon therapy in patients with chronic airway disease such as cystic fibrosis. IL-24, a novel tumor suppressor and unique member of IL-10 family is suppressed in tuberculosis infections and exogenous introduction activates CD8⁺ T cells driving production of IFN γ . Therapy with IFN γ was used in a refractory case of *M. abscessus complex* cutaneous disease with marked success.⁵⁸ Inhaled therapy of IFN γ was effective in those with functional IFN γ deficiency,⁵⁹ however no such therapy has been trialed on patients without IFN γ defects.

Patients with NTM have increased peripheral mucus plugging.⁶⁰ This would lead to the concept of increased airway clearance as a method of combating pulmonary NTM infections in general.³⁷ Limiting the degree of mucosal damage, as seen to be a cause for increased disease due to exposure of fibronectin,³⁵ may lead to decreased NTM attachment to the epithelial airway walls. Therefore in theory, alleviating mucoid impaction and allowing for an intact mucosa in CF and primary ciliary dyskinesia patients may lead to decreased NTM bacterial colonization and disease. This has yet to be well studied in either basic science or clinical research and further evaluation is warranted.

Conclusion

Patients with tracheostomy associated *M. abscessus complex* infections do not appear to require treatment and often clear cultures spontaneously within months. Those who continued to have sporadic isolation, including the one who met the ATS/IDSA diagnostic criteria for clinical disease remain clinically stable without therapy. Alternatively, the disease process in patients with chronic bronchiectatic disease such as cystic fibrosis or primary ciliary dyskinesia may have clinical disease warranting intervention. Current antimicrobial therapy demonstrates limited success when comprehensively treating these patients. Surgical intervention remains an option, though morbidity and mortality remain a concern, especially given questionable clinical improvement. As *M. abscessus complex* gains prevalence, standardized guidelines for diagnosis and therapy are needed in the pediatric population. Multicenter cohort analysis is necessary to achieve such guidelines.

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