One Center's Guide to Outpatient Management of Pediatric Cystic Fibrosis Acute Pulmonary Exacerbation

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ABSTRACT: Cystic fibrosis (CF) is a chronic disorder characterized by acute pulmonary exacerbations that comprise increased cough, chest congestion, increased mucus production, shortness of breath, weight loss, and fatigue. Typically, severe episodes are treated in the inpatient setting and include intravenous antimicrobials, airway clearance therapy, and nutritional support. Children with less-severe findings can often be managed as outpatients with oral antimicrobials and increased airway clearance therapy at home without visiting the specialty CF center to begin treatment. Selection of specific antimicrobial agents is dependent on pathogens found in surveillance culture, activity of an agent in patients with CF, and the unique physiology of these patients. In this pediatric review, we present our practice for defining acute pulmonary exacerbation, deciding treatment location, initiating treatment either in-person or remotely, determining the frequency of airway clearance, selecting antimicrobial therapy, recommending timing for follow-up visit, and recognizing and managing treatment failures.

KEYWORDS: cystic fibrosis, pulmonary exacerbation, antibiotics, telemedicine

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Introduction

Cystic fibrosis (CF) is an autosomal-recessive inherited disorder in which there is dysfunction of the protein and chloride channel, Cystic Fibrosis Transmembrane conductance Regulator (CFTR). Lung disease in CF is characterized by thick sputum colonized with bacteria, resulting in inflammation and chronic infection. Recurrent, acute flare-ups of these lung infections are known as acute pulmonary exacerbations (APEs). Although variable in their severity, exacerbations manifest in a constellation of symptoms and findings that may include increased cough, shortness of breath, chest pain, weight loss, change in sputum production, fatigue, hemoptysis, and a decline in lung function testing.[1] While contributing to progressive lung damage,[2,3] these exacerbations also inflict economic and social pressures on patients and their families through both the acute illness and its associated treatment.[4] Parenteral antimicrobial therapy and hospitalization is considered the gold standard of pulmonary exacerbation management.[5,6] Inpatient management results in missed work and/or school, increased medical costs, and risk of exposure of patients to health-care-associated pathogens. Parenteral antimicrobial therapy may be employed or needed for outpatient management of APE; however, this review focuses on treatment with oral agents as may be encountered in the community.

Oral antibiotics are often prescribed for pulmonary exacerbations to circumvent the need for parenteral therapy and inpatient treatment.[1,7,8] Although this practice appears common among CF centers, a literature search reveals no well-established practice guidelines defining when a pulmonary exacerbation merits a trial of oral therapy.[7] The currently available Cystic Fibrosis Foundation guidelines for the treatment of pulmonary exacerbations do not provide advice regarding oral versus intravenous (IV) therapy for APE.[5] The management guidelines of infants and preschoolers with CF both recommend utilization of oral antimicrobials for mild-to-moderate exacerbations.[9,10] In 2003, a state-of-the-art publication on APE treatment made recommendations of antimicrobial agents and susceptible pathogens; however, these do not reflect contemporary antibiotics.[6] A Cochrane review suggests the need for research in this area.[11]

Oral antibiotics are well accepted by patients with CF.[12] Oral therapy can avoid hospitalization, be just as effective in young children as IV therapy,[8,13] and may be less disruptive to

the patient's activities of daily living. One caveat of outpatient therapy is the inability to monitor adherence with medications, increased airway clearance, and nutritional supplementation. If the exacerbation persists or progresses, inpatient-based therapies will become necessary but are now delayed. Such delays have been associated with permanent loss of lung function.[3] Our experience suggests that, overall, 73% of pediatric patients treated with one or more courses of oral antibiotics at home for pulmonary exacerbations demonstrate resolution of symptoms.[1]

Rather than reviewing the pathophysiology of CF pulmonary exacerbations and treatment, which has been presented elsewhere,[14] we have focused our discussion on the rationale and practical approach to the management of outpatient-specific, oral antimicrobial-based APE management in children with CF. These approaches were developed through quality initiatives by the Doernbecher Children's Hospital CF center team at Oregon Health and Science University (OHSU Doernbecher). We then reasoned that the management of fungal and nontuberculous mycobacterium pathogens in patients with CF is beyond the aim of this review.

Defining an APE

No single consensus statement clearly provides a diagnostic definition for an acute CF pulmonary exacerbation.[15] When to treat signs and symptoms of CF pulmonary exacerbation varies widely within and between CF centers.[16] Additional challenges include determining the severity due to unreliable reporting by patients and families and the difficulty in obtaining accurate data from pulmonary function tests (PFTs) in young children. Thus, the provider and family are often burdened with the paraphrased colloquialism of "I don't know what *it* is but I know *it* when I see *it*".

Definitions for APE may differ in pediatric patients with less severe lung disease compared to adults.[7] A large retrospective study identified new crackles on physical examination, increased cough, increased sputum, and decline in weight percentile at a single clinic visit before the age of six years, as prognostic of future pulmonary function, nutrition, and hospitalization.[17] Thus, these four findings need to be included when defining APE in early childhood.

As part of a process to evaluate our use of oral antimicrobials during APE, our providers came to a consensus on the signs and symptoms of a CF pulmonary exacerbation that warrant treatment (Table 1). These include increased cough from baseline, chest pain, increase or change in the character of sputum production, increased fatigue, hemoptysis, change in lung examination, and/or a decline in forced expiratory volume in one second (FEV1) from baseline.[1] Additional criteria include duration of five or more days of illness, missed school or work, and/or fever, and severity of exacerbation. Alternate explanations for the clinical presentation apart from APE include pneumothorax, allergic bronchopulmonary aspergillosis (ABPA), and influenza, which are also entertained while discussing utility and feasibility of oral antimicrobials. Acute onset of pain and dyspnea suggestive of pneumothorax would warrant urgent imaging and examination and would exclude a patient from home-based oral therapy. ABPA may produce symptoms resembling APE. Our first approach would typically be conventional APE therapies, and then if unsuccessful, consider ABPA in the differential of failed outpatient (OP) APE management. ABPA diagnosis and treatment is discussed here[18] and is not presented further in this review. When a viral illness is suspected as an initiating cause of APE symptoms, we wait five to seven days for resolution of upper respiratory infection (URI) symptoms to aid in the decision process of when to treat. As discussed by Waters and Ratjen, due to impaired mucociliary clearance, children with mild lung disease where APE symptoms may be due to acute viral infection may benefit from antimicrobial treatment nonetheless.[7] During influenza season, our center prescribes neuraminidase inhibitors for patients exhibiting symptoms of influenza infection, although there is no specific evidence in people with CF.[19]

Table 1. Definition of APEs at OHSU Doernbecher Pediatric CF Center.

Pulmonary signs and symptoms*	Increased cough ≥1 week Increased chest congestion Crackles or wheezes on exam New or increased hemoptysis Dyspnea Decrease in FEV1 by10–15% Chest pain
Systemic signs and symptoms	Malaise Fever Lethargy/fatigue Anorexia Weight loss Sinus pain/tenderness Sinus discharge

Note: *A treatable exacerbation would need to include any or all of the pulmonary findings.

When and Where to Treat APE

Telephone encounters are often the first contact that an ill patient has with their CF care team. Because our center's service region is large (>100,000 square miles) and appointment time is limited, our clinic adopted a modified form of the Akron Children's Hospital CF Pulmonary Exacerbation Score (PES)[20] as a telephone triage tool to enhance our ability to define and treat APEs.[21,22] The telephone PES (Table 2) uses systemic signs including fever, fatigue, appetite, and missed school/work and pulmonary signs including change in chest congestion, cough, dyspnea, and/or hemoptysis, but lacks objective data (eg, pulmonary function testing, weight) and physical examination findings. Reported symptoms are individually given a weighted score from 0 to 16. A combined PES of 3 or more, including at least one from the pulmonary domain, suggests CF pulmonary exacerbation, and a treatment plan is subsequently initiated. The score lends itself to

Table 2. Pulmonary Exacerbation Scoring (PES) telephone triage tool used at OHSU Doernbecher Pediatric CF Center.

1. Fevers >100.4F in the prior 2 weeks? No = 0, Yes = 1 2. Malaise or fatigue in the prior 2 weeks? No = 0, Yes = 1 3. Increased or new school/work abseentism in the prior 2 weeks? No = 0, Yes = 2 4. Anorexia or poor appetite in the prior 2 weeks? No = 0, Yes = 1
Systemic Signs and Symptoms _____ Total
1. Increased cough (frequency/duration/intensity) for 1 or more weeks? None = 0, Mild = 1, Significant = 2 2. Major change in sputum (new onset/inc/change in consistency) or change in chest congestion for 1 or more weeks? None = 0, Mild = 1, Significant = 2 3. Increased SOB at rest? None = 0, Mild = 1, Significant = 2 4. Hemoptysis? Mild-3, New/Increased = 5
Pulmonary Signs and Symptoms _____ Total
_____ Combined Total PES

easy electronic medical record entry, and an online version for patient entry is being studied.

During in-person CF clinic visits, an inventory of symptoms and recent treatments, if any – in combination with clinical examination, pulmonary function testing, and possible evaluation by radiograph, when indicated – is used to determine if the patient has CF APE. Specifically, we evaluate date last seen, events since last clinic visit, oral/IV course of antibiotics since last clinic visit, ER visits/hospitalizations since last clinic visit, pulmonary symptoms (cough, wheeze, chest pain, shortness of breath, exercise intolerance, hemoptysis, nasal discharge, sinus pain), and GI symptoms (decreased appetite, weight loss). The determination of who is a good candidate for outpatient management as opposed to inpatient admission at our center is made by a multidisciplinary pediatric CF care team, including a nurse, pharmacist, social worker, registered dietitian, pulmonologist, and respiratory therapist, each of whom provide input and evaluation of each patient during outpatient clinic visits.

Determining that a patient has a severe exacerbation is an exclusion to outpatient management. However, there are no current CF guidelines, or any other well-established definitions,[15] to distinguish the severity of an exacerbation (eg, mild, moderate, severe). In fact, a review of CF exacerbation points out the need for a definition, as this is important in guiding treatment of pulmonary exacerbations and selecting the appropriate treatment location.[15]

Until an accepted severity index for APE is published, our physician providers agree that acute shortness of breath, hypoxia, concomitant weight loss, a decrease in FEV1 of greater than 10%–15% of predicted, and a frank or first episode of hemoptysis would be considered a *severe* exacerbation and would generally exclude patients from consideration of home-based oral therapy.

Precautions against outpatient management of APE include: a history of multiple episodes of failed outpatient therapy, colonization with *Pseudomonas aeruginosa*, FEV1 < 75% of predicted, and/or concurrent ABPA.[1] Our providers engage in conversations with patients and their caregivers regarding the risks/benefits of home treatment with the possibility for subsequent admission if there is inadequate improvement, versus electing for immediate inpatient admission. Other considerations for treatment location include adherence concerns and availability of support or parental supervision to ensure an increased airway clearance therapy regimen during illness. Families that travel far distances may choose inpatient treatment of APE due to difficulty with follow-up at our center and lack of access to a local provider or hospital comfortable with CF care. The decision-making process regarding treatment location for patients is complex, but relies on the interplay of the described different factors.

Airway Clearance Techniques and Inhaled Therapeutics

Airway clearance techniques (ACT) are an essential component of APE treatment (Table 3), particularly since exacerbations lead to airway obstruction from increased mucus and chest congestion.

Mechanical clearance techniques aid in the expectoration of sputum and are a cornerstone of APE management.[5,23] A 2009 expert panel recommended ACT be increased during APE,[5] which was also recommended in the infant and preschool CF guidelines.[9,10] Increasing ACT is often the first advice given to our families prior to initiation of antimicrobial therapy when symptoms begin but may not warrant antimicrobial therapy (eg, onset of URI symptoms).

There are a variety of airway clearance techniques available to patients.[23] These include clapping (chest percussion), postural drainage, positive expiratory pressure (PEP), oscillating PEP, huff coughing, and high-frequency chest wall oscillation (eg, the Vest™). Typically, we employ huff coughing, accompanied by either a PEP device or high-frequency chest wall oscillation. ACT is classically administered in combination with inhaled therapies in the following order: (1) bronchodilator therapy with albuterol to open the airways and prevent bronchospasm, (2) hypertonic saline (HTS) to hydrate thick secretions, (3) dornase alfa to thin mucus, (4) ACT and huff coughing, and (5) inhaled antibiotics as needed to treat bacterial colonization. Dornase alfa is often given in the morning to reduce risk of nocturnal cough and up to 30 minutes prior to ACT.[24] The inhaled antibiotics are given after the ACT ses-

Table 3. Follow-up approach at OHSU Doernbecher Pediatric CF Center.

USUAL INITIAL TREATMENT LOCATION	USUAL FOLLOW-UP PLAN
Home	2 weeks post-treatment
Failed Home -> Hospital	3–4 weeks post-treatment

sion, so they are not expectorated or denatured.[24] For home APE treatment, we advise at least three ACT sessions each day (increased from their baseline of two sessions per day). Airway clearance techniques, when combined with breathing treatments, typically take 15–60 minutes per session.

HTS is a sterile solution containing salt water at a concentration of 3%–7% that is aerosolized and inhaled by a patient. It has been shown to improve mucociliary clearance in the CF airway by drawing fluid into the airway, thinning sputum, and stimulating cough.[25,26] HTS, especially at higher concentrations, can be irritating to the airways and lead to bronchospasm; hence, albuterol is often dosed before HTS.[24] A recent study has shown that the dosage of 7% HTS three times per day resulted in more rapid improvement of symptoms compared to 0.12% saline during inpatient APE treatment.[27]

Dornase alfa (Pulmozyme®), a recombinant human deoxyribonuclease, is a mucolytic treatment that cleaves white blood cell DNA to then decrease sputum viscosity and open up the CF airway.[28] Although a study found no added benefit of twice daily dornase to antimicrobials and ACT[28] during exacerbation, the Cystic Fibrosis Foundation recommends continuing all maintenance medications during treatment for APE.[9] As APE is associated with increased inflammation and sputum production, continuing mucolytic therapy during illness is logical. Some patients and other CF centers may increase from standard once daily to twice daily dornase alfa during APE. In these cases, insurance coverage becomes an issue if supply is diminished too quickly in patients who do not have a surplus of medication.

Poor adherence to pulmonary therapy is a large problem in CF and leads to more exacerbations and higher costs.[29] For pulmonary maintenance therapies, adherence is about 50%.[29] Infants and young children depend on caregiver support to complete treatments, while older children may be able to complete treatments on their own. In our experience, children and adolescents require supervision during ACT to maintain adherence. Utilizing a reward system, such as screen time (eg, access to computer tablet or TV) only during CF treatments, may facilitate adherence in children. Recent advances in technology that ease the delivery and reduce duration of treatments, including the eFlow® Rapid nebulizer, have the potential to improve adherence. The best ACT modality in CF is one that a given patient is motivated to complete and may differ by age of the patient and personal preference.[23]

Antimicrobial Therapy Approach

Antimicrobial therapy remains as a critical treatment in APE, and seeking a prescription is the leading reason for sick calls to the CF center or primary care physician (PCP). In this section, we review, by cultured pathogen, our preferred agent, rationale and dosing strategy in patients with CF. A dosing table is also presented (Table 4). Antimicrobial selection and dosing consensus was developed through collaboration between the CF pharmacist, pediatric infectious disease specialist, and pediatric CF providers at OHSU Doernbecher. In many cases, oral antimicrobials used for treatment of CF APE, specific CF dosing recommendations, are not available. In these instances, relevant pediatric literature was consulted and a consensus opinion was made, typically favoring maximum dosing for each agent based on enhanced drug clearance seen in CF patients.[30,31] Health-care providers involved in CF care should review local epidemiologic data and confer with local experts, regarding antimicrobial selection and dosing.

Dosing antimicrobials in CF differs from the general pediatric population. Patients with CF have unique pharmacokinetics of medications due to an altered volume of distribution and increased clearance.[30] Thus, increased dosage and/or increased frequency of administration in patients with CF is warranted.[31] Oral antimicrobials generally have good bioavailability and may be noninferior to IV therapy in pathogen-specific pediatric and adult trials of pulmonary exacerbation.[12,32] Patients with CF also have different pathogens, which require different medication dose and frequency of administration than the usual pathogens seen in the general pediatric population. Treatment of patients with CF for eradication of new bacterial growth of bacteria such as *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* (MRSA),[9,33–36] in the absence of APE, is not presented in this review.

Treatment guidelines for pulmonary exacerbations published by the Cystic Fibrosis Foundation do not include recommendations for duration of therapy.[5] While there do not appear to be any data regarding duration of oral antimicrobial therapy, there are retrospective studies assessing the length of therapy for IV treatment of APE. A study of 1535 patients found that patients with higher FEV1s may achieve optimal efficacy with treatment durations of 8–10 days,[13] whereas older, sicker patients may benefit from treatment durations longer than 14 days.[37] A study of 95 patients found that 93.7% of patients achieved peak FEV1 by 13 days, and maximal peak FEV1 was achieved at a mean time of 10 days in patients with FEV1 $<$ 40% achieved, suggesting that max PFT improvement consistently occurs by day 14 of treatment, regardless of FEV1.[38] Thus, we have settled on 14 days of therapy. Patients not responding to therapy, either by continued symptoms or no improvement in lung function testing, likely require hospital-based care.

Expectorated sputum cultures, or throat swabs in patients unable to expectorate, are collected quarterly per Cystic Fibrosis Foundation guidelines,[39] or more frequently as clinically appropriate. Cultures are used as a guide for antimicrobial selection during APE. Throat swabs (oropharyngeal cultures) may not be representative of all bacteria in lower respiratory tract.[40] Sputum or throat cultures may demonstrate only oral flora or bacteria not commonly seen as a CF pathogen, yet the APE symptoms still respond to standard antimicrobial treatment.[41] Because any one single culture may not fully characterize airway bacteria, we typically target bacteria resulted within the last one year and as far out as two years in some circumstances.

Table 4. Surveillance culture pathogen specimen result and recommended pediatric oral antimicrobial dosing used at OHSU Doernbecher Pediatric CF Center.

BACTERIA	ANTIMICROBIAL	DOSE
Staphylococcus aureus	Cephalexin	100 mg/kg/day divided TID (max 1 gram/dose)[73]
	Amoxicillin/clavulanate	50–100 mg/kg/day divided BID (max 875 mg BID)[74]
	Clindamycin	40 mg/kg/day divided TID (max 600 mg/dose)[45]
	Flucloxacillin€	100 mg/kg/day divided QID (max 2 g/dose)[47]
Haemophilus influenzae	Amoxicillin/clavulanate	90 mg/kg/day divided BID (max 875 mg BID) or 45 mg/kg/day divided TID (max 500 mg TID)[45]
	Cefpodoxime	10 mg/kg/day divided BID (max 200 mg/dose)
	Cefdinir	14 mg/kg/day divided BID (max 300 mg/dose)
	TMP/SMX	15 mg/kg/day divided TID (max 1 DS^ tab/dose) or 15–20 mg/kg/day divided BID (max 2 DS^ tab/dose)
MRSA	Clindamycin	40 mg/kg/day divided TID (max 600 mg/dose)[45]
	TMP/SMX	15 mg/kg/day divided TID (max 1 DS^ tab/dose) or 15–20 mg/kg/day divided BID (max 2 DS^ tab/dose)
	Linezolid	<12 years old: 10 mg/kg† TID (600 mg TID)[45,55] ≥12 years old: 600 mg BID
	Doxycycline	4 mg/kg/day divided BID (max 100 mg/dose)[74]
	Minocycline	4 mg/kg/day divided BID (max 100 mg/dose)[74]
Pseudomonas aeruginosa	Ciprofloxacin	40 mg/kg/day divided BID[33,60] (max 750 mg/dose**)
	Levofloxacin	<5 years old: 20 mg/kg/day divided BID 5–16 years old and <60 kg: 10 mg/kg daily (max 500 mg) ≥60 kg: 750 mg daily[45]
Stenotrophomonas maltophilia	TMP/SMX	15 mg/kg/day divided TID*¥ (max 1 DS^ tab/dose)[62,65]
	Levofloxacin	<5 years old: 20 mg/kg/day divided BID 5–16 years old and <60 kg: 10 mg/kg daily (max 500 mg) ≥ 60 kg: 750 mg daily
	Minocycline	4 mg/kg/day divided BID (max 100 mg/dose)[74]
	Doxycycline	4 mg/kg/day divided BID (max 100 mg/dose)[33]
Achromobacter spp	TMP/SMX	15 mg/kg/day divided TID (max 1 DS^ tab/dose) or 15–20 mg/kg/day divided BID (max 2 DS^ tab/dose¥)
	Minocycline	4 mg/kg/day divided BID (max 100 mg/dose)[33]
Burkholderia spp	TMP/SMX	15 mg/kg/day divided TID (max 1 DS^ tab/dose) or 15–20 mg/kg/day divided BID (max 2 DS^ tab/dose¥)
	Minocycline	4 mg/kg/day divided BID (max 100 mg/dose)
	Doxycycline	4 mg/kg/day divided BID (max 100 mg/dose)

Notes: Maximum daily doses are generally used. €Flucloxacillin is not available in the United States. ^TMP/SMX DS tab = TMP/SMX 160mg/800mg. †Linezolid dosing of 15 mg/kg may be used by some centers due to results of mathematical modeling study to achieve PK goals.[55] *TMP/SMX dosing for *S. maltophilia* should be given three times daily.[62,65] **Ciprofloxacin maximum dosing of 1000 mg Q12h has been suggested for pediatric patients.[60] ¥Some centers use a max dose of 3 DS TMP/SMX tablets (320 mg trimethoprim component).[33]

Multidrug-resistant (MDR) bacteria are not uncommon in CF disease, with an estimated prevalence with MDR *Pseudomonas* in adults with CF of 13%–45%.[42,43] Bacteria colonized in the CF lung become MDR due to the formation of biofilms, which protect bacteria and/or due to prolonged courses of broad-spectrum antimicrobials.[43] MDR bacteria may respond to outpatient treatment. Combinations of antimicrobial agents, with different mechanisms of action, may be utilized to combat resistant bacteria. Patients with MDR bacteria and advanced illness may have comorbidities that suggest they would not respond to outpatient therapy.

Pathogens

Methicillin-sensitive *S. aureus* (MSSA) is a gram-positive cocci and is the most prevalent bacteria in pediatric patients with CF.[44] Oral antimicrobials of choice for APE treatment include cephalexin[45] and amoxicillin/clavulanate. MSSA has beta-lactamase activity that results in amoxicillin resistance.[46] Amoxicillin/clavulanate remains effective against MSSA as clavulanate inhibits beta-lactamase. Dicloxacillin is active against MSSA; however, this requires every six-hour dosing, which may impede adherence. Clindamycin is a reasonable alternative in patients with beta-lactam allergies.[45] Outside of the United States, flucloxacillin is a primary treatment option for MSSA.[47] Although an effective agent for MSSA, trimethoprim/sulfamethoxazole (TMP/SMX) should be used judiciously for treatment of MSSA as small colony variant (SCV) *S. aureus* is associated with TMP/SMX use.[48,49] In chronic infections such as those in CF, *S. aureus* can revert to altered phenotypic *S. aureus* SCV. SCV infections are slow growing, have high rates of resistance, and are associated with a greater decline in lung function.[48–50]

Methicillin-resistant *S. aureus* (MRSA) prevalence rates have been on the rise within the North American CF community.[44,50,51] The current MRSA rate is 24% in patients with CF under 18 years of age (Table 5).[44] TMP/SMX is our preferred agent used to treat APE outpatient in patients with MRSA.[34] Doxycycline or minocycline are another agents used routinely in patients who are allergic or unable to take TMP/SMX.[34] TMP/SMX and doxycycline-resistant rates remain

Table 5. Infection rates in patients with CF <18 years old (adapted from 2014 CF Foundation Center Specific Registry Report).[44]

PATHOGEN	NATIONAL INFECTION RATE* (%)	OHSU DOERNBECHER INFECTION RATE** (%)
Pseudomonas aeruginosa	30.4	23
Methicillin sensitive Staphylococcus aureus	62.3	62.3
Methicillin resistant Staphylococcus aureus	24.1	14.1
Stenotrophomonas maltophilia	13.8	13.6
Burkholderia cepacia complex	1.4	1.6
Haemophilus influenza	21.8	47.1
Achromobacter	4	3.1

Notes: *n = 28,676. **n = 191.

below 10% (doxycycline resistance inferred from tetracycline rates).[52] Of note, TMP/SMX is not a preferred or alternate agent in the pediatric community-acquired pneumonia (CAP) guidelines for MRSA.[45]

Staining of developing teeth is a concern with tetracycline in children less than eight years old; however, this is not true of doxycycline and minocycline, hypothesized due to the latter agents' decreased affinity to calcium.[53,54] Therefore, our center views doxycycline or minocycline as a reasonable choice in pediatric patients with MRSA, regardless of age.

When susceptible, clindamycin is a reasonable antimicrobial for MRSA.[45] At our institution, the 2014 clindamycin-resistant rates were 35%; however, this included patients without CF. Resistant rates of up to 75% have been demonstrated in children with CF,[52] thus limiting its use.

Linezolid is the next appropriate option for patients with MRSA unable to tolerate or who have failed other antimicrobials.[34,45] Although linezolid-resistant *S. aureus* is rare in the CF population,[52] our institution has had a few cases, all in patients treated with multiple courses of linezolid. A shorter dosing interval of every 8 hours of linezolid is necessary in children less than 12 years old due to increased clearance.[35,55] Linezolid bioavailability is 100% in the non-CF population; however, one study in adults with CF found a decreased mean bioavailability of about 85%.[56] Current pediatric CAP guidelines recommend a dose of 10 mg/kg.[45] A pharmacokinetic (PK) study of 10 pediatric patients on IV linezolid suggested, through mathematical modeling, that higher dosing of 15 mg/kg is needed in patients with CF to achieve PK goals; therefore, some CF centers may recommend this higher dosing.[55] Higher dosing may increase side effects of linezolid such as nausea and myelosuppression.[50] Myelosuppression may occur in 1.9%–6.4% of pediatric patients[57] receiving prolonged treatment courses (>2 weeks) of linezolid. Although weekly complete blood counts are recommended to monitor for myelosuppression, our practice does not routinely check complete blood counts, given that outpatient therapy is usually complete at two weeks.[58] For patients treated with serotonin reuptake inhibitor antidepressants, serotonin syndrome is a risk with concurrent linezolid.[50] Other serious side effects of peripheral and optic neuropathy have been noted in a handful of pediatric patients and occurred after 28 days of linezolid therapy.[57]

***Haemophilus influenzae* (*H. influenzae*)** is a gram-negative coccobacillus, which is prevalent in younger pediatric patients.[44] Although culture results at our center specify whether the *H. influenzae* is beta-lactamase negative or positive, we often treat with the assumption that the *H. influenzae* is beta-lactamase positive; therefore, we use a third-generation cephalosporin (cefpodoxime, cefdinir) or amoxicillin/clavulanate in lieu of amoxicillin.[45] Our center's *H. influenzae* prevalence is higher than the national average (Table 5).[44] We commonly treat patients coinfected with *H. influenzae* and MSSA. Treatments of choice are amoxicillin/clavulanate or a third-generation cephalosporin. TMP/SMX is a reasonable alternative agent in patients with beta-lactam allergies or treatment failure.

P. aeruginosa is a gram-negative rod and is the most prevalent bacteria in adults with CF.[59] *P. aeruginosa* is associated with an accelerated decline in lung function, and the decision to use IV therapy may be expedited in patients with history of treatment failures with oral agents. Fluoroquinolones (FQs) are the only oral anti-*P. aeruginosa* antimicrobial option, with ciprofloxacin having the best activity versus *P. aeruginosa*.[60] A randomized, multicenter trial found that ciprofloxacin oral monotherapy was as successful as IV ceftazidime and tobramycin combination in pediatric patients.[32] Levofloxacin may be used in patients who cannot tolerate ciprofloxacin; however, there is a paucity of data for use in pediatric patients with CF and it is less active against *P. aeruginosa*.[60] Other FQs (moxifloxacin and gatifloxacin) have variable *P. aeruginosa* activity and are not utilized. If a feeding tube is being used for medication delivery, ciprofloxacin tablets should be crushed, else the suspension may adhere to the tube.[61] An adverse side effect of FQ use is tendonitis; thus, patients are cautioned against heavy lifting while on quinolones. Some providers will advocate the concurrent administration of inhaled antipseudomonal agents during APE, in particular in patients with MDR *P. aeruginosa*.

Stenotrophomonas, *Achromobacter*, and *Burkholderia* are biofilm-forming gram-negative rods, allowing for increased surface attachment and resistance to antimicrobials.[62] All three agents exhibit significant intrinsic resistance to beta-lactams, FQs, and aminoglycosides, resulting in few options for treatment, only a handful of which are available for oral use.[62] Inhaled antimicrobials may be utilized during treatment with oral antimicrobial agents to add double or triple coverage.

Stenotrophomonas maltophilia. Although there have been mixed studies on the clinical impact of *S. maltophilia*,[35,51,63] our center treats *S. maltophilia*-positive cultures in our CF

population. The drug of choice is TMP/SMX.[62,64] Because TMP/SMX exhibits bacteriostatic killing of *S. maltophilia*, frequent dosing is used (5 mg TMP/kg every 8 hours).[62,65] Resistance rates to TMP/SMX were less than 5% in 2003; however, resistance is increasing in the CF population, above that already seen in the general population.[51,65] Other reasonable oral antimicrobials include doxycycline, levofloxacin, moxifloxacin, and minocycline.[51,65] Moxifloxacin or levofloxacin may cause inducible resistance per *in vitro* data; thus, combination therapy may be pertinent.[62,64] For combination therapy, concurrent inhaled colistin may be added to treatment.[62]

Achromobacter species. Risk factors for developing *Achromobacter* include increasing age, advanced disease, and *P. aeruginosa* colonization.[51] Our center has observed siblings with CF to have *Achromobacter* colonization. *Achromobacter* is typically MDR. Two oral antimicrobial agents that may be utilized include TMP/SMX and minocycline.[62] *Achromobacter* has been noted to be resistant to TMP/SMX[51]; our institution has susceptible isolates, and therefore, this has been a useful agent. Levofloxacin or moxifloxacin may be helpful but should only be used in combination with a second agent due to inducible resistance.[62] For combination therapy, concurrent inhaled colistin may be added to treatment.[62]

Burkholderia cepacia complex (Bcc). Fortunately, Bcc prevalence remains low in the CF population as colonization with *Burkholderia* has been shown to result in a significant decrease in FEV1% decline.[66] The treatment of choice is TMP/SMX,[33] an alternate agent is minocycline.[62] Bcc is resistant to colistin; for combination therapy, concurrent inhaled tobramycin may be added to treatment.[62]

Specific Medication Issues

Sun sensitivity is an adverse effect of many commonly used antimicrobials for APE, such as doxycycline, tetracycline, TMP/SMX, ciprofloxacin, and levofloxacin, which is a concern during the summer months. Patients may easily sunburn or may develop a sun rash. Patients should be consulted to use sunscreen and cover up during sun exposure.

Tendonitis and tendon rupture are serious risks for both ciprofloxacin and levofloxacin. A review of the FDA Adverse Event Reporting System[67] discovered that levofloxacin is the FQ associated with greatest risk of tendon rupture, followed by ciprofloxacin. Patients treated with a FQ and concomitant systemic steroids are at increased risk for tendon rupture. FQ treatment should be discontinued if a patient exhibits symptoms of tendonitis.

Concurrent use of azithromycin with other antibiotics may increase side effects. Prolonged corrected QT interval (QTc) has been reported with azithromycin[70] and other antimicrobials such as FQs. QTc prolongation has not been a clinically significant issue in our CF population, and therefore, continuation of azithromycin is recommended during APE treatment. A study found that adolescent males may have an increase in QTc interval with azithromycin; however, no patients exhibited overt QTc prolongation.[70] An electrocardiogram (EKG) may be obtained if there is a concern; this is not a usual practice at our center unless a third QTc-prolonging agent is added to treatment regimen. Cumulative use of azithromycin[71] and aminoglycosides may result in hearing loss and should be monitored.

We continue anti-inflammatory azithromycin during APE treatment with oral antimicrobials. Azithromycin accumulates in polymorphonuclear leukocytes, which are well known to inhabit CF airways in large numbers (hence dornase alfa therapy). As a result, azithromycin continues to be detectable in lung tissue 14 days after discontinuation of medication.[68,69] Azithromycin should be discontinued if surveillance cultures detect nontuberculous mycobacteria, as it is a primary treatment modality for this bacteria.

Last, the underlying assumption is that APE results in acute increase in inflammatory mediators, which may respond to a brief course of oral systemic steroids. However, neither our group nor the most recent consensus paper has come to conclusion on their role in APE.[5]

Monitoring and Follow-up

In a 2010 paper by Sanders et al, approximately one in four patients with CF failed to recover to their baseline lung function after an APE, despite treatment with IV antibiotics.[72] This suggests that early identification of pulmonary exacerbations, including timely treatment and follow-up, is important to prevent decline in lung function in patients with CF.

If a patient with APE has been managed by utilizing oral therapies at home, treatment is deemed successful if there is resolution in clinically significant symptoms along with an improvement in spirometry (return to $\pm \geq 3\%$ of baseline PFTs) and return of appetite and/or weight gain. Otherwise, it is termed failed outpatient therapy and usually results in admission to the hospital as previously agreed upon by the patient and parent. Exceptions would include: patients with concurrent reactive airway disease (may prescribe steroids and reevaluate), a new pathogen is identified during treatment, or families who refuse admission but seek continued treatment.

APEs managed in the inpatient setting allow for close monitoring of the patient including objective measures of treatment progress such as spirometry, reviewing inpatient progress notes, and daily rounds. Outpatient therapy does not permit the same degree of monitoring, and thus, close follow-up is needed. To date, there are no published guidelines for appropriate outpatient follow-up following treatment of a pulmonary exacerbation. In our center, we aim for close monitoring practices to prevent an unfortunate decline in lung function (Table 3). When distance is an issue to attending a follow-up appointment, local repeat spirometry and PCP office visit has proven useful.

Our current practice evolved through an understanding of oral antimicrobial use at our institution, and the optimization of telephone sick encounters with our patients. At our center, in 2009, the median FEV1 for 6–17-year old was 89% predicted, and in 2014, the median FEV1 was 97.1% of predicted.[44] Although these practices may not have directly improved lung function, our efforts at standardizing care helps our families understand what to expect when their child is ill.

Author Contributions

Analyzed the data: KM, CM, JS, BM. Wrote the first draft of the manuscript: KM, CM. Contributed to the writing of the manuscript: CM, JS, BM, DN, KM. Agree with manuscript results and conclusions: CM, JS, BM, DN, KM. Jointly developed the structure and arguments for the paper: KM, CM. Made critical revisions and approved final version: CM, JS, BM, DN, KM. All authors reviewed and approved of the final manuscript.

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