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Antibiotic Management of Lung Infections in Cystic Fibrosis: Part II. Nontuberculous Mycobacteria, Anaerobic Bacteria, and Fungi

James F. Chmiel¹, Timothy R. Aksamit², Sanjay H. Chotirmall³, Elliott C. Dasenbrook⁴, J. Stuart Elborn⁵, John J. LiPuma⁶, Sarath C. Ranganathan⁷, Valerie J. Waters⁸, Felix A. Ratjen⁹

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Key Words: Anaerobic bacteria, Aspergillus fumigatus, Candida albicans, Fungi, Mycobacterium abscessus, Mycobacterium avium complex, Nontuberculous mycobacteria, Scedosporium species complex

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Abstract

Airway infections are a key component of cystic fibrosis (CF) lung disease. While the approach to common pathogens such as Pseudomonas aeruginosa is guided by a significant body of evidence, other infections often pose a considerable challenge to treating physicians. In Part I of this series on the antibiotic management of difficult lung infections, we discussed bacterial organisms including MRSA, Gram-negative bacterial infections and treatment of multiple bacterial pathogens. Here, we summarize the approach to infections with nontuberculous mycobacteria, anaerobic bacteria and fungi.

Nontuberculous mycobacteria can significantly impact the course of lung disease in CF patients, but differentiation between colonization and infection is difficult clinically as co-infection with other micro-organisms is common. Treatment consists of different classes of antibiotics, varies in intensity, and is best guided by a team of specialized clinicians and microbiologists. The ability of anaerobic bacteria to contribute to CF lung disease is less clear, even though clinical relevance has been reported in individual patients. Anaerobes detected from CF sputum are often resistant to multiple drugs, and treatment has not yet been shown to positively affect patient outcome. Fungi have gained significant interest as potential CF pathogens in recent years. While the role of Candida is largely unclear, there is mounting evidence that Scedosporium species and Aspergillus fumigatus, beyond the classical presentation of allergic bronchopulmonary aspergillosis, can be relevant in CF patients and treatment should be considered. Currently, however there remains limited information on how best to select patients that could benefit from antifungal therapy.

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Introduction

Lung disease accounts for the majority of the morbidity and mortality in cystic fibrosis (CF) (1). Bacteria typically found in airway secretions of CF patients include *Staphylococcus aureus*, *Hemophilus influenzae*, *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and *Achromobacter* species (2). Many of these bacteria have been associated with a decline in lung function in CF (3-6). However, other microorganisms have been isolated from CF lung fluids in recent years including nontuberculous mycobacteria (NTM), anaerobic bacteria, and fungi. While the isolation of some of these microorganisms is temporally associated with deterioration in baseline health in some individuals, it is not clear whether they are relevant pathogens in all patients. Clinicians must discern how to proceed if one of these organisms is isolated in the absence of clinical manifestations, changes in lung function, or radiographic changes. In addition, the clinician must also balance the potential for development of toxicities from prescribed therapies with the possibility of beneficial effect.

Further complicating the decision whether treatment should be initiated is determining the best therapeutic regimen for the individual patient. These regimens may carry a large treatment burden and interfere with other therapies.

A scientific symposium was held at the 2013 American Thoracic Society (ATS) International Conference in Philadelphia, PA to discuss the management of difficult to treat lung infections in CF. From this symposium, two companion manuscripts were written to summarize the current evidence presented at that meeting. In Part I, the lung microbiome, methicillin-resistant *S. aureus*, Gram-negative bacteria, and treating multiple infections in CF were discussed (7). In this manuscript (Part II), NTM, anaerobic bacteria, and fungi are discussed. Practical treatment approaches are discussed in both manuscripts. These approaches summarize
the current evidence. However, it is imperative to recognize that these treatment approaches are evolving as the results of ongoing and future research studies become available. The reader should realize that these documents are not portrayed as guideline documents or consensus recommendations. The discussions contained within these manuscripts are not meant to represent the finish line for treating lung infections in CF but rather should be taken to represent the starting line.

**Nontuberculous Mycobacteria**

NTM lung infections are increasingly observed in the general population and in patients with CF (8). The incidence of NTM lung disease in patients with CF, which most often occurs in patients older than fifteen years and increases with age, has been estimated to be 13% - 20% (9-11). *Mycobacterium avium complex* (MAC) and *Mycobacterium abscessus* represent the two most common NTM species causing infection in CF. Accelerated loss of lung function has been observed in patients with *M. abscessus* (12). In patients with CF under evaluation for lung transplantation, up to 20% of patients were found to have NTM (13). *M. abscessus* in particular is associated with worse outcome and the need for NTM treatment post-transplant (13). As a result, many transplant centers now consider the presence of NTM lung disease a relative contraindication for transplantation (13).

NTM is ubiquitous in water and soil, and can frequently be isolated from residential sources including shower heads and other home water sources (14-16). Peat moss exposure in some studies has been identified as a potential exposure risk for NTM lung disease (14, 17, 18). However, case-control studies have not clearly demonstrated an association between exposure to residential water sources or other activities including gardening and NTM lung disease (19).
Furthermore, patient NTM isolates do not always match environmental NTM isolates, matching in 22% - 41% of cases when the same MAC species were isolated (14, 16). Nonetheless, certain environmental precautions may reduce exposure. Simple environmental controls implemented at home that may reduce exposure to NTM include increasing the temperature of hot water heaters to greater than 130°F, installing large droplet shower heads to reduce aerosolization, avoiding tap water rinses of equipment and avoiding tap water mouth rinses prior to sputum collection, and avoiding peat moss dust exposure by wearing a facemask and moistening the soil prior to working with it (18, 20). It is not clear, however, whether these risk modifications impact the development of NTM lung disease. Recent reports of the transmissibility of *M. abscessus* species in two outpatient CF clinics is worth noting given the previous experience of lack of human to human transmissibility of NTM lung disease (21, 22). Although both reports describe the transmissibility of *M. abscessus ssp. massiliense*, it is unclear as to whether the risk of transmission is restricted to only this subspecies or whether it may be generalized to all *M. abscessus* or even other NTM isolates. Therefore, close collaboration with the infection control team and abiding by infection control procedures in CF and bronchiectasis clinics, including respiratory isolation for patients with *M. abscessus* is warranted in outpatient as well as inpatient settings to prevent transmission of *M. abscessus* in high risk situations.

The diagnosis of NTM lung disease is based on criteria outlined by the ATS including a combination of clinical, radiographic, and microbiologic elements (9). It is worth noting that in most circumstances and for most NTM respiratory isolates (especially MAC), one positive culture, especially with low numbers of organisms, smear negative, or growth on liquid media only, is not adequate for establishing a diagnosis of NTM lung disease. A presumptive diagnosis based on clinical and radiographic features is equally inappropriate for the initiation of empiric
therapy. As such, longitudinal monitoring and multiple cultures may be required before a
diagnosis of NTM lung disease is firmly established. Further contributing to this conundrum is
the well-recognized waxing and waning of radiographic abnormalities, without overall
radiographic progression, that is known to occur in patients with NTM lung disease regardless of
treatment status. Establishing a more certain diagnosis prior to committing to treatment of NTM
lung disease is thus required. Over-diagnosis results in the unnecessary exposure to complicated
drug regimens, and under-diagnosis may result in the development of progressive lung disease
with irreversible loss of lung function from inadequate treatment.

The decision regarding whether to treat NTM lung disease must therefore balance the
risks and benefits of treatment versus observation. Individualized patient factors include the risk
of progression, goals of therapy (sputum conversion versus suppression), status of co-morbid
medical conditions (gastroesophageal reflux, sinus disease, and bronchiectasis), medication
tolerance, and patient acceptance (Fig. 1). Similarly, the intensity of the NTM regimen should
be proportionate to disease severity and goals of therapy. In the case of MAC lung disease, the
treatment options range from observation to thrice weekly oral therapy to daily therapy plus
parenteral therapy. Special attention regarding macrolide use for anti-inflammatory purposes is
warranted to avoid the development of resistance in macrolide susceptible NTM lung disease
(23-27). Recent CF guidelines have re-affirmed the need to screen patients at baseline and then
every six to twelve months (28). This recommendation has not changed despite preliminary
recent data not finding increased macrolide resistance in CF patients with NTM infections
receiving chronic macrolide therapy (29).

Specific treatment regimens for NTM lung disease are outlined in the ATS Statement (9).
While these recommendations remain appropriate for treating MAC lung disease, the use of
nebulized amikacin and increased understanding of the various treatment approaches for *M. abscessus* lung disease warrants special comment. Inhaled amikacin has been increasingly used for the treatment of both MAC and *M. abscessus* lung disease despite limited published clinical experience (30-32). Dosing of nebulized amikacin is variable but most often ranges between 250 mg to 500 mg once or twice daily. Higher dosing is generally less well tolerated (32). Results from a recently completed phase II study of liposomal amikacin for refractory NTM lung disease are expected to be released soon. The use of nebulized amikacin when treating NTM lung disease should be considered as part of a multidrug mycobacterial regimen.

The recent recognition of a variably expressed erythromycin ribosomal methylolation (*erm*) gene in *M. abscessus* has been associated with variable clinical response to macrolide-based regimens for *M. abscessus* (33-35). This may also explain some of the apparent macrolide resistance in other NTM organisms such as *M. fortuitum*. This is in contrast to *M. chelonae* which does not express an active *erm* gene. The *erm* gene encodes for enzymes that methylate the 23S ribosomal RNA within the 50S ribosomal subunit, resulting in reduced binding affinity of macrolides for their specific target, to impair protein synthesis. The additional importance of the presence or absence of an active *erm* gene is highlighted by the difference between *M. abscessus* subspecies. *M. abscessus* ssp *abscessus* has universal expression of an active *erm* gene conferring macrolide resistance whereas other *M. abscessus* subspecies, such as *M. abscessus* ssp *bolletii* also known as *M. massiliense*, does not express an active *erm* gene. It is important to note, however, that even in the absence of the *erm* gene, NTM species may be resistant to macrolides through other mechanisms. Expression of the *erm* gene can be variable; there is some data to suggest that clarithromycin induces greater expression of the gene than does azithromycin (34). The inclusion of a macrolide in treatment regimens for *M. abscessus* lung
disease thus relies heavily on the presence or absence of an active \textit{erm} gene or, as a surrogate, 
differentiation of \textit{M. abscessus} ssp \textit{abscessus} from \textit{M. abscessus} ssp \textit{bolletii} (\textit{M. massiliense}). 
Initial \textit{M. abscessus} isolates should be incubated with macrolide for 14 days prior to a 
determination of macrolide susceptibility and by inference, the presence or absence of an active 
\textit{erm} gene. Other potential mechanisms of drug resistance have been described, but the clinical 
significance of these require further study (36). Thus, the approach to the treatment of \textit{M.} 
\textit{abscessus} ssp \textit{abscessus} lung disease most often involves a regimen including other non-
macrolide agents, such as amikacin with a combination of two or more additional antibiotics 
including cefoxitin or imipenem, tigecycline, or linezolid. In the absence of inducible macrolide 
resistance or an active \textit{erm} gene, regimens for \textit{M. abscessus} ssp \textit{bolletii} (\textit{M. massiliense}) should 
include clarithromycin or azithromycin in addition to multiple other antibiotics. A typical 
practice pattern, even without clear supporting data in the literature, is to begin with an intensive 
treatment regimen including both parenteral and oral agents followed by de-escalation to an 
iinhaled and oral regimen after a period of weeks or months. The timing and specifics of this 
transition can be particularly variable given the essential need to avoid monotherapy and to 
maintain a multidrug regimen with effective non-parenteral agents; the efficacy of which must be 
weighed against the risks of toxicity and the technical challenges of extended use of parenteral 
agents. Consultation with a pulmonary disease, infectious disease, and/or NTM expert is 
generally recommended. Common treatment regimens for NTM lung disease are given in the 
\textbf{Table}. Surgical resection in conjunction with medical therapy should be considered for 
localized cavitary NTM lung disease, macrolide resistant MAC lung disease, and \textit{M. abscessus} 
ssp \textit{abscessus} lung disease in highly selected patients. Surgery, when considered, should be
undertaken by an experienced team of mycobacterial physicians including surgeons with robust experience in mycobacterial lung surgery.

In summary, NTM lung disease in patients with CF presents variably and remains a complex problem with respect to establishing a diagnosis and treatment program when indicated. Longitudinal follow up may be required before specific treatment recommendations can be made. CF patients with NTM lung disease are best cared for by teams of clinicians experienced in the care of patients with mycobacterial infections who work closely with their laboratory colleagues to optimize the timing and intensity of multidrug mycobacterial lung disease treatment regimens, carefully weighing risks and benefits and, when necessary, also considering surgical intervention.

## Anaerobic Bacteria

Anaerobes are organisms that do not require oxygen for growth. They can be obligate or facultative; *P. aeruginosa* is an example of the latter. In this state, *P. aeruginosa* exists as a slow-growing organism that is relatively resistant to antibiotics. Obligate anaerobes have been implicated in a number of non-CF infections, such as infections of the upper respiratory tract and aspiration pneumonia. Steep oxygen gradients exist within CF mucus such that even at relatively shallow depths within mucus, the environment is considered to be hypoxic, or even frankly anaerobic (37). Conventional culture-dependent approaches are not optimized for identifying anaerobes. Specific anaerobic culture methods, or culture-independent techniques, may be more appropriate. Several studies on tracheal aspirates, sputum or bronchoalveolar lavage (BAL) fluid have confirmed the presence of anaerobes in the lower airways in CF in up to 80% samples and at bacterial densities of between $10^7$ and $10^9$ colony forming units/mL in sputum (38–43). The
most common genera identified were *Prevotella, Veillonella, Propionibacterium, Actinomyces, Staphylococcus saccharolyticus, Peptostreptococcus* and *Clostridium*. (44). Using terminal restriction fragment length polymorphism, Rogers and colleagues (45) identified differences between paired mouthwash and sputum samples obtained from subjects with CF, both in the bands identified and the band volume, suggesting that the finding of anaerobes in the lower airways is not explained by aspiration of the oral anaerobiota.

Although the inflammatory response to individual aerobic organisms identified in BAL fluid from infants and young children with CF has been described (46), no such data linking anaerobes to inflammation or clinical outcomes are available. Studies in younger subjects might help to elucidate the role of anaerobes in disease pathogenesis and whether or not their presence in the lower airways represents an epiphenomenon (47). Existing studies are in older subjects who have therefore experienced a more complex infection history. Longitudinal studies are also lacking, although a comprehensive longitudinal study conducted in a single patient suggested that anaerobes of the *Streptococcus milleri* group contributed to the development of pulmonary exacerbations (48). Ulrich and colleagues reported that 16/17 patients with CF produced antibodies against two immunoreactive antigens of *P. intermedia* compared with 0/30 controls (49), suggesting that anaerobes are, indeed, immunogenic in CF. Culture supernatant fluid of *P. intermedia* was also cytotoxic to respiratory epithelial cell lines, associated with neutrophil and macrophage recruitment into lung tissue in mice, and cytotoxic to human-derived neutrophils. Its pathogenicity is estimated at being intermediate between that of aerobic and anaerobic *P. aeruginosa*. In studies where anaerobes were specifically targeted during treatment for pulmonary exacerbations, the results have been conflicting. Worlitzsch and colleagues (43) did not identify any significant reduction in the density of anaerobes in sputum after treatment with
antibiotics despite an increase in pulmonary function during the period of treatment. Similarly, Tunney and colleagues identified only limited reduction in the density of anaerobes at the end of two-weeks of treatment (50). An important factor to consider when treating anaerobic infections is that anaerobic organisms are often resistant to the commonly administered antibiotics. For example, resistance to metronidazole was reported to occur in nearly all Peptostreptococci and Streptococci species, whereas resistance to meropenem is more rare (44). Although meropenem is commonly included in CF antibiotic protocols as a second- or third-line intravenous drug in the treatment of pulmonary exacerbations, it remains unclear whether any clinical improvements associated with its administration are related directly to its targeting of anaerobes.

Data from culture-based studies, and more recently from studies utilizing culture-independent techniques, therefore indicate that anaerobes are prevalent in the lower airways of people with CF but whether these organisms play a part in the pathophysiology of progressive lung damage remains unknown. How anaerobes interact with the microbiota of the lower airways and other CF organisms also requires study. Resistance in vitro is common, meaning that antibiotics usually considered for the treatment of anaerobes may not be effective. Anaerobes appear to play a role in CF lung disease, but this requires clarification before the targeting of obligate anaerobes in the treatment of CF lung infections becomes routine.

**Fungi**

Patients with CF are at increased risks of fungal colonization owing to impaired mucus clearance, local immunogenic dysfunction and antibiotic use. While CF lung disease is classically dominated by bacteria, fungal isolates are increasingly described because the respiratory tract anatomically communicates with the atmosphere, a rich source of airborne
fungal spores. Inability to clear such inhaled particles results in their persistence, colonization, and potential airway infection. This spectrum of clinical consequences combined with enhanced detection methods makes it probable that we have thus far underestimated fungal prevalence and importance in clinical practice over the last decade of CF care (51-58).

While vast arrays of fungal species are described in CF, methods used for their isolation primarily dictate the species and populations detected. Although traditional methodologies of fungal culture remain, emerging molecular techniques and genotyping provide greater sensitivity. Despite fungal biodiversity (Fig. 2), the major clinical challenges are caused by *Aspergillus fumigatus* (59, 60), *Candida albicans* (61, 62), and *Scedosporium* species complex. Clinicians are often left wondering about the significance of isolating fungi from a patient with CF and whether treatment is indicated.

*A. fumigatus* is detected in sputum in approximately 30% of patients with CF. Allergic bronchopulmonary aspergillosis (ABPA) remains a key consequence, but sputum isolation does not correlate with ABPA occurrence (63). The difficulty in diagnosis of ABPA exists due to overlapping clinical, radiological, immunological and microbiological features similar to that of an infective exacerbation in CF (63, 64). To address this, biomarkers such as recombinant *Aspergillus* antigens, precipitins, anti-*Aspergillus* IgG, thymus activation and regulated chemokine (TARC), and the basophil surface marker CD203c have been proposed, but pose difficulties due to their variability and lack of sensitivity, standardization, and accessibility (65).

In acute ABPA, corticosteroids suppress the inflammatory response. One treatment protocol employed includes prednisone at 40mg once daily for two weeks with taper over three months tailored to clinical symptoms, lung function and total serum IgE concentration. Concerns over side effects of long-term steroid administration has prompted use of alternative regimes such as
high-dose methylprednisolone (10-15mg/kg) daily for three days monthly for up to ten months (66). Anti-fungal therapy may be concurrently administered. However, no randomized controlled trials to date support use in CF-ABPA (67). Itraconazole is preferred with a favorable side effect profile, but it does possess variable absorption and food interactions necessitating close serum monitoring. In addition, the development of azole resistance remains a concern (68). Voriconazole is an alternative drug option but has significant associated photosensitivity especially in patients with CF (69). Steroid-resistant cases may necessitate anti-fungal therapy or administration of an anti-IgE monoclonal antibody, but existing evidence is limited to case series reports (70).

Clinically distinct from ABPA, Aspergillus-sensitization independently affects pulmonary function, however the mechanism through which it does so remains unclear (71). Allergic sensitization does not correlate with sputum detection of Aspergillus. Unlike Candida sensitization, Aspergillus sensitization is associated with greater lung function decline and pulmonary exacerbations (72). The presence of severe CF mutations, mild lung disease (FEV1>70%), absence of Pseudomonas and prior azithromycin exposure all remain predictive for Aspergillus sensitization (73). Recently, a novel immunological classification for CF aspergillosis was proposed. Based on serum IgE and IgG concentrations combined with sputum galactomannan and the presence of PCR detectable Aspergillus, four distinct sub-groups are defined. These include ABPA, Aspergillus-sensitized, Aspergillus bronchitis, and those without disease. Improved classification and definition can assist with clinical phenotyping and may impact future treatment decisions in Aspergillus-associated CF disease (74).

Controversy persists over the significance of non-ABPA Aspergillus colonization. It is often associated with worse radiologic findings and is an independent risk factor for
hospitalization (75, 76). Itraconazole treatment reduces the burden of Aspergillus, attenuates radiological mosaic perfusion, reduces exacerbations, and stabilizes pulmonary function in this setting (77). Such effects are mediated by down-regulation of the vitamin D receptor (VDR) through the virulence factor gliotoxin. Itraconazole treatment has been shown to decrease BAL gliotoxin concentrations and restore VDR expression with concomitant reduction in Th2 cytokines IL-5 and IL-13, drivers of ABPA (77). Despite these findings, a double-blind, placebo-controlled trial failed to demonstrate clinical benefit, but treatment efficacy may have been impacted by failing to achieve therapeutic itraconazole concentrations in a significant proportion of patients (78). Further study in this area is warranted before treatment recommendations can be issued (if necessary) for the non-ABPA Aspergillus colonized population.

*C. albicans* is capable of causing oral and genital candidiasis and vascular device infections in CF (62, 79). It is frequently isolated from CF sputum. Patients with CF are at increased risk of pulmonary colonization due to inhaled steroid use, CF-related diabetes, and lifelong antibiotic exposure. A prospective longitudinal study showed high (49.4%) colonization rates best predicted by pancreatic insufficiency, osteopenia and co-colonization with *P.* aeruginosa, all features of advanced disease (61). Colonization presaged increases in hospitalizations for exacerbations and longitudinal declines in BMI and FEV$_1$ (61). At present, its clinical role (if any) is unclear, and there is no evidence to suggest treatment benefit.

The *Scedosporium* species complex are chronic colonizers and emerging pathogens in CF (80, 81). A major risk exposure includes potted plants. However, they also have an environmental presence (82, 83). Colonization is not associated with FEV$_1$ or steroid or anti-fungal use. Interestingly, those harboring the fungus are less likely to be colonized with *P. aeruginosa* (84). Discordance between relatively high isolation frequency (6.5-10%) and low
environmental abundance prompts questions about how initial acquisition actually occurs in CF (80, 81). Genotype analysis of sequential isolates demonstrates that individual patients are colonized by unique phenotypes that remain conserved over time (85). Clinical consequences include allergic responses and risk of dissemination in immunocompromised hosts (86). Eradication remains difficult once colonization is established with voriconazole the agent of choice.

While our knowledge regarding the role of fungi in CF is improving, many questions remain. Are certain fungi pathogenic and if so what mechanisms do they use? When do they become pathogenic? Are they pathogenic from the time they enter into the airway or only after a certain time of colonization and sensitization? Does clinical setting matter? Should attempts be made to eradicate them? If so when, with what drugs, and for how long? These are all valid questions, which are difficult to answer based on existing data (60).

There is limited knowledge regarding treatment approaches for fungi in CF. *A. fumigatus* is commonly detected in the CF airway. It is a proven fungal pathogen in CF-ABPA. Sputum isolation is discordant with ABPA occurrence thereby making diagnosis difficult. Treatment should always be pursued in CF-ABPA. However it remains controversial in the non-ABPA *Aspergillus* colonized patient. There is no evidence that *C. albicans* isolated from CF sputum should be treated because its pathological significance in the airway is unknown. No current evidence exists to suggest treatment benefit in this context. However, when *C. albicans* causes mucosal or vascular device infection, prompt treatment is indicated. Infection rates with *Scedosporium* species are underestimated due to difficulties with diagnosis as this mold’s clinical, radiological and pathological appearance is similar to *Aspergillus*. Such misdiagnosis may be lethal considering that *Scedosporium* is almost always resistant to amphotericin B, the
agent frequently used in presumptive *Aspergillus* infection. Consequently, eradication should be attempted at first isolation in view of its potentially devastating clinical consequences if misdiagnosed or allowed to persist long term.

Summary

For decades, clinicians have been treating a narrow array of bacteria that infect the CF airway (2). Under selective pressure of frequent antibiotic use and with improved techniques to identify microorganisms, that array is expanding. Physicians must treat not only the classic pathogens associated with CF, such as *S. aureus* and *P. aeruginosa*, they may also have to treat other microorganisms like NTM, anaerobic bacteria, and fungi. Less evidence regarding treatment of these organisms is available than the typical bacteria known to infect the CF airway. These organisms often grow slowly, if at all, on typical microbiological cultures. However, when a new organism is identified, CF clinicians are often left wondering about the pathologic significance of this new finding. Furthermore, determining a treatment regimen is often frustrating to even the most experienced individual. The airway environment in CF is continually evolving. Niches are being created which will allow new potential pathogens to gain a foothold in the CF airway. Therefore, clinicians must be constantly vigilant for the emergence of new microorganisms infecting the CF airway, and researchers must be prepared to develop novel antimicrobial therapies to treat these infections.
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27


Guarro J, Kantarcioglu AS, Horre R, Rodriguez-Tudela JL, Cuenca Estrella M,

Figure Legends

Figure 1. Determining treatment of NTM lung disease requires assessment of diagnostic strategies, treatment options, and individualized risk-benefit analyses. When deciding whether to treat a patient with NTM lung disease, the risk and benefits of treatment must be weighed against observation. This decision is influenced by many factors including the risk of progression, goals of therapy, and patient factors.

Figure 2: Cystic fibrosis fungal biodiversity grouped according to frequency of isolation (x-axis) and established pathogenicity (y-axis). The fungi are further divided in terms of chronicity as illustrated. The most frequently isolated filamentous fungi *Aspergillus fumigatus* and *Scedosporium* species complex and yeast *Candida albicans* are highlighted and further discussed in this manuscript.
### Table.° Empiric antibiotic therapy for the treatment for nontuberculous mycobacteria lung infections in CF

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<tr>
<td><strong>Mycobacterium abscessus</strong></td>
<td>Clarithromycin or azithromycin†</td>
<td>Clarithromycin15 mg/kg orally (max 500 mg) twice daily or azithromycin 5 mg/kg/d (max 250 mg)</td>
<td>Clarithromycin 500 mg orally twice daily or azithromycin 250 - 500 mg orally daily</td>
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<td>PLUS: Amikacin**</td>
<td>10 - 30 mg/kg intravenously daily or 25 - 30 mg/kg thrice weekly followed by 250 - 500 mg nebulized daily to twice daily</td>
<td>10 - 30 mg/kg intravenously daily or 25 - 30 mg/kg thrice weekly followed by 250 - 500 mg nebulized daily to twice daily</td>
<td>-Ototoxicity, nephrotoxicity</td>
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<td>AND Cefoxitin</td>
<td>200 - 250 mg/kg/day in divided doses (max 12 gm)</td>
<td>200 – 250 mg/kg/d in divided doses (max 12 gm)</td>
<td>-GI, rash, myelosuppression</td>
</tr>
<tr>
<td></td>
<td>OR Imipenem</td>
<td>60 – 100 mg/kg/d intravenously divided doses (max 2 gm)</td>
<td>1 – 2 gm intravenously divided doses</td>
<td>-GI, rash, myelosuppression, rarely seizures</td>
</tr>
<tr>
<td></td>
<td>OR Tigecycline</td>
<td>1.2 mg/kg intravenously every 12h (max 50 mg)</td>
<td>25 - 50 mg daily intravenously</td>
<td>-GI, cholestasis, myelosuppression</td>
</tr>
<tr>
<td></td>
<td>OR Linezolid (include pyridoxine 50 mg daily)</td>
<td>if &lt;11yrs: 10 mg/kg intravenously or orally every 8h if &gt;11yrs: 10 mg/kg (max 600 mg) intravenously or orally daily to twice daily</td>
<td>300 - 600 mg intravenously or orally daily to twice daily</td>
<td>-Optic/peripheral neuropathy, myelosuppression</td>
</tr>
<tr>
<td><strong>Mycobacterium avium complex</strong></td>
<td>Clarithromycin or azithromycin</td>
<td>Clarithromycin 15 mg/kg orally (max 500 mg) twice daily or azithromycin 5 mg/kg/d (max 250 mg)</td>
<td>Clarithromycin 500 mg orally twice daily or azithromycin 250 - 500 mg orally daily</td>
<td>-GI, ototoxicity</td>
</tr>
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</tr>
<tr>
<td>PLUS: Rifampin</td>
<td>10-20 mg/kg orally once daily (max 600 mg)</td>
<td>450 - 600 mg orally once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AND Ethambutol</td>
<td>15 mg/kg orally once daily</td>
<td>15 mg/kg orally once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLUS for ADVANCED DISEASE: Amikacin**</td>
<td>10 - 30 mg/kg intravenously daily or 25 - 30 mg/kg thrice weekly followed by 250 - 500 mg nebulized daily to twice daily</td>
<td>10 - 30 mg/kg intravenously daily or 25 - 30 mg/kg thrice weekly followed by 250 - 500 mg nebulized daily to twice daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GI: gastrointestinal

§The antibiotic doses given in this table come from a compilation of sources and practice patterns including commonly prescribed off-label doses and uses. Sources include the pharmacy formulary of The Hospital for Sick Children in Toronto, ON, which is based upon product inserts and the published literature. The doses given are general guidelines, and may vary somewhat between institutions. It is recommended that the clinician consult his/her institution's pharmacy, product inserts, and published literature before prescribing these drugs. Consultation with a pulmonary disease, infectious disease and/or NTM expert to individualize treatment regimens is recommended.

†Consider alternative antibiotic if erm gene (encoding for inducible macrolide resistance) detected or inducible macrolide resistance noted.

**Serum concentrations should be monitored and aim for a maximum serum concentration (Cmax) in the range of 80–120 mg/L with a minimum serum concentration (Cmin) of <1 mg/L. Alternatively, peak levels may also be used with a target peak serum level between 20 and 40–35 ug/mL. It is known that CF patients generally have an increased volume of distribution and more rapid clearance which may require higher dosing than others without CF.
Figures

Fig. 1

Diagnosis +/− Treatment

• Disease severity (risk of progression)
• Goals (sputum conversion vs. suppression)
• Co-morbid conditions
  • Gastroesophageal reflux disease
  • Sinus disease
  • Bronchiectasis
• Medication tolerance
• Patient acceptance
• Cost
Fig. 2

Pathogenicity established

Aspergillus fumigatus

Scedosporium species complex
(S. apiospermum, P. boydii, S. aurantiacum,
  P. minutispora)

T. mycotoxinivorans
E. dermatitidis
A. terreus
S. prolificans
C. dubliniensis

Pathogenicity still unknown

Low Chronicity

Candida albicans

A. flavus
A. nidauls
A. niger
A. Fusispora
N. pseudofischeri
C. bracarensis, C. nivariensis
C. metapsilosis, C. orthopsilosis

High Chronicity