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PEDIATRIC INFECTIOUS DISEASES (I BROOK AND Y SHACHOR, SECTION EDITORS)

Nontuberculous Mycobacteria Pulmonary Infection in Children with Cystic Fibrosis

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Abstract

Purpose of Review As children and adolescents with cystic fibrosis (CF) have lived longer, they have become more susceptible to pulmonary infection with nontuberculous mycobacteria (NTM). Most NTM infections are caused by the *Mycobacterium avium* complex (MAC) or *Mycobacterium abscessus*. We review what is currently known and recommended for treatment of these infections.

Recent Findings Treatment of MAC infection is standardized and evidence-based, involving a combination of three oral drugs for 12 months. Treatment of *M. abscessus* infections is more difficult and not standardized owing to the: lack of bactericidal drugs; variability of drug susceptibilities; inability of in vitro antibiotic susceptibility testing to predict clinical success; lack of randomized trial data to guide therapy; need for initial parenteral therapy; higher rate of adverse reactions to the necessary medications; and high cost and limited availability of some of the drugs. Treatment involves an initial several month period including one or more parenteral antibiotics followed by a prolonged continuation phase using several of the best available oral antibiotics. Dual beta-lactam antibiotic and phage therapies offer some hope for improved outcomes in refractory cases.

Summary The goals for therapy of *M. abscessus* infections should be considered prior to the onset of treatment, and often are aimed toward improvement in symptoms and quality of life rather that eradication of the organism.

Keywords Nontuberculous Mycobacteria · Cystic Fibrosis · *Mycobacterium avium* Complex · *Mycobacterium abscessus* · Phage Therapy

Introduction

Children and adolescents living with cystic fibrosis (CF) are at risk for numerous types of pulmonary infections. Early in life, the most common pathogens are bacteria such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenza*. As an individual with CF becomes older, pulmonary infections caused by nontuberculous mycobacteria (NTM) become increasingly common. These chronic infections are difficult to treat, require very long-term antibiotic regimens, and can contribute significantly to diminishing pulmonary function. The treatment regimens can cause significant adverse effects which are often the limiting factor in completing successful treatment. The management of NTM infections in patients with CF often requires shared decision-making among the patient and family, the pulmonologist and the infectious disease clinician.

Microbiology of the Nontuberculous Mycobacteria

Mycobacterium is a genus of organisms that are aerobic and rod shaped. Members of this genus have cell walls rich in mycolic acid, and stain positive with various acid-fast and

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fluorescent stains. Nontuberculous mycobacteria (NTM) include all mycobacteria other than the organisms of the *Mycobacterium tuberculosis* complex (including *Mycobacterium bovis*, *Mycobacterium microti*, *Mycobacterium africanum*, *Mycobacterium pinnipedii*, *Mycobacterium caprae*, and *Mycobacterium canetti*).

Traditionally, NTM are divided into slow and rapid growing categories based on their replication times in the laboratory. In patients with CF the most commonly isolated slow-growing NTM organisms are members of the *Mycobacterium avium* complex (MAC, including Mycobacterium *avium*, *Mycobacterium intracellulare*, *Mycobacterium scrofulaceum* and *Mycobacterium chimaera*) [1]. *Mycobacterium kansasii* and *Mycobacterium simiae* also are occasionally isolated from respiratory specimens [2].

The most commonly isolated rapid-growing NTM organism from CF patients is *Mycobacterium abscessus*, including the subspecies *abscessus* (*M. a. abscessus*), *bolletti* (*M. a. bolletii*), and *massiliense* (*M. a. massiliense*). Identification to the subspecies level for *M. abscessus* is clinically relevant due to the presence of the *erm* [41] gene. Two of the three *M. abscessus* subspecies, *M. a. abscessus* and *M. a. bolettii*, possess an erm [41] gene which confers inducible macrolide resistance [3]. *M. a. massilense* possesses a deletion in the *erm* [41] gene rendering it non-functional and inducible macrolide resistance is not a concern. (Floto) Standard broth microdilution methods for antibiotic susceptibilities, which are read on the day of growth of the control, will not detect inducible macrolide resistance [4]. Either direct detection of the *erm* [41] allele or a later reading of the broth microdilution assay for clarithromycin susceptibility at 14 days of incubation is utilized in vitro to detect inducible resistance [4]. This testing is available at reference and some commercial laboratories. In a study of 129 *M. abscessus* isolates with clarithromycin resistance detected at 14 days of incubation, only 13 of the isolates had clarithromycin resistance detected at the standard, earlier reading done at a median of 5 days [4]. In addition, acquired clarithromycin resistance can also be conferred via mutations in the *rrl* gene and can be detected at the early reading of the broth microdilution assay [5].

Isolation

Cultures are usually obtained from sputum, bronchoalveolar lavage, or bronchial washings. For mycobacterial assessment, samples generally first undergo acid-fast staining. Liquid and solid media can both be inoculated for culture to increase sensitivity; however, inoculation of liquid media using an automated growth detection system (such as Mycobacteria Growth Indicator Tube [MGIT]) is the singular most rapid and sensitive generally available method [1, 6]. Rapid growing species typically take 3–10 days to grow in culture while slow growing species may need > 14 days. The recommended incubation duration is a minimum of 6 weeks. Rapid growing species also may grow in standard bacterial and fungal cultures.

Unfortunately, the decontamination process used for sputum samples - a non-sterile specimen - can reduce the viability of NTM in culture [6]. Therefore, use of special agar for rapidly growing mycobacteria (RGM agar) has a higher yield. Extended incubation for slow-growing mycobacteria on RGM media has also shown to have a high yield of recovery [7].

Laboratory Speciation

Molecular detection and identification is key for the rapid distinction between NTM and *M. tuberculosis* complex organisms. Identification to the species level (with the exception of MAC) and the identification to the sub-species level for *M. abscessus* are important for determining optimal antimicrobial management of NTM infections. In most general microbiology laboratories, Gen Xpert (Cepheid, Sunnyvale, California) is used to rapidly determine if a mycobacterial isolate is *M. tuberculosis* or an NTM. Unfortunately, there is no readily available rapid test to speciate an NTM isolate. Mass spectrometry methods such as MALDI-TOF have increasingly become more efficient at NTM identification. This type of procedure works best with NTM isolates from solid media as they yield the purest cultures [6, 8, 9]. Alternatively, heat shock protein 65 (*hsp65*) partial gene sequencing has been shown to have high discriminatory power in NTM species identification. Some studies even suggest that this type of sequencing serve as a first-line identification method for NTM [10].

Susceptibility Testing

The Clinical and Laboratory Standards Institute (CLSI) has recommendations for antimicrobial susceptibility testing (AST) of NTM. Wild-type isolates of MAC are presumed to be macrolide-susceptible; however, there are instances when testing for macrolide susceptibility is warranted. CLSI recommends macrolide AST for MAC isolates from: patients who previously received treatment with macrolides; blood cultures of patients who become bacteremic when receiving macrolide prophylaxis; and patients with refractory disease on macrolide therapy. Azithromycin has poor solubility at high concentrations, so clarithromycin is used to establish the MIC for this antibiotic class. An intermediate MIC for clarithromycin can indicate emerging resistance [11].

Standard therapy for *M. kansaii* includes rifampin, isoniazid (alternatively clarithromycin), and ethambutol. AST is

typically not required for *M. kansaii* as the MICs tend to be very narrow and, therefore, difficult to interpret. In patients with treatment failure, usually the isolate of *M. kansaii i*s resistant to rifampin. In this case, the CLSI and IDSA recommend susceptibility testing [11].

Given that rapid-growers, in particular *M. abscessus*, are particularly difficult to manage, multiple antimicrobials are recommended for AST. The CF foundation recommends susceptibility testing for clarithromycin, cefoxitin and amikacin, and ideally also tigecycline, imipenem, minocycline, moxifloxacin, and linezolid [1]. Clofazimine and bedaquiline are being used more commonly to treat *M. abscessus* infections; clofazimine susceptibility testing is now performed by many commercial laboratories, but bedaquiline susceptibility testing often requires use of a reference laboratory.

Epidemiology of the Nontuberculous Mycobacteria

NTM are environmental organisms found in natural and commercial water sources (including tap water), soil, wild and domesticated animals, and food and milk products [12]. Person-to-person transmission of MAC has not been documented. Most acquisition of Mab is from the environment, but several CF centers have reported clusters of Mab infections for which whole genome sequencing of isolates and epidemiologic investigation were suggestive of either direct or indirect person-to-person transmission [13, 14]. In pediatric patients with CF, increasing age is associated with increased likelihood of positive airway cultures for NTM [1]. Patients diagnosed with CF in adulthood have an even higher prevalence of positive airway cultures for NTM with estimates over 50% [15, 16]. Fortunately, individuals with CF with or without NTM pulmonary infection rarely develop NTM disease at other anatomic sites.

NTM pulmonary disease has been associated with a faster rate of decline in pulmonary function in children and adolescents with CF [17]. Current CF guidelines recommend annual screening for NTM pulmonary disease using sputum cultures [1, 17, 18]. A large study using data from the CF Foundation patient registry demonstrated that 1 in 5 patients had at least one pathogenic NTM species isolated from sputum during a five-year period [19]. Of those patients, 61% had MAC detected and 39% had *M. abscessus*. It is estimated that approximately 30% of NTM pulmonary infections may be transient and resolve without treatment [12, 18]. Given that isolation of NTM is only one component used to define NTM pulmonary disease, the true prevalence of NTM pulmonary disease in patients with CF is likely lower, with estimates ranging between 2% and 20% [1]. Over the last 20 years it appeared that NTM pulmonary infections were becoming more prevalent over time in patients with CF, but it has been unclear if the increase was secondary to better awareness, enhanced surveillance, improved diagnostics, refining of case definitions, increased numbers of susceptible hosts and/or other factors [20]. Some CF studies have shown yearly increases in frequency of NTM infections after controlling for surveillance frequency and microbiologic methodology, suggesting a true rise [1].

The development of a new class of drugs for CF will likely decrease the incidence and prevalence of NTM pulmonary infections in the future. In 2019, elexacaftor/ivacaftor/tezacaftor (ETI) was approved for the 75–90% of patients with CF who have at least one F508del mutation. ETI potentiates the effect of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, and contributes to lower rates of airway infections in eligible patients via direct antimicrobial effects as well as by improving mucociliary clearance and host immune response [18, 21, 22]. Current observational case series provide optimism that ETI use will positively impact NTM pulmonary infections. A review of 15 patients by Wiesel et al. showed eradication of NTM infection in 66% of patients treated with ETI and a reduction in annual isolations in some patients who did not achieve eradication [22]. However, some patients were also receiving antibiotic treatment for NTM and information was not provided on how many prior positive cultures each patient had before starting ETI. A prospective clinical trial comparing patients with CF and NTM pulmonary disease and those without NTM pulmonary disease is ongoing and anticipated to provide more insight on the impact of ETI on NTM pulmonary disease [23].

Diagnostic Criteria for Nontuberculous Mycobacterial Pulmonary Disease and Response to Therapy

Because NTM are present in the environment, it is not uncommon for them to be cultured from non-sterile parts of the anatomy, such as the upper respiratory tract. As a result, differentiating colonization from infection can be challenging. True infection is more likely to be present if:

1) the anatomic site is prone to NTM infection.
2) the species of NTM is a recognized pathogen at the anatomic site.
3) there is repeated isolation of the same NTM species from that anatomic site.
4) there is a higher quantity of growth/faster time to isolation.
5) the host has risk factors for NTM infection at that site.

The 2007 American Thoracic Society (ATS)/Infectious Disease Society of America (IDSA) guidelines recommended criteria for the diagnosis of NTM pulmonary infections, and these recommendations were reconfirmed in the 2020 ATS/European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/IDSA guidelines [17] (Table 1). They use the combination of clinical, radiologic and microbiologic criteria to define infection. While two positive sputum culture results for the same NTM is considered acceptable, positive culture from a bronchial wash or lavage is often preferred [24], and by taking multiple samples from various lobes can help determine if the NTM disease is more localized or disseminated throughout the lungs. The radiologic criteria are not specific for NTM infection but are highly suggestive if NTM is isolated from the lungs. The most diagnostic findings are nodular infiltrates or cavitary opacities seen on a chest radiograph, or bronchiectasis and multiple small nodules seen on a high-resolution computed tomography scan. So-called "tree-in-bud" lesions - multiple areas of centrilobular nodules with a linear branching pattern - also are commonly seen but occur in many pulmonary infections and conditions, and are not a specific part of the diagnostic criteria.

Unfortunately, the criteria for determining response to therapy are more controversial and not standardized. Response can be measured in at least four ways: clinical, functional (pulmonary function testing), radiologic and microscopic. While eradication of the NTM organism is ideal, it can be difficult to achieve because of inadequate response to therapy, the limited choice of effective drugs for *M. abscessus* infections, and the adverse effects of antimycobacterial drugs, which tend to be more common and severe than with other antibiotics. The four elements often do not synchronize in terms of improvement; for instance, one can see functional and clinical improvement with continued positive cultures and incomplete radiographic improvement. When treating patients with CF and NTM pulmonary disease, it is imperative that the goals of therapy be established, and that management is directed by shared decision-making among the patient and family, pulmonary and infectious disease clinicians.

Management of MAC Pulmonary Infection

The 2020 ATS/ERS/ESCMID/IDSA guidelines give extensive details about management of pulmonary infections cause by MAC. The recommended long-term management of MAC pulmonary disease in patients with CF is similar to that for patients without CF. Notably, some patients with mild CF disease and/or mild symptoms, who are culture positive for MAC but without significant radiographic or functional disease, can be closely monitored without therapy [25]. For patients with significant MAC pulmonary disease, drug susceptibility-based management is preferred over empiric therapy [17], and testing should always include susceptibility to macrolides and amikacin [26, 27]. For macrolide susceptible, non-cavitary pulmonary disease, recommended therapy includes daily oral azithromycin, ethambutol, and rifampin. Clarithromycin can be used but azithromycin is preferred because of better tolerance, single daily dosing, fewer drug interactions and equal efficacy [17, 28]. (Table 2).

The ATS/ERS/ESCMID/IDSA treatment guidelines for NTM pulmonary disease in adults *without CF* recommends three times weekly rather than daily dosing for non-cavitary disease [16]. However, recommendations for adult and pediatric patients with CF usually includes daily dosing of antimicrobials [1].

In patients with isolates that have macrolide resistance, significant MAC pulmonary disease (cavitary lesions, significant bronchiectatic changes), or significant systemic illness, the initial treatment regimen should include intravenous amikacin or streptomycin for an "induction" period [17, 29]. The duration of this more intensive period of therapy is typically based on clinical response, but is generally used for the first 3–12 weeks. The CF Foundation specifically recommends amikacin [1]. Patients and families require extensive counseling prior to amikacin administration given the risk of hearing damage with prolonged treatment.

Amikacin also can be delivered directly to the lungs via inhalation therapy using either the parenteral formulation or amikacin liposomal inhalation suspension (ALIS). The ATS/ERS/ESCMID/IDSA guidelines do not recommend any form of inhaled amikacin for initial treatment, but they

Table 1 Diagnostic criteria for the diagnosis of NTM pulmonary disease

Clinical:	Pulmonary or systemic symptoms
Radiologic:	Chest radiograph - nodular or cavitary opacities High-resolution computed tomography – bronchiectasis with multiple small nodules *Both with appropriate exclusion of other diagnoses*
Microbiologic:	Positive culture results from at least two separate expectorated sputum samples ***or*** Positive culture results from at least one bronchial wash or lavage ***or*** transbronchial or other lung biopsy with mycobacterial histologic features (granulomatous inflammation or AFB) or positive culture for NTM or biopsy showing mycobacterial histologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM

Table 2 Select antibiotics indicated in NTM Pulmonary Disease

Medication	CF Dose Specified	Dose	Route	Notable Adverse Reactions
Azithromycin[a, b]	Not available	Infants and Children 10-12 mg/kg/dose once daily, max dose 500 mg Adolescents 500 to 600 mg daily	Oral	Diarrhea Nausea Hepatotoxicity Prolonged QTc Tinnitus/hearing loss
Clarithromycin[a, b]	Available	Infants, Children, and Adolescents 7.5 mg/kg/dose every 12 h, max dose 500 mg	Oral	Diarrhea Nausea Hepatotoxicity Prolonged QTc Tinnitus/hearing loss
Ethambutol[a]	Not available	Infants, Children, and Adolescents 15 mg/kg/dose once daily, max dose 2500 mg	Oral	Optic neuropathy Visual disturbance Peripheral neuritis
Rifampin[a]	Available	Children and adolescents 10 to 20 mg/kg/dose once daily max dose 450 mg for patients < 50 kg max dose 600 mg for patients > 50 kg	Oral	Hepatotoxicity Cytopenias Hypersensitivity
Amikacin[a, b]	Available	Infants and Children 15 to 30 mg/kg/dose once daily, max dose 1500 mg Adolescents 10 to 15 mg/kg once daily, max dose 1500 mg	IV	Vestibular ototoxicity Auditory ototoxicity Nephrotoxicity Hypomagnesemia
Streptomycin[a]	Available	Infants, Children, and Adolescents 20 to 40 mg/kg/dose once daily doses, max 1000 mg	IV	Vestibular ototoxicity Auditory ototoxicity Nephrotoxicity
Imipenem[b]	Available	Children and Adolescents, 15 to 20 mg/kg/dose, every 12 h, max dose 1000 mg	IV	Cytopenias Hepatotoxicity Nephrotoxicity
Cefoxitin[b]	Available	Children and Adolescents, 50 mg/kg/dose, every 8 h, max 12 g per day	IV	Diarrhea Hypersensitivity Cytopenias
Tigecycline[b]	Available	Children 8–11 years, 1.2 mg/kg/dose, every 12 h, max dose 50 mg Adolescents 12 years or older, 100 mg loading dose then 50 mg every 12–24 h	IV	Nausea, vomiting Diarrhea Anemia Hepatotoxicity Pancreatitis Headache
Linezolid[b]	Available	Children < 12 years, 10 mg/kg/dose, every 12–24 h Adolescents 12 years or older, 10 mg/kg/dose, every 12–24 h, max dose 600 mg	IV or Oral	Cytopenias Diarrhea Lactic acidosis Peripheral neuropathy Optic neuritis
Tedizolid[b]	Not available	Children and Adolescents, 3 mg/kg/dose, every 12–24 h, max 200 mg per day	Oral	Cytopenias Nausea Peripheral neuropathy
Ciprofloxacin[b]	Not available	Children and Adolescents, 10–20 mg/kg/dose, every 12 h, max dose 1500 mg	Oral	Tendinopathy Prolonged QTc Photosensitivity Peripheral neuropathy Hepatotoxicity
Minocycline[b]	Available	Children and Adolescents, 2 mg/kg/dose, once daily, max dose 200 mg	Oral	Arthralgias Dizziness Hepatotoxicity Photosensitivity

Table 2 (continued)

Medication	CF Dose Specified	Dose	Route	Notable Adverse Reactions
Doxycycline[b]	Not available	Children and Adolescents, 2.2 mg/kg/dose, every 12 h, max 200 mg per day	Oral	Diarrhea Esophagitis Photosensitivity
Clofazamine[b]	Available	Children and Adolescents 1 to 2 mg/kg/dose, once daily doses, max dose 100 mg	Oral	Skin dryness, tanning Prolonged QTc Hepatotoxicity Clofazimine enteropathy

a. Used frequently in the treatment of *M. avium* infection

b. Used frequently in the treatment of *M. abscessus* infection

should be added to the treatment regimen for patients with MAC pulmonary disease who have failed at least 6 months of guideline-based therapy [17, 30]. The clinical benefit of ALIS has yet to be demonstrated in the pediatric CF population.

There has been some study of fluoroquinolone antibiotics as a replacement for ethambutol or rifampin, especially in patients who experience adverse effects from the standard therapy regimen. In a study of more than 400 adult patients with pulmonary MAC disease, substituting a fluoroquinolone for ethambutol resulted in inferior outcomes for patients with cavitary disease, while there was no difference in substituting a fluoroquinolone for rifampin [31]. There are no comparable data for children, and there are some concerns with the prolonged use of fluoroquinolone antibiotics in the younger age groups.

The optimal duration of treatment for pulmonary MAC disease in patients with CF is unknown, and there is a paucity of published data regarding duration of treatment in children [32]. Treatment duration can vary from patient to patient, but generally involves assessing culture conversion and improvement in clinical signs and symptoms, radiographic appearance and pulmonary function testing. In a multi-center study of the treatment of NTM pulmonary infection in children with CF, culture conversion was defined as no positive respiratory samples after 6 months of therapy, with eradication defined as no further positive samples for 12 months of follow up [33]. The median duration of treatment in this study was 275 days; 80% of patients with MAC achieved culture conversion without recurrence. Of the population that achieved culture conversion, 75% had stable lung function while 25% had decreased function. About 20% of patients with MAC did not have culture conversion at 12 months and subsequently developed refractory disease [33].

Management of *Mycobacterium kansasii* Pulmonary Infection

Mycobacterium kansasii has a drug susceptibility pattern that is closer to that of the *M. tuberculosis* complex than of most other NTM organisms [2, 34]. Although the organism is often susceptible to isoniazid, using a TB-like regimen including isoniazid often led to a suboptimal outcome before the development of rifampin [17]. Rifampin is now the key drug in the regimen with almost all isolates being susceptible initially. Ethambutol and the macrolide antibiotics also have good activity against *M. kansasii*.

The most commonly used initial regimens are rifampin and ethambutol with the addition of either isoniazid or a macrolide. There have been no randomized clinical trials directly comparing isoniazid and a macrolide as the third drug, but case series have demonstrated successful treatment with either drug. Although most isolates are also susceptible to amikacin and streptomycin, these drugs are not routinely recommended for therapy of pulmonary disease due to the need for parenteral administration and the higher rates of adverse effects. Similarly, *M. kansasii* is usually susceptible to fluoroquinolone antibiotics. This class is not recommended for routine treatment, but should be used when the isolate is rifampin-resistant or there is intolerance to one of the first-line antibiotics [17]. When isoniazid is used in the regimen, treatment should be given daily; treatment of non-cavitary disease can be treated three times weekly with a macrolide-containing regimen, but cavitary disease caused by *M. kansasii* should be treated daily with any regimen. Total treatment duration should be treated for at least 12 months.

Management of *Mycobacterium abscessus* Pulmonary Infection

Treatment of pulmonary infections caused by *M. abscessus* is particularly difficult due to increased rates of antibiotic resistance, inability of in vitro antibiotic susceptibility testing

to predict clinical success. adverse effects of the parenteral and oral antibiotics that must be used, antibiotic interactions with other medications, cost of available medications, and the often difficult accessibility of the medications through insurance and the Federal Drug Administration [35]. Slow response to therapy is typical and may be discouraging to patients, families and clinicians [36, 37]. The prognosis is often better for subspecies *massiliense* because of its susceptibility to macrolide antibiotics [38, 39]. Owing to the combination of these factors, approach to management of *M. abscessus* pulmonary infection should include shared decision-making among the patient, family, pulmonologist and infectious disease specialist. Elimination of the offending organisms is not possible in all cases. The goals of treatment should be discussed and may include any combination of improvement in symptoms, pulmonary function testing, radiographic findings or microbiologic burden [1, 37].

There have been no randomized clinical trials of any specific regimens for *M. abscessus* pulmonary infection, and the optimal drug combinations and length of therapy are unknown [17, 33]. The general approach to treatment includes an induction phase using 3 to 5 antibiotics simultaneously, including at least one administered intravenously, followed by a longer continuation phase using the best available oral antibiotics (Table 3). Common options for intravenous antibiotics include amikacin, imipenem, cefoxitin or tigecycline. Although the MIC for tigecycline is often low, it is less clear how effective it is within a multidrug regimen [17, 40]. The aim of the induction phase is to decrease the bacterial burden as rapidly as possible [1]. The induction regimen is continued for 3–12 weeks with duration primarily dependent on severity of illness and tolerance of antibiotics. Following the induction phase, a continuation regimen of at least 2 oral antibiotics and/or inhaled amikacin is initiated, usually for a full treatment duration of at least 12 months.

Oral antibiotics which have demonstrated in vitro activity against *M abscessus* and can be used in the induction and continuation phases include macrolides (if the isolate is susceptible), clofazimine, omadacycline, linezolid/tedizolid, and bedaquiline. The backbone of treatment in both phases should be the macrolide antibiotic unless drug resistance is demonstrated. Ciprofloxacin, minocycline and doxycycline have also been included in treatment regimens despite not demonstrating in vitro activity consistently [1]. In patients with *M. abscessus* strains with inducible or constitutional macrolide resistance, a macrolide is often still included in the treatment regimen for immunomodulatory effects; however, it should not be counted as an active drug in the regimen for *M. abscessus* [17, 41].

Macrolides and amikacin are the only antibiotics for which an association between in vitro susceptibilities and outcomes of treatment has been shown [17, 41]. As a result, treatment regimens often contain antibiotics that have intermediate susceptibility or even resistance in standard laboratory testing. Clofazimine, when obtainable, is an excellent oral option as it acts synergistically in vitro with amikacin and macrolides [17]. The in vitro activity of clofazimine is usually excellent, but it is unclear how effective it really is. It is unclear if the addition of clofazimine protects against the development of macrolide-resistant organisms [42, 43]. Clofazimine is not commercially available but can be obtained for eligible patients through the Novartis expanded access program, which first requires FDA approval with an IND application. The clinical situation is similar with omadacycline – low MICs but uncertain effectiveness - although there is some evidence that its inclusion in a multidrug regimen may improve functional outcomes [44–46].

Combination beta-lactam antibiotics have been explored in vitro to attempt to overcome the broad-spectrum chromosomal beta-lactamase produced by *M. abscessus* [47]. *M. abscessus* makes significant use of L, D-transpeptidases in peptidoglycan synthesis, which are inhibited by advanced cephalosporins and carbapenems. The combination of ceftaroline and imipenem has demonstrated a significant reduction in MICs [47]. Several case reports have described successful outcomes with this combination which may be used if more usual therapy is ineffective.

Table 3 General antibiotic approach to *M. abscessus* pulmonary infections

Initial Therapy		
Number of Drugs	Parenteral Drugs [1 to 3]	Oral/Inhaled Drugs [1 to 2]
≥ 3 [≥ 4 if macrolide resistant]	Amikacin Imipenem of cefoxitin Tigecycline	Azithromycin [if susceptible] Omadacycline[a] Clofazimine[b] Linezolid/Tedizolid Bedaquiline
Continuation Therapy		
≥ 2 [often 3]		Azithromycin [if susceptible] Omadacycline Clofazimine Linezolid/Tedizolid Bedaquiline Inhaled Amikacin[c]

a. Omadacycline is extremely expensive and not covered by all insurance plans

b. Clofazimine requires an FDA IND and communication with Novartis

c. May be inhaled parenteral formulation of amikacin or amikacin liposomal inhalation suspension [ALIS]

The optimal duration of antimicrobial therapy for pulmonary disease caused by *M. abscessus* is unknown and, in practice, depends on the goals of treatment [17]. Most patients receive greater than 12 months of antibiotics; however, even this duration does not always result in negative respiratory cultures. Occasionally, intermittent shorter courses of multi-drug regimens have been used after the induction phase but only scant data about the efficacy of this strategy have been published [17].

Phage therapy has been given to a handful of patients with *M. abscessus* pulmonary disease [48, 49]. About 40% of *M. abscessus* isolates have a smooth colony morphology for which no effective phages have been identified. However, about 80% of isolates with a rough colony morphology can be killed by at least one identified phage. In a series of 17 patients (15 with CF) with *M. abscessus* infection who failed usual antimicrobial therapy and then were treated with at least one phage: 7 had a favorable or partial response; 4 had a complex, inconclusive or incomplete response; and 4 had no clinical improvement [48]. This treatment modality is in its infancy, and can be considered only when no feasible alternatives are available.

Finally surgery has been used as adjunctive treatment in highly selected patients who have evidence of localized pulmonary disease caused by *M. abscessus* [50, 51]. In one series of 33 patients with *M. abscessus* pulmonary disease - limited disease in 54% and extensive disease in 46% – 22 had lobectomies, 5 segmentectomies, 4 combined resections, 2 bi-lobectomies and 1 pneumonectomy [51]. Post-operative sputum-negative status was achieved in 94% of the patients. However, all patients were adults and none had CF. Surgical experience with *M. abscessus* pulmonary infections in children and adolescents with CF is extremely limited.

Summary

Pulmonary infections caused by MAC and *M. abscessus* are among the most challenging facing patients with CF and their medical providers. While treatment of MAC infections is fairly standardized with oral drug regimens, albeit prolonged, and results are often favorable, treatment of *M. abscessus* infections is more challenging and not standardized owing to the lack of bactericidal drugs, variability of drug susceptibilities, inability of in vitro antibiotic susceptibility testing to predict clinical success (except for macrolides and amikacin), lack of randomized trial data to guide therapy, the usual need for initial parenteral therapy, initially higher rates of adverse reactions to the necessary medications, and high cost and limited availability of some of the drugs. The goals of NTM treatment for patients with CF should include shared decision making among the patient, family and clinicians, and often consider clinical, radiographic, microbiologic and pulmonary functional parameters to guide expectations.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare that they have no competing interests.

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