Antibiotic Management of Lung Infections in Cystic Fibrosis

I. The Microbiome, Methicillin-Resistant *Staphylococcus aureus*, Gram-Negative Bacteria, and Multiple Infections

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Abstract

Despite significant advances in treatment strategies targeting the underlying defect in cystic fibrosis (CF), airway infection remains an important cause of lung disease. In this two-part series, we review recent evidence related to the complexity of CF airway infection, explore data suggesting the relevance of individual microbial species, and discuss current and future treatment options. In Part I, the evidence with respect to the spectrum of bacteria present in the CF airway, known as the lung microbiome is discussed. Subsequently, the current approach to treat methicillin-resistant *Staphylococcus aureus*, gram-negative bacteria, as well as multiple coinfections is reviewed. Newer molecular techniques have demonstrated that the airway microbiome consists of a large number of microbes, and the balance between microbes, rather than the mere presence of a single species, may be relevant for disease pathophysiology. A better understanding of this complex environment could help define optimal treatment regimens that target pathogens without affecting others. Although relevance of these organisms is unclear, the pathologic consequences of methicillin-resistant *S. aureus* infection in patients with CF have been recently determined. New strategies for eradication and treatment of both acute and chronic infections are discussed. *Pseudomonas aeruginosa* plays a prominent role in CF lung disease, but many other nonfermenting gram-negative bacteria are also found in the CF airway. Many new inhaled antibiotics specifically targeting *P. aeruginosa* have become available with the hope that they will improve the quality of life for patients. Part I concludes with a discussion of how best to treat patients with multiple coinfections.

Keywords: *Burkholderia cepacia*; methicillin-resistant *Staphylococcus aureus*; microbiome; *Pseudomonas aeruginosa*; *Stenotrophomonas maltophilia*

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Cystic fibrosis (CF) lung disease is characterized by airway obstruction, chronic bacterial infection, and a vigorous host inflammatory response (1). Antibiotic therapy of bacterial lung infections has tremendously contributed to the increased survival in CF (2). However, many bacteria form biofilms in the CF lung that make their eradication difficult (3). In addition, it has also become clear that only a small fraction of the microbes present in the CF airway are being identified with routine laboratory techniques (4, 5), and both extended culture methods and molecular techniques have identified organisms that

previously were not routinely cultured (6). Traditional antibiotic susceptibility testing performed on planktonic bacteria has been found to be of limited clinical use in chronic airway infection as most bacteria in the CF lung exist in biofilms (7). Although it has long been recognized that patients clinically respond even when their infecting organisms are pan-resistant, 25% of patients do not reach preexacerbation values in lung function measures despite aggressive treatment for their bacterial lung infections (8), demonstrating that current treatment is inadequate when addressing the complexity of airway infection. In addition to bacteria identified by routine sputum culture methods, clinicians are often faced with an array of multidrug-resistant organisms that are difficult to treat.

In this article and its companion article, we provide a summary of current aspects of airway infection in CF. These manuscripts are derived from a symposium organized by the Scientific Assemblies on Pediatrics and Clinical Problems and presented at the 2013 American Thoracic Society (ATS) International Conference in Philadelphia, Pennsylvania. In Part I, we discuss the lung microbiome in CF, methicillin-resistant *Staphylococcus aureus* (MRSA), gram-negative bacteria, and approaches to treating multiple infections. In Part II, we discuss nontuberculous mycobacteria, anaerobic bacteria, and fungi. The current evidence for treatment of these lung infections in CF, which we summarized, is limited. Within these documents, we also provide a pragmatic approach as to how one might treat these infections. However, it is important to note that these manuscripts are not meant to represent definitive treatment guidelines or consensus recommendations. For available guideline recommendations, the reader is referred elsewhere in the published literature (9–13).

The Lung Microbiome in CF

The conventional view of CF airway microbiology has been based on the recovery in culture of a suite of bacterial pathogens, including *S. aureus* and opportunists such as *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Achromobacter* spp., and *Stenotrophomonas maltophilia*. The Human Microbiome Project, a National Institutes of Health–sponsored initiative launched in 2007, applying culture-independent methods to assess bacterial ecology, has significantly broadened this view. Numerous studies now provide compelling evidence that the airways of persons with CF may be inhabited by diverse bacterial communities composed of dozens of species (14–23). In addition to "typical" CF pathogens, "nonpathogenic oral bacteria," including many obligate and facultative anaerobic species, are often present in densities that well exceed those of the traditional opportunists associated with CF (4). Although most of these studies analyzed expectorated sputum samples that would be expected to be "contaminated" with bacteria residing in the nonsterile oropharynx during expectoration, several lines of evidence indicate that this has only a marginal impact on measures of airway microbiota (17, 24, 25).

Limited studies of children with CF indicate that bacterial community diversity (a measure of both the number and relative abundances of the species present) increases with age (14, 26). In contrast, several cross-sectional and longitudinal studies of adults have shown that diversity decreases with age and declining lung function (14, 18, 22, 23). Analyses of respiratory specimens from persons with end-stage lung disease or from lung explants show very constrained communities, often limited to a single dominant species (23, 27). These observations suggest that after an initial increase during childhood, airway bacterial diversity peaks in young adulthood and then declines with advancing age and disease progression (Figure 1). Antibiotic use may be the primary driver of decreasing diversity with advancing disease (23).

The change in the airway microbiota around the time of exacerbations of pulmonary symptoms is an area of intense interest. Fodor and colleagues (15) showed that bacterial community richness decreased transiently with antibiotic therapy but rebounded quickly thereafter. Zhao and colleagues (23) similarly showed a significant decrease in diversity with antibiotic therapy of exacerbation but did not find significant changes in diversity when comparing samples from periods of clinical stability to those taken at the onset of exacerbation symptoms, a finding that was subsequently confirmed in a larger study (28). Interestingly, this latter study showed a decrease in the relative and absolute abundance of *P. aeruginosa* in communities dominated by this species at the onset of symptoms leading to exacerbation.

Thus, our traditional view of CF airway microbiology is changing. Although bacterial communities likely become more diverse during childhood, they become increasing confined with advancing lung disease and antibiotic treatment in adulthood. Eventually, a single species representing one of the traditional CF pathogens (*S. aureus*, *P. aeruginosa*, *B. cepacia* complex, or *Achromobacter* spp.) dominates the community. Despite this dramatic decrease in diversity, total bacterial density appears to remain rather constant. The dynamics of bacterial communities around the time of exacerbation suggest that the dominant pathogen in the community

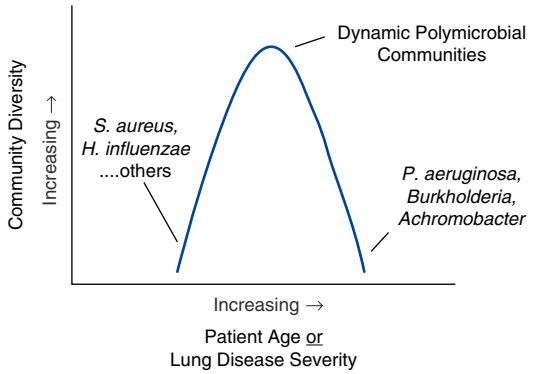

Figure 1. Schematic representation of airway bacterial community diversity versus patient age or lung disease severity. Available data suggest that after an initial increase during childhood, airway bacterial diversity peaks in young adulthood and then declines with advancing age and lung disease progression. At end-stage disease, bacterial communities may be dominated by a single species, most often a "typical" cystic fibrosis opportunistic pathogen. *H. influenza* = *Haemophilus influenzae*; *P. aeruginosa* = *Pseudomonas aeruginosa*; *S. aureus* = *Staphylococcus aureus*.

may decrease with onset of symptoms. As our understanding of the dynamics of airway bacterial ecology continues to expand, so too will the opportunities to develop novel strategies to better manage airway infection in CF.

Methicillin-resistant *Staphylococcus aureus*

The prevalence of MRSA has increased dramatically over the last decade and now is detected in the respiratory tract of greater than 25% of patients with CF in the United States (29). The prevalence of MRSA in Canada and Europe is lower, ranging from 3 to 11% of patients with CF (30). Chronic MRSA infection in patients with CF is associated with increased rate of lung function decline, failure to recover lung function after a pulmonary exacerbation, and decreased survival (8, 31, 32). Currently, there are no conclusive studies demonstrating an effective and safe treatment protocol for MRSA respiratory infection in CF (33). Here, we provide a practical framework on how to treat MRSA infection in different clinical scenarios by first describing antibiotic choices and then subsequently provide guidance for defining patients that require treatment.

In patients with CF infected with MRSA who are experiencing an acute pulmonary exacerbation, vancomycin and linezolid are the first-line antimicrobial choices (34, 35). Dosing of vancomycin is based on the patient's weight and creatinine clearance. A trough concentration of 15 to 20 μg/ml, which is the practice of most CF physicians based on a recent survey (36), should be the considered target. Linezolid dosing may need adjustment in children with CF (37) but not adults (38). Because approximately 80% of patients with CF with chronic MRSA may also be infected with *P. aeruginosa*, linezolid, rather than vancomycin with its associated renal effects, may be a good option in these patients who require antipseudomonal treatment with other nephrotoxic drugs, such as aminoglycosides. As depression is detected in greater than 20% of adults with CF (29), it is important to note that linezolid can be associated with the serotonin syndrome in patients with CF taking serotonergic psychiatric drugs (39). Chronic linezolid use may also be associated with the development of potentially irreversible peripheral and optic neuropathies and linezolid-resistant MRSA (40). In patients with allergies or contraindications to the above medications, alternative antibiotics include rifampin, Fucidin (not available in the United States), ceftaroline, tigecycline, chloramphenicol, and/or clindamycin.

The approach to patients with CF with MRSA infection seen in the outpatient clinic has recently been reviewed (30). Doe and colleagues (41) reported that patient segregation and aggressive antibiotic eradication therapy can achieve eradication in the majority of patients with CF. Numerous antibiotic regimens were used; however, the most successful were those regimens that included two oral antibiotics (one of which was rifampin) and nebulized vancomycin. Rifampin has been a component of successful MRSA eradication protocols due to its high mucosal concentrations and activity against biofilms, but it should be used in combination with another antibiotic as resistance develops quickly with monotherapy (30). Rifampin can also be associated with worsening gastroesophageal reflux and decreased efficacy of oral contraceptives (42).

Inhaled antibiotics have been used as a treatment for CF respiratory tract infections since penicillin first became available (43). Fosfomycin tobramycin (FTI) for inhalation has activity against anaerobic, gram-negative, and gram-positive bacteria, including MRSA. In a clinical trial of FTI in patients with CF with *P. aeruginosa* infection, 29 patients with MRSA at baseline had significant decreases in the concentration of MRSA after 28 days of FTI (n = 19) compared with placebo (n = 10) (44). Current published experience with aerosolized vancomycin suggests that it is safe and well tolerated (45, 46). There are two ongoing studies investigating the use of inhaled vancomycin, including one assessing a novel dry powder formulation (47, 48). The results of these trials will help to delineate the risks and benefits of treating chronic MRSA infection.

Because there are no definitive studies to guide the decision to treat (or not to treat) MRSA infections in CF, the following approach is based on uncontrolled studies and anecdote. The MRSA population can be split into four groups: (*1*) new MRSA infection in an asymptomatic patient, (*2*) new MRSA infection in a symptomatic patient, (*3*) chronic

Table 1. Serum and sputum antibiotic concentrations

Drug	Mean Peak Serum Concentrations (μg/ml)	Mean Peak Sputum Concentrations (μg/g)
Tobramycin		
Intravenous, 8 mg/kg/d (range)	29.4 (23.1–35.5)	3.88 (1.8–5.7)
Aerosolized		
Solution, 300 mg, ±SD	1.04 ± 0.58	737 ± 1,028
Powder, 112 mg, ±SD	1.02 ± 0.53	1,048 ± 1,080
Amikacin		
Intravenous, 35 mg/kg, ±SD	121.4 ± 37.3	10.95 ± 7.55
Aerosolized, 560 mg, ±SD	1.29 ± 0.77	2,286 (11.6–11,220)
Levofloxacin		
Oral, 500 mg	6.5	5.1
Aerosolized, 240 mg, ±SD	1.71 ± 0.62	4,691 ± 4,516
Aztreonam		
Intravenous, 2 g	80.1	5.2
Aerosolized, 75 mg, range	0.622 (0.31–1.7)	537 (0.2–3,010)
Colistimethate (colistin)		
Intravenous, 7 mg/kg/d, ±SD	23 ± 6	N/A
Aerosolized, 2 million units, ±SEM	0.178 ± 0.018	40 ± 5

Table 2. Empiric antibiotic therapy for the treatment of difficult pulmonary bacterial infections in cystic fibrosis

Organism	Antibiotic	Pediatric Dose	Adult Dose	Side Effects
Gram-positive organisms				
Methicillin-resistant *Staphylococcus aureus*	Vancomycin	15 mg/kg Intravenously every 6 h	1 g intravenously every 12 h	Oto/nephrotoxicity, red man syndrome
	OR Linezolid	If < 11 yr: 10 mg/kg intravenously or orally every 8 h If > 11 yr: 10 mg/kg intravenously or orally every 12 h	600 mg intravenously or orally every 12 h	Optic/peripheral neuropathy, myelosuppression
Gram-negative organisms				
Pseudomonas aeruginosa	Tobramycin*	10 mg/kg intravenously every 24 h	10 mg/kg intravenously every 24 h	Ototoxicity, nephrotoxicity
	OR Amikacin†	30 mg/kg intravenously every 24 h	30 mg/kg intravenously every 24 h	
	OR Colistin (colistimethate sodium)	8 mg/kg/d intravenously divided every 8 h	8 mg/kg/d intravenously divided every 8 h (max 480 mg/d)	Nephrotoxicity, neurotoxicity
	PLUS (choose one): Ticarcillin/ clavulanate	100 mg/kg of ticarcillin component intravenously every 6 h	3 g of ticarcillin component intravenously every 6 h	GI, rash, hepatitis, neutropenia
	Ceftazidime	50 mg/kg intravenously every 6 h‡	2 g intravenously every 8 h‡	GI, rash
	Meropenem	40 mg/kg intravenously every 8 h	2 g intravenously every 8 h	GI, rash, hepatitis, neutropenia
	Ciprofloxacin	15 mg/kg intravenously or 20 mg/kg orally every 12 h	400 mg intravenously or 750 mg orally every 12 h	GI, rare seizure, tendinopathy
Burkholderia cepacia complex	Meropenem	40 mg/kg intravenously every 8 h	2 g intravenously every 8 h	GI, rash, hepatitis, neutropenia
	PLUS (choose 1): Ceftazidime	50 mg/kg intravenously every 6 h	2 g intravenously every 8 h	GI, rash
	Chloramphenicol§	15-20 mg/kg intravenously every 6 h	1 g intravenously every 6 h	Bone marrow suppression/failure
	Trimethoprim/ sulfamethoxazole	4–5 mg/kg (max 240 mg) of trimethoprim component intravenously or orally every 12 h	4–5 mg/kg (max 240 mg) of trimethoprim component intravenously or orally every 12 h	GI, hypersensitivity neutropenia, serum sickness
	Aztreonam	50 mg/kg intravenously every 8 h	2 g intravenously every 8 h	GI, rash
Stenotrophomonas maltophilia	Trimethoprim/ sulfamethoxazole	4–5 mg/kg (max 240 mg) of trimethoprim component intravenously or orally every 12 h	4–5 mg/kg (max 240 mg) of trimethoprim component intravenously or orally every 12 h	GI, hypersensitivity neutropenia, serum sickness
	PLUS (choose 1): Ticarcillin/ clavulanate	100 mg/kg of ticarcillin component intravenously every 6 h	3 g of ticarcillin component intravenously every 6 h	GI, rash, hepatitis, neutropenia
	Levofloxacin	If < 5 yr: 10 mg/kg intravenously or orally every 12 h If > 5 yr: 10 mg/kg intravenously or orally once daily	500–750 mg intravenously or orally once daily	GI, rarely seizure, tendinopathy
	Doxycycline‖	2 mg/kg intravenously or orally every 12 h	100 mg intravenously or orally every 12 h	GI, photosensitivity
	Tigecycline	1.2 mg/kg intravenously every 12 h	50 mg intravenously every 12 h	GI, cholestasis

(Continued)

Table 2. (*Continued*)

Organism	Antibiotic	Pediatric Dose	Adult Dose	Side Effects
Achromobacter species	Meropenem	40 mg/kg intravenously every 8 h	2 g intravenously every 8 h	GI, rash, hepatitis
	OR Imipenem	15–25 mg/kg intravenously every 6 h	500 mg–1 g intravenously every 6 h	GI, rarely seizures
	PLUS (choose 1): Trimethoprim/ sulfamethoxazole	4–5 mg/kg (max 240 mg) of trimethoprim component intravenously or orally every 12 h	4–5 mg/kg (max 240 mg) of trimethoprim component intravenously or orally every 12 h	GI, hypersensitivity neutropenia, serum sickness
	Ciprofloxacin	15 mg/kg intravenously or 20 mg/kg orally every 12 h	400 mg intravenously or 750 mg orally every 12 h	GI, rarely seizure, tendinopathy
	Minocycline[‖]	2 mg/kg intravenously or orally every 12 h	100 mg orally every 12 h	GI, photosensitivity

Definition of abbreviations: Cmax = maximum serum concentration; Cmin = minimum serum concentration; 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, Ontario, which is based on 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.
[*]Serum concentrations should be monitored and aim for a Cmax in the range of 20–40 mg/L with a Cmin of <1 mg/L.
[†]Serum concentrations should be monitored and aim for a Cmax in the range of 80–120 mg/L with a Cmin of <1 mg/L.
[‡]Continuous infusion of ceftazidime may be considered in cases of clinical failure or for the treatment of multidrug-resistant *Pseudomonas aeruginosa* to maximize the time above the minimum inhibitory concentration.
[§]Serum concentrations should be monitored; the peak concentration ranges from 15–25 μg/ml and the trough from 5–15 μg/ml.
[‖]Should not be given to children < 8 yr of age.

MRSA infection in an asymptomatic patient, and (*4*) chronic MRSA infection in a symptomatic patient. There is no standard definition for chronic MRSA infection, but previous and ongoing studies typically have defined chronic infection as having at least three MRSA-positive cultures within the previous 6 to 12 months (32, 47, 48). The most straightforward decision for treatment occurs in those patients in whom MRSA is cultured from the respiratory tract and who are also experiencing an acute pulmonary exacerbation. Ninety-eight percent of CF providers in the United States who responded to a survey regarding MRSA treatment stated they would give oral or intravenous antibiotics in this situation (36). The advantages and disadvantages of various treatment regimens are detailed in the above paragraphs.

Many CF providers have wondered if there is a role for eradication of respiratory tract MRSA infection. Arguments for recommending and withholding systemic therapy can be made for eradication of a new MRSA infection. Previous studies have suggested that one-third of new MRSA infections may subsequently clear, suggesting that the risks of treatment may not outweigh the benefits (32). However, the easiest time to eradicate MRSA is most likely when it is first cultured, before it becomes entrenched in the lung. Unfortunately, at the time of first culture, it is not possible to determine which patients will clear spontaneously and which will progress to chronic MRSA infection. For these reasons, one approach to a new MRSA infection is to perform an eradication attempt with oral antibiotics. Because MRSA is often found outside of the respiratory tract, an eradication attempt may also include treatment with nasal mupirocin and chlorhexidine or bleach baths. Interestingly, in contrast to *P. aeruginosa*, there is some evidence that chronic MRSA may be eradicated from the respiratory tract (41). Given that oral antibiotics alone may not be enough to eradicate chronic MRSA, the addition of inhaled antibiotics targeting MRSA also may be considered.

The most difficult-to-treat patients with MRSA are those who are chronically infected and who do not have enough symptoms to trigger the administration of intravenous antibiotics but who have persistent respiratory symptoms. These patients may respond temporarily to repeated courses of oral antibiotics, but eventually this treatment may become associated with decreased efficacy, resistance, and/or side effects. One suggested approach is to administer 250 mg of the intravenous formulation of vancomycin reconstituted in 5 ml of sterile water via nebulization mist treatment (48). The patient inhales the medication twice daily for 28 days. Albuterol is often inhaled before the administration of the antibiotic, although a pilot study did not demonstrate that bronchospasm was a significant issue (46). At the conclusion of the 28-day treatment period, a repeat culture is obtained to determine if MRSA can still be detected in the respiratory tract. If the patient becomes symptomatic when not taking inhaled vancomycin and has not eradicated MRSA, then suppressive treatment with either every other month or continuous inhaled vancomycin may be given. Again, these are potential options for patients with new or chronic MRSA infection while we are awaiting the results of ongoing clinical trials that will further inform treatment decisions (47–49).

Gram-Negative Bacteria

As individuals with CF age, their airways become more frequently infected with gram-negative bacteria. In the United States, the overall prevalence of pulmonary infection with multidrug-resistant *P. aeruginosa*, *S. maltophilia*, and *B. cepacia* complex in patients with CF is 9, 14, and 3%, respectively (29). Infection with these gram-negative organisms is associated with poorer clinical outcomes, such as rapid lung function decline, increased risk of

Table 3. Typical susceptibilities to commonly used antipseudomonal antibiotics of bacteria frequently cultured from the cystic fibrosis airway

Bacteria	Antibiotic					
	CAZ	PIP/TAZ	MER	AZT	TOB	COL
Stenotrophomonas maltophilia	+/−	—	—	—	—	+/−
Achromobacter spp.	+/−	✓	+/−	—	—	✓
BCC	+/−	+/−	+/−	—	—	—
MSSA	+/−	✓	✓	—	✓	—
MRSA	—	—	✓	—	—	—
Streptococci	+/−	✓	✓	—	—	—
Haemophilus influenzae	✓	✓	✓	✓	✓	—
Pseudomonas aeruginosa	✓	✓	✓	✓	✓	✓
Anaerobes	—	✓	✓	—	—	—

Definition of abbreviations: AZT = aztreonam; BCC = *Burkholderia cepacia* complex; CAZ = ceftazidime; COL = colistimethate; MER = meropenem; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; PIP/TAZ = piperacillin-tazobactam; TOB = tobramycin.
✓ Indicates *in vitro* susceptibility; +/− indicates borderline susceptibility; — indicates resistant or resistance not known.

pulmonary exacerbation, and greater rates of mortality or need for lung transplantation (50–55).

P. aeruginosa, *B. cepacia* complex, and *S. maltophilia* are found in the environment and have consequently developed ways of surviving in harsh milieus with exposure to naturally occurring antimicrobials. Treatment is thus difficult due to their impressive array of antimicrobial resistance mechanisms, which include efflux pumps, chromosomally encoded β-lactamases, decreased outer membrane permeability, and biofilm formation (56). Given these numerous mechanisms of antimicrobial resistance, these bacteria are deemed resistant to drugs such as aminoglycosides, β-lactams, and fluoroquinolones by *in vitro* testing according to Clinical Laboratory Standards Institute guidelines (57). However, aerosolized antibiotics can yield higher sputum concentrations, in areas of the lung that remain well ventilated, through direct delivery to the site of infection (Table 1) (58–65). There is a relationship between the maximal drug concentration achieved and the minimum inhibitory concentration (MIC) required to inhibit bacterial growth, with higher ratios associated with greater reduction in bacterial density (66). Therefore, newer inhaled antibiotics, herein discussed, have the potential to be used as chronic suppressive treatment for pathogens traditionally considered resistant to these agents.

Table 4. Typical susceptibilities to less commonly used antipseudomonal antibiotics of bacteria frequently cultured from the cystic fibrosis airway

Bacteria	Antibiotic				
	CO-T	DOX	CHL	FOS	TIG
Stenotrophomonas maltophilia	✓	+/−	✓	—	✓
Achromobacter spp.	—	—	+/−	—	—
BCC	+/−	+/−	+/−	+/−	+/−
MSSA	✓	+/−	+/−	✓	✓
MRSA	✓	+/−	—	✓	✓
Streptococci	✓	+/−	✓	—	✓
Haemophilus influenzae	+/−	+/−	✓	—	✓
Pseudomonas. aeruginosa	—	—	—	+/−	—
Anaerobes	—	+/−	✓	—	✓

Definition of abbreviations: BCC = *Burkholderia cepacia* complex; CO-T = cotrimoxazole; CHL = chloramphenicol; DOX = doxycycline; FOS = fosfomycin; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; TIG = tigecycline.
✓ Indicates *in vitro* susceptibility; +/− indicates borderline susceptibility; — indicates resistant or resistance not known.

One of the new inhalational antibiotics available is tobramycin inhalation powder (TIP) delivered by the podhaler device. TIP has been shown to result in comparable increases in FEV_1 and decreases in hospitalization as tobramycin inhalation solution (TIS) in the treatment of chronic *P. aeruginosa* in patients with CF (67). However, TIP can achieve up to 1.5- to 2-fold higher sputum tobramycin concentrations (up to 2,000 μg/g) than TIS. *In vitro* studies of 180 *B. cepacia* complex and 103 *S. maltophilia* isolates demonstrated a minimum inhibitory concentration at which 50% of isolates were susceptible (MIC_{50}) of 100 μg/ml, tested by planktonic and biofilm growth (68). This suggests that a maximum serum concentration/MIC ratio of up to 20 may be achievable with TIP treatment of these pathogens. Clinical trials of TIP in patients with CF with *B. cepacia* complex and *S. maltophilia* infection to decrease sputum bacterial density are planned.

Inhaled aztreonam solution is another aerosolized antimicrobial for the treatment of chronic *P. aeruginosa* in CF. Noninferiority studies have shown that it is comparable, if not superior, to TIS in non–treatment-naive individuals with respect to increases in lung function (69). When used in trials for patients with CF with chronic *B. cepacia* complex infection, however, inhaled aztreonam did not result in any statistically significant improvement in FEV_1 or decreases in sputum bacterial density compared with placebo (70). The ability of β-lactam antibiotics to function in the CF lung could be limited by the slow, anaerobic biofilm growth of organisms (71). *In vitro* studies of biofilm growth of *P. aeruginosa* on CF airway cells have demonstrated little additional benefit of aztreonam in combination with tobramycin, likely due to bacterial exopolysaccharide production causing tolerance to aztreonam (72). In addition, in an ongoing clinical trial of biofilm susceptibility testing of more than 1,000 clinical *P. aeruginosa* CF isolates, the percentage of β-lactam–susceptible isolates was reduced when grown as a biofilm compared with planktonically. These data suggest that, despite the known limitations of antimicrobial susceptibility testing in CF, this class of antimicrobials may be less effective in this context (73).

Finally, studies of aerosolized levofloxacin have demonstrated improvements in lung function (8.7% increase in FEV_1 vs. placebo) and decreases

in bacterial pulmonary burden (0.96 log difference in density vs. placebo) in *P. aeruginosa*–infected patients with CF (74). Levofloxacin is a second-generation fluoroquinolone that in addition to having anti–*P. aeruginosa* effects has activity against *S. maltophilia* (56). In an *in vitro* study of a large number of clinical *S. maltophilia* CF isolates, levofloxacin, at levels achievable by inhalation, was the most active antibiotic alone and in combination against *S. maltophilia* grown as a biofilm or planktonically (75). In addition to achieving high levels of drug in the lung (4,000 μg/g), levofloxacin also has antiinflammatory effects (58, 76). Inhaled levofloxacin may thus be an effective chronic suppressive antimicrobial therapy in patients with CF with chronic *S. maltophilia* infection and warrants further investigation as it may have usefulness beyond the treatment of *P. aeruginosa* infection.

The treatment of multidrug-resistant gram-negative bacteria in patients with CF with advanced lung disease is challenging given the intrinsic resistance of these organisms to antimicrobials of several different classes. Engaging a microbiologist and/or infectious disease expert in a discussion about potential therapeutic options for these patients may thus be fruitful.

Treating Multiple Infections

The recognition that there is a diverse microbiota in sputum samples from people with CF raises questions about how we approach antibiotic therapy. Conventional bacterial culture in aerobic conditions allows isolation of a limited number of organisms. Extended culture methods identify a much wider range of bacteria, which include more difficult to culture bacteria, such as anaerobic bacteria (4, 15, 23). At present, there is no readily available methodology to identify all of these organisms in a way that makes this information valuable for clinical treatment (77). Studies are under way to develop technologies to allow molecular identification without prior culture (78). The choice of antibiotics for pulmonary exacerbations associated with multiple bacteria is an area that has not been extensively studied. A number of different oral and intravenous antibiotics may be combined to tailor antibiotic therapy as best possible to particular combinations of positive bacterial culture results. Antimicrobial susceptibility testing with single agents or synergy protocols for *P. aeruginosa* and *B. cepacia* complex organisms are not helpful as they do not predict response to treatment (79–81). However, treatment with antibiotics for a pulmonary exacerbation to which the main bacterial species is resistant is associated with treatment failure (82). These studies have been observational, and there are few randomized controlled trials to help in choosing antibiotics for pulmonary exacerbations. The choice is largely empirical and based on the experience of the physician, patient, and previous occurrence of drug allergy. In addition, there are no data to suggest that this also applies to other bacteria cultured in CF sputum. The dosages and side effects of common antibiotics used to treat MRSA and gram-negative bacteria are provided in Table 2.

Combinations of organisms that are commonly encountered with *P. aeruginosa* are *S. aureus*, *Haemophilus influenzae*, *S. maltophilia*, *B. cepacia* complex, and *Achromobacter* spp. Other combinations can occur, and studies describing the airway microbiome indicate that coinfection is common and often complex. Two or more organisms may be cultured in approximately 25% of sputum samples. Table 3 and 4 indicate the susceptibility of these bacteria to antibiotics used to treat *P. aeruginosa*. These susceptibilities are a guide to consider combinations of intravenous and oral antibiotics for pulmonary exacerbations where multiple bacteria are present to maximize the appropriateness of antibiotic choice against the organisms isolated. As molecular diagnostics for a wider range of bacteria in the CF airway microbiome become available, clinical trials will be needed to better inform the choice of antibiotics for long-term bacterial suppression and treatment (6).

Summary

MRSA and *P. aeruginosa* are two of the most prevalent bacteria isolated from CF sputum from patients in the United States (29). In addition, several gram-negative bacteria, which rapidly become resistant to multiple antibiotics, have been described over the last several years. These bacteria are often difficult to treat and have garnered much attention from clinicians, investigators, and pharmaceutical companies with respect to the development of drugs for the treatment of acute exacerbations and chronic suppression. Antibiotics have been the cornerstone of CF care for decades (11). However, the frequent use of antibiotics likely alters the host's microbiota with yet poorly defined consequences. Because of this selective pressure and with the advent of new laboratory isolation techniques, many previously unrecognized microorganisms are being identified from CF lung secretions. The pathogenic significance of many of these microorganisms is still unknown. This information is important to the CF clinician and the patient with CF, as we need to understand which organisms to treat, whereas treatment of other organisms may actually be detrimental by enabling pathogenic bacteria to expand. As antimicrobials will likely remain a cornerstone of CF therapy far into the future, research into CF lung microbiology must continue until that time when the disease is cured and its associated airway infection is eradicated. ■

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