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. While contributing to progressive lung damage, these exacerbations also inflict economic and social pressures on patients and their families through both the acute illness and its associated treatment. Parenteral antimicrobial therapy and hospitalization is considered the gold standard of pulmonary exacerbation management. 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. 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. 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. The management guidelines of infants and preschoolers with CF both recommend utilization of oral antimicrobials for mild-to-moderate exacerbations. 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. A Cochrane review suggests the need for research in this area.

Oral antibiotics are well accepted by patients with CF. Oral therapy can avoid hospitalization, be just as effective in young children as IV therapy, 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.³

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 here¹⁸ 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

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.¹¹,²² 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 (e.g., 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
Management of pediatric CF acute pulmonary exacerbation

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

| 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/increase 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

1. FEVERs >100.4°F 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 absenteeism in the prior 2 weeks? No = 0, Yes = 2
4. Anorexia or poor appetite in the prior 2 weeks? No = 0, Yes = 1

Combined Total PES = 0, Yes

... (remaining text continues)
sion, so they are not expectorated or denatured. 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. HTS, especially at higher concentrations, can be irritating to the airways and lead to bronchospasm; hence, albuterol is often dosed before HTS. 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.

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. Although a study found no added benefit of twice daily dornase to antimicrobials and ACT during exacerbation, the Cystic Fibrosis Foundation recommends continuing all maintenance medications during treatment for APE. 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. For pulmonary maintenance therapies, adherence is about 50%. 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.

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. 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. Thus, increased dosage and/or increased frequency of administration in patients with CF is warranted. Oral antimicrobials generally have good bioavailability and may be noninferior to IV therapy in pathogen-specific pediatric and adult trials of pulmonary exacerbation. 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), 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. 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, whereas older, sicker patients may benefit from treatment durations longer than 14 days. A study of 95 patients found that 93.7% of patients achieved peak improvement consistently occurs by day 14 of treatment, regardless of FEV1. 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, 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. 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. 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.
Management of pediatric CF acute pulmonary exacerbation

Multidrug-resistant (MDR) bacteria are not uncommon in CF disease, with an estimated prevalence with MDR *Pseudomonas* in adults with CF of 13%–45%.1,2 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.3 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.4 Oral antimicrobials of choice for APE treatment include cephalexin5 and amoxicillin/clavulanate. MSSA has beta-lactamase activity that results in amoxicillin resistance.6 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.46 Although an effective agent for MSSA, clindamycin/sulfamethoxazole (TMP/SMX) should be used judiciously for treatment of MSSA as small colony variant (SCV) *S. aureus* is associated with TMP/SMX use.47

**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.44 Doxycycline or minocycline are another agents used routinely in patients who are allergic or unable to take TMP/SMX.44 TMP/SMX and doxycycline-resistant rates remain

| BACTERIA | ANTIMICROBIAL | DOSE |
|----------|--------------|------|
| Staphylococcus aureus | Cephalexin | 100 mg/kg/day divided TID (max 1 gram/dose) |
| Amoxicillin/clavulanate | 50–100 mg/kg/day divided BID (max 875 mg BID) |
| Clindamycin | 40 mg/kg/day divided TID (max 600 mg/dose) |
| Flucloxacinil 1 | 100 mg/kg/day divided QID (max 2 g/dose) |
| Haemophilus influenzae | Amoxicillin/clavulanate | 90 mg/kg/day divided BID (max 875 mg BID) |
| Cefpodoxime | 45 mg/kg/day divided TID (max 500 mg/dose) |
| Ceftinir | 10 mg/kg/day divided BID (max 200 mg/dose) |
| TMP/SMX | 14 mg/kg/day divided BID (max 300 mg/dose) |
| | 15 mg/kg/day divided TID (max 1 DS tab/dose) |
| MRSA | Clindamycin | 40 mg/kg/day divided TID (max 600 mg/dose) |
| TMP/SMX | 15 mg/kg/day divided TID (max 1 DS tab/dose) |
| Linezolid | or 15–20 mg/kg/day divided BID (max 2 DS tab/dose) |
| Doxycycline | <12 years old: 10 mg/kg TID (600 mg TID) |
| Minocycline | ≥ 12 years old: 600 mg BID |
| Pseudomonas aeruginosa | Ciprofloxacin | 40 mg/kg/day divided BID (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 |
| Stenotrophomonas maltophilia | TMP/SMX | 15 mg/kg/day divided TID (max 1 DS tab/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 |
| Minocycline | 4 mg/kg/day divided BID (max 100 mg/dose) |
| Doxycycline | 4 mg/kg/day divided BID (max 100 mg/dose) |
| Achromobacter spp | TMP/SMX | 15 mg/kg/day divided TID (max 1 DS tab/dose) |
| Minocycline | or 15–20 mg/kg/day divided BID (max 2 DS tab/dose) |
| Burkholderia spp | TMP/SMX | 15 mg/kg/day divided TID (max 1 DS tab/dose) |
| Minocycline | or 15–20 mg/kg/day divided BID (max 2 DS tab/dose) |

**Notes:** Maximum daily doses are generally used. *Flucloxacillin is not available in the United States.* † TMP/SMX DS tab = TMP/SMX 160mg/800mg. *Linezold dosing of 15 mg/kg may be used by some centers due to results of mathematical modeling study to achieve PK goals.50 **TMP/SMX dosing for S. maltophilia should be given three times daily.**12–15 *Ciprofloxacin maximum dosing of 1000 mg Q12h has been suggested for pediatric patients.*90 Some centers use a max dose of 3 DS TMP/SMX tablets (320 mg trimethoprim component).25
below 10% (doxycycline resistance inferred from tetracycline rates). Of note, TMP/SMX is not a preferred or alternate agent in the pediatric community-acquired pneumonia (CAP) guidelines for MRSA.

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. 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. 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, thus limiting its use.

Linezolid is the next appropriate option for patients with MRSA unable to tolerate or who have failed other antimicrobials. Although linezolid-resistant S. aureus is rare in the CF population, 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. Linezolid bioavailability is 100% in the non-CF population; however, one study in adults with CF found a decreased mean bioavailability of about 85%. Current pediatric CAP guidelines recommend a dose of 10 mg/kg. 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. Higher dosing may increase side effects of linezolid such as nausea and myelosuppression. Myelosuppression may occur in 1.9%–6.4% of pediatric patients 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. For patients treated with serotonin reuptake inhibitor antidepressants, serotonin syndrome is a risk with concurrent linezolid. 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.

*Haemophilus influenzae* (H. influenzae) is a gram-negative coccobacillus, which is prevalent in younger pediatric patients. 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 (ceftriaxone, cefdinir) or amoxicillin/clavulanate in lieu of amoxicillin. Our center’s *H. influenzae* prevalence is higher than the national average (Table 5). We commonly treat patients coinfection 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. *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*. A randomized, multicenter trial found that ciprofloxacin oral monotherapy was as successful as IV ceftazidime and tobramycin combination in pediatric patients. 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* antimicrobial activity, with ciprofloxacin having the best activity versus *P. aeruginosa*. 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. 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 maltophilia*. Although there have been mixed studies on the clinical impact of *S. maltophilia*, 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. maltophi,
which is frequent dosing is used (5 mg TMP/kg every 8 hours).62,65
Resistance rates to TMP/SMX were less than 5% in 2003; how-
however, resistance is increasing in the CF population, above
that already seen in the general population.51,65 Other rea-
sonable oral antimicrobials include doxycycline, levofloxa-
cin, 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 com-
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/SMX51; 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 induc-
ible 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 coloniza-
tion with Burkholderia has been shown to result in a signifi-
cant decrease in FEV1% decline.66 The treatment of choice
is TMP/SMX, a3 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 con-
cern 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
of ciprofloxacin and levofloxacin. A review of the FDA Adverse
Event Reporting System67 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 symp-
toms of tendonitis.

Concurrent use of azithromycin with other antibiot-
ics may increase side effects. Prolonged corrected QT inter-
val (QTc) has been reported with azithromycin20 and other
antimicrobials such as FQs. QTc prolongation has not been
a clinically significant issue in our CF population, and there-
fore, 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.20 An electro-
cardiogram (EKG) may be obtained if there is a concern; this
is not a usual practice at our center unless a third QTc-pro-
longing agent is added to treatment regimen. Cumulative use
of azithromycin23 and aminoglycosides may result in hearing
loss and should be monitored.

We continue anti-inflammatory azithromycin during
APE treatment with oral antimicrobials. Azithromycin accumu-
lates 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 detect-
able in lung tissue 14 days after discontinuation of medica-
tion.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 antibiot-
ics.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 ±3% of
baseline PFTs) and return of appetite and/or weight gain.
Otherwise, it is termed failed outpatient therapy and usu-
ally 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 pre-
scribe 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 guide-
lines 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 attend-
ing 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 2007, the median FEV1 for 6–17-year-old was 89% predicted, and in 2014, the median FEV1 was 97.1% of predicted. 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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