Pulmonary exacerbations: diagnoses, and therapeutic regimens

In this issue...

Pulmonary exacerbations are episodes in which respiratory symptoms are increased and are often associated with acute reductions in lung function. Treatment of pulmonary exacerbations often includes the use of antibiotics. However, analysis of outcomes following treatment of exacerbations suggests that patients have a high risk of losing lung function, from which they do not recover. Could these outcomes be related to how we treat pulmonary exacerbations? There is a wide variation in how patients are treated, and a systematic review of the literature did not find clear evidence to provide guidelines on optimal treatment. The cystic fibrosis (CF) community is now poised to test the important questions regarding management of CF exacerbations.

In this issue, we review published research:

- Assessment of the use of antibiotics in pulmonary exacerbations
- Risk factors leading to nonrecovery to baseline after a pulmonary exacerbation
- Current antibiotic choices for managing pulmonary exacerbations
- Antibiotic susceptibility testing and pulmonary exacerbation outcomes
- Treatment of pulmonary exacerbations in mild lung disease

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:
- Summarize the current use of antibiotics in exacerbations
- Describe hypotheses for why there is incomplete recovery following a pulmonary exacerbation
- Describe current approaches to prevent pulmonary exacerbations

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LAUNCH DATE

This program launched on November 12, 2014 and is published monthly; activities expire two years from the date of publication.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, Windows Media Player 9.0 or later, 128 MB of RAM Monitor settings: High color at 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

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Clinicians do not fully understand how to manage the complexities of pancreatic enzyme replacement therapy to achieve optimal results in their patients. *Pseudomonas Aeruginosa* • Clinicians have unanswered questions about *P. aeruginosa* eradication in asymptomatic patients with positive cultures. • New data and new choices for selecting initial inhaled anti-pseudomonal agents have created confusion. • Conflicting data about pulmonary exacerbations has led to incorrect clinical assumptions and inappropriate treatment regimens.

Clinicians have unanswered questions about *P. aeruginosa* eradication in asymptomatic patients. New data and new choices for selecting initial inhaled anti-pseudomonal agents have created confusion. Conflicting data about pulmonary exacerbations has led to incorrect clinical assumptions and inappropriate treatment regimens.

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  - Pulmonary exacerbations in early lung disease

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**Guest Faculty Disclosures**

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Pulmonary exacerbations are a common event in the life of the patient with cystic fibrosis (CF). Although we do not have a specific definition of an exacerbation, in general we describe them as an acute worsening of respiratory signs and symptoms, such as cough and increased sputum, often accompanied by an acute decrease in lung function as measured by spirometry (ie, forced expiratory volume at 1 second [FEV₁]).

Implicated causes of
pulmonary exacerbations include viral infections, changes in the bacterial community, gastrolesophageal reflux disease with aspiration, and exposure to environmental stimuli (eg, pollution, allergens). However, some events may be due to poor adherence to therapies, so the pulmonary exacerbation may not be acute as much as the consequence of a growing process over time. In all, however, we believe various stimuli lead to worse respiratory symptoms because of the infection, inflammation, and airway obstruction. For these reasons, the standard treatment of a pulmonary exacerbation includes continuing chronic therapies, increasing airways-clearance therapies, and antibiotics.

Pulmonary exacerbations are associated with considerable morbidity and cost. They are generally resource intensive, particularly if the patient is hospitalized and missing work or school; they have a negative effect on the patients' quality of life; and they are associated with decreased survival. Treatment goals are generally stated as returning the patient to baseline status. Typically, we do not objectively measure symptoms, so it is not easy to know whether the patient has fully recovered, but we do frequently measure lung function. We now have convincing evidence that many patients do not recover all of their lost lung function, and a fair percentage (15%) will lose a large amount of lung function (ie, >10%). This is a critical observation, as many clinicians use return to baseline lung function as their stated treatment goal, often leading to much longer courses of antibiotics.

There are a number of general hypotheses why patients may not fully recover their lung function. First could be the etiology of the exacerbation, ie, a viral infection that causes injury to the airways. The second hypothesis is that there are patient factors that contribute to the airways injury, such as the host inflammatory response, the underlying severity of their disease, or other comorbitities such as CF-related diabetes. Finally there may be treatment-related explanations why patients do not recover fully, which could include a delay in treatment or an inadequate treatment. For the first two hypotheses we would suggest that we need to implement prophylactic treatment to prevent exacerbations. Some examples might include greater adherence to the use of the chronic medications that have been shown to reduce the frequency of exacerbations, as well as proper immunization. Beyond that, we should look to develop novel treatments that might temporize the effect of an acute exacerbation (eg, antiinflammatory therapy). For the final hypothesis we must find methods to institute timely therapy as well as determine optimal therapeutic strategies.

A systematic review of important treatment factors found little published evidence to support much of what we do when we treat our patients. Simple questions remain unanswered, such as: How should we choose antibiotics? Should we treat with corticosteroids? How long should we continue antibiotics? The last question — determining the optimal duration of antibiotic therapy (as has already been evaluated in other types of lung infection, eg, hospital-acquired pneumonia) — is especially vital. Treating for too short a period risks treatment failure, but treating for too long not only adds to cost, but also increases the risk of toxicity from the medications. This is not trivial, as our patients are exposed to a large, cumulative dose of aminoglycosides over their lifetimes, potentially leading to an increased incidence of ototoxicity and nephrotoxicity.

In developing a solution, the first question to consider is whether we are likely to find that a fixed duration is optimal for most (if not all) patients or whether there is a clinical endpoint that could be reached. However, it has already been shown that exacerbation symptoms are not measured and that lung function does not return to baseline. An ideal study that would compare two durations (longer vs shorter), and would be a placebo-controlled, blinded study in which the patients in the shorter-duration treatment arm would receive placebo for the final days to ensure that all patients would complete at the same time. However, this study design is impractical and costly, and enrollment would likely suffer. A pragmatic study would not be placebo-controlled or blinded but would present the challenge of when to measure the clinical endpoints. Do we measure at the completion of the antibiotics, which is not identical for the two groups, or at some later date that is common for all? What is the relevant clinical endpoint? Some examples could include an objective measure of symptoms (ie, a patient-reported outcome), pulmonary function, treatment failure (ie, treatment within a short period after completion of therapy), and time to next exacerbation.
Finally, we can look at the study design. Should this be a superiority study, where one treatment duration is hypothesized to result in better clinical outcomes than the other? Or should we design a noninferiority study, where the hypothesis is that patients would fare no worse with shorter treatment durations? Such trials may require a large number of patients so feasibility is a key issue when considering study design.

In conclusion, pulmonary exacerbations commonly occur in individuals with CF. We have existing therapies that can prevent some exacerbations and we need to find ways to encourage our patients to adhere to a regular treatment regimen. However, we still need novel therapies that may yet prove more effective in preventing exacerbations or ameliorating their consequences. Finally, while we lack evidence to define optimum treatment of pulmonary exacerbations, the CF community is poised to perform the research necessary to answer those key questions.

Commentary References
Pulmonary exacerbations are common events in the lives of people with cystic fibrosis (CF). Pulmonary exacerbations are generally described as episodes of acute worsening of the symptoms of CF lung disease (eg, cough and sputum production) but there is no specific definition for pulmonary exacerbations. Epidemiologic studies of exacerbations have typically used antibiotic treatment of pulmonary signs and symptoms as a surrogate marker of an exacerbation. Using this as a definition, previous studies have demonstrated that pulmonary exacerbations tend to occur more commonly in patients with more advanced lung disease. In addition, many of the recommended medications (eg, dornase alfa and inhaled antibiotics) used to treat CF lung disease have been shown to reduce the frequency of exacerbations when compared to placebo. Therefore, since people with CF have seen improved lung function over time and there is greater use of the recommended medications, one might predict that the occurrence of pulmonary exacerbations would also be reduced.

This article analyzed the Epidemiologic Study of Cystic Fibrosis (ESCF) database over 10 years to assess the use of exacerbation-associated antibiotic treatments. The first, most notable observation is that over 209,000 exacerbations were reported, demonstrating how commonly these events occur. Half of the antibiotic treatments included intravenous (IV) therapy. The incidence of antibiotic treatment was much greater in older patients compared to younger patients; adults had a treatment incidence nearly three times that for children < 6 years. Consistent with the hypothesis noted above, there was a reduction in the overall incidence of treatment with antibiotics for pulmonary exacerbations over the decade. However, this was mainly an effect in older patients, as younger patients (age < 12 years) actually had an increased incidence of treatment, mainly because of the increase in non-IV treatments (eg, oral antibiotics).

The authors were cautious in their conclusions. Although they were able to observe a reduction in the incidence of pulmonary exacerbations, there was also evidence that clinicians may have evolved to have a lower threshold for treatment with antibiotics, especially in younger patients. The authors concluded that using historical data on treatments for exacerbations may not prove useful in future study designs because of this changing threshold for treatment.

A common finding in patients with pulmonary exacerbations is an acute drop in lung function. Several studies have noted that some patients do not recover their lung function following treatment of a pulmonary exacerbation. In an attempt to identify patients who are at risk for not
recovering baseline lung function, an analysis of the CF Foundation Patient Registry was performed. Data between 2003 and 2006 were used for the analysis. Of the 27,000 patients followed in the CF Foundation Patient Registry, there were approximately 8500 eligible exacerbations after excluding patients under age 6 years, lung transplants, and missing data. Of these, 25% failed to recover to baseline FEV₁ within the three months after treatment. The baseline lung function was established as the best FEV₁ recorded value in the six months preceding the event. Also of note, the definition of full recovery was any FEV₁ in the three months after treatment that was ≥ 90% of the baseline FEV₁. The reader is advised to be wary of considering such a low threshold to be full recovery; this means patients can lose as much as 10% of their lung function after treatment of an exacerbation and the loss would be considered acceptable for this analysis. These authors had previously shown that the likelihood of full (ie, 100%) recovery was only 60% in the general CF population. The goal for this research was to identify risk factors for patients who could not recover back to their baseline lung function.

Patients who had better lung function at the start and who were receiving care at larger CF centers (> 150 patients) were more likely to regain the lost lung function. Risk factors associated with failure to recover after therapy included being insured by Medicaid, undernourished, female, pancreatic-insufficient, persistently infected with specific pathogens (ie, Pseudomonas aeruginosa, Burkholderia cepacia complex, and methicillin-resistant Staphylococcus aureus [MRSA]), and allergic bronchopulmonary aspergillosis (ABPA).

This study is relevant as we try to understand better ways to prevent or treat pulmonary exacerbations with the intent to maintain good lung health in our patients. The authors suggest that earlier intervention may be an important step and that closer monitoring of patients at risk may allow for such earlier treatment. Although there are considerable limitations to using the CF Foundation Patient Registry to understand exacerbations and their management, there is also considerable value as so many patients are included in the database. This analysis only looked at patients treated with intravenous (IV) antibiotics, and we know a great many more patients treated with oral antibiotics were not included in this analysis, yet they may be suffering losses of lung function nonetheless.

ANTIBIOTIC CHOICES FOR TREATING PULMONARY EXACERBATIONS


Pulmonary exacerbations are characterized by increased respiratory symptoms such as cough and sputum production. Although a number of etiologies of pulmonary exacerbation are hypothesized, they are typically treated with antibiotics because of the chronic infection present in the airways. Studies have shown that many patients fail to fully recover the loss of lung function that is often seen in pulmonary exacerbations, but these observations are based on data from patients treated with intravenous (IV) antibiotics. It has been increasingly recognized that patients are often treated with antibiotics not delivered by the IV route, but these patients have not been included in most of the epidemiological studies of exacerbations. This study used the Epidemiological Study of Cystic Fibrosis (ESCF) database to look at the use of antibiotics for treating pulmonary exacerbations, as that registry captured all treated exacerbations independent of whether IV therapy was used. The analysis specifically looked at data captured between 2003 and 2005.

For this report, an exacerbation was defined as any new or increased respiratory symptoms or worsening of pulmonary status for which the clinician initiated new antibiotic therapy. Over 43,000 exacerbations were reported in just over 13,000 patients. Overall, the frequency of treated pulmonary exacerbations was similar across all age groups but was highest in patients < 6 years old. Antibiotics were given in a myriad of patterns. Forty-five percent were treated
with oral antibiotics alone, while 20% were treated with intravenous (IV) antibiotics alone. Multiple combinations of oral, IV, and inhaled antibiotics were used. In fact, nearly 6% of patients were treated with all three forms of antibiotic delivery.

Intravenous antibiotics were used in nearly 40% of patients and were more likely to be used in older patients, those with more advanced lung disease (as measured by spirometry), and those who had the greatest drop in lung function with the exacerbation. A key message in this analysis is that a wide variety of treatments are given to patients with pulmonary exacerbations, making it difficult to determine what is optimum therapy.

**GUIDELINES FOR PULMONARY EXACERBATIONS**


There is no generally applicable definition of a cystic fibrosis pulmonary exacerbation, but typical clinical features include increased cough, increased sputum production, shortness of breath, chest pain, loss of appetite, loss of weight, and a decrease in lung function (eg, FEV₁). Pulmonary exacerbations cause considerable morbidity, with an adverse impact on patients’ quality of life and a loss of lung function that is not recovered, and as many result in hospitalization, there is a major impact on the overall cost of care. The identification of optimal treatment methods for these events could produce significant improvements in quality and length of life for individuals with CF. The CF Foundation established the Pulmonary Therapies Committee to review published evidence and develop recommendations for common treatment methods for exacerbations. These guidelines were developed using a systematic review of the literature to evaluate the evidence supporting therapies and approaches for the management of pulmonary exacerbations.

The committee was able to make only a few specific recommendations including continuation of chronic medications and airway clearance therapies, as most studies of these therapies included patients during an exacerbation. There was also sufficient evidence to suggest that once-daily dosing of aminoglycosides is as safe and as effective as traditional dosing of two to three times daily. The routine use of synergy-testing of antibiotics against *Pseudomonas aeruginosa* was not recommended since no benefit has been demonstrated; however, there may be instances in which such information could prove useful, such as the patient who is not responding to conventional treatment or who is being evaluated for lung transplantation. However, the most notable finding of this review is how little published evidence exists for other commonly used therapies. For example, no studies define the optimal duration of antibiotic therapy. Therefore, most of the questions in this review resulted in an "I" recommendation, meaning there was insufficient evidence from which to make a specific recommendation.

Guidelines typically demonstrate what we know from clinical studies, but there is value in making transparent that which we do not know. This allows a determination of what studies should be done. Some questions ultimately will not be answered, but others are so important that studies should be performed to determine the optimal treatment strategy. This systematic review illuminates important questions regarding pulmonary exacerbations that remain unanswered, including whether the patient should be treated in the hospital or at home; which combination of antibiotics are the most effective; and what is the optimal duration of antibiotic therapy. Given the frequency at which a pulmonary exacerbation is diagnosed, these are questions for which there should be answers.

The committee did not attempt to define a pulmonary exacerbation, nor was there any discussion of the severity of the exacerbation. Perhaps the most important conclusion from this review is that there is a great need for a validated and accepted definition of a pulmonary exacerbation. Only then can we move forward with determining optimal treatment.
Antibiotic Susceptibility and Clinical Outcomes


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Pulmonary exacerbations are very often treated with antibiotics; in epidemiologic studies, this is often how pulmonary exacerbations are defined. Presumably, antibiotic choices are based on the results of culture and susceptibility testing, although multiple observations suggest that microbiologic test results are poorly predictive of clinical outcomes with antibiotics. Specifically, patients who have culture results that suggest bacteria are resistant to the antibiotics used for treatment still have a good clinical response. Yet, standard practices at CF centers often prescribe antibiotics based on susceptibility testing. This paper is an audit of a single site in the United Kingdom to assess their practice and the outcomes associated with it.

The authors reviewed data between 2005 and 2010, and specifically looked at patients with chronic infection with Pseudomonas aeruginosa. They reviewed the records of 40 patients who had received 306 antibiotics courses, of which 55% were given by the intravenous (IV) route. Antibiotic susceptibility test results were available for 94% of the treatments. In no case were the antibiotics changed completing susceptibility test results during the treatment episode. Of the 103 antibiotic courses that coincided with an isolation of P. aeruginosa, the pathogen was found to be fully susceptible to the antibiotics chosen on 34 (33%), fully resistant on 17 (16.5%), and partially susceptible on 46 (44.76%) of occasions. Where the antibiotics were changed during treatment, the decision was based on the clinical response and was not concordant with the test results.

As for the outcomes of interest, there was no difference in recovery of lung function or time to next exacerbation in any of the three groups (fully susceptible, fully resistant, and partially resistant).

Cystic fibrosis airways infection is complex, and the results of standard culture and susceptibility testing provide only one part of the story. This study adds to the increasing evidence that microbiological test results do not predict a clinical response to treatment of infection. It also shows that clinicians are influenced more by the patient's clinical response than they are by the test results, a finding that stands in stark contrast to the data from acute respiratory infections in patients without CF (eg, ventilator-associated pneumonia).

One might question the value of microbiological testing in patients with chronic airways infection. Testing patients who are not infected with Pseudomonas aeruginosa has become standard practice, a practice no one would question as it is intended to identify early infection with Pseudomonas aeruginosa so that an attempt at eradication is possible. But what is the value of recurrent testing in the patient with chronic infection? The answer is not to be found here, or in any other literature, although there are clinics that have shown they can reduce their cost by reducing the frequency of susceptibility testing, although there is the potential cost of not testing when a patient does not respond positively to treatment. Given the frequency of finding other pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA) and Stenotrophomonas maltophilia, it seems there is still value to identifying pathogens present in the cultures, even in the absence of susceptibility testing.

Pulmonary Exacerbations in Early Lung Disease

Much of what we know about pulmonary exacerbation has relied on large registry databases, and although they have provided useful observations, they are incomplete in their data collection, leaving us unable to make hypotheses about specific patient populations. One of these groups includes young patients with very mild lung disease. Previous epidemiologic studies have focused on patients who are treated with intravenous (IV) antibiotics, and younger patients, especially those not infected with *Pseudomonas aeruginosa*, are less likely to get IV therapy and be included in those databases.

This 2014 study, intended to assess the efficacy of azithromycin in CF children unaffected by *P. aeruginosa*, included an a priori case definition of pulmonary exacerbations, allowing us to better understand exacerbations and how they are treated in this population. The study randomized 260 patients to either azithromycin (n = 131) or placebo (n = 129) over a six-month study period. The definition for a pulmonary exacerbation required meeting at least one major criterion (decrease in FEV1 of ≥ 10% from baseline, hypoxemia, new lobar infiltrates, or hemoptysis) or two minor criteria (increased respiratory rate, new findings on chest exam, weight loss, increased cough, decreased exercise tolerance, change in sputum), plus the requirement that the symptoms be present for at least three days.

The study found a lower incidence of pulmonary exacerbations in the treatment group (21% vs. 39%) compared to placebo. Most exacerbations met the definition by the minor criteria (57%), with all of these having increased cough and many having increased chest congestion. For patients who met the definition because of major criteria, nearly all were because of a drop in lung function exceeding 10% of their baseline. No patients met the criteria because of weight loss or hypoxemia.

Nearly all of the exacerbations, no matter whether met by major or minor criteria, were treated with oral antibiotics. This is perhaps not surprising, as these patients did not have *P. aeruginosa* present in sputum cultures. This paper did not report the pathogens found in sputum or oropharyngeal cultures, but those data are available in another report on this study.

What makes this study important is the description of patients with mild disease (even normal lung function) and without *P. aeruginosa* who present with signs and symptoms leading to a diagnosis of a pulmonary exacerbation. Nearly all of these patients were treated with oral antibiotics, confirming the observation that this group would be excluded from epidemiological studies that depend on IV therapy to define pulmonary exacerbations. Even among this group, a pulmonary exacerbation is a common event, with 35% treated during a six-month period. Roughly 5% suffered more than one exacerbation in this short period of time.