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eCysticFibrosis Review

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eCysticFibrosis Review Volume 3 Issue 3

Pulmonary Exacerbation Therapies



In this Issue...

One of the most important clinical events for patients with cystic fibrosis (CF) in the course of this disease is an acute pulmonary exacerbation. Acute pulmonary exacerbations have been associated with more rapid decline in lung function, increased mortality, and lower quality of life.

In this issue, we review reports that assess the recovery of baseline lung function after an exacerbation, describe the connection between frequent exacerbations and lung function decline, reevaluate the evidence basis supporting current treatment approaches, and present new research into epidemic *Pseudomonas aeruginosa*.

LEARNING OBJECTIVES

After participating in this activity the participant will demonstrate the ability to:

- Discuss the clinical implications of acute pulmonary exacerbations in cystic fibrosis,
- Describe the evidence that supports common treatment approaches to acute pulmonary exacerbation in cystic fibrosis,
- Explain the complexities of assessing antimicrobial resistance patterns via sputum isolates in cystic fibrosis.

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Expiration Date October 17, 2013

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COMMENTARY

The large majority of cystic fibrosis (CF) patients die from respiratory failure despite extensive advances in our understanding of the basic science of CF. This decline is due in part to acute clinical events termed pulmonary exacerbations.¹ These exacerbations are very common and present clinically with changes in cough, sputum production, dyspnea and decreases in energy, appetite, weight and spirometry. Bacterial concentrations of *Pseudomonas aeruginosa* are high during exacerbations and decrease with treatment; further, treatment with antimicrobial agents reduces symptoms and improves lung





function.² While new antibiotics and new treatments to reverse the primary defect are desperately needed, interventions that maximize our current treatments could have an immediate impact on the lung health of patients with CF.

Acute pulmonary exacerbations are sentinel events in CF lung disease, with major implications in the lives of patients with CF. The annual rate of CF pulmonary exacerbations has clearly been associated with 2 year survival by our group and 5 year survival by a separate group in prediction models evaluating the odds of death during follow-up.^{3,4} CF pulmonary exacerbations requiring intravenous antibiotics have also been associated with later diminished lung function in children, CF related diabetes, sleep disturbances and health related quality of life.⁵ The paper by de Boer and colleagues reviewed herein provides strong supporting evidence regarding the overall clinical importance of these events by showing that those patients who are frequent exacerbators have more rapid lung function decline and an increased risk of death or lung transplant.

One of the primary assumptions clinicians make is that following treatment with antibiotics for acute pulmonary exacerbations, patients recover fully. Sanders and colleagues have recently put this notion into question with 2 epidemiologic studies evaluating recovery to baseline lung function in CF (the larger of these studies is highlighted in this review). The authors note that upwards of 25% of patients with CF do not recover to their baseline lung function 3 months following an acute exacerbation. While these data come from a large population-based patient registry with all of its limitations, such a finding has important implications to CF care. Perhaps closer clinical follow-up could ensure recovery in all. Another interesting finding in the study was that those patients who dropped the most from baseline had an increased risk of failing to recover. Perhaps earlier detection of these events would reduce the rate of failure to recover.

Despite the central role that acute pulmonary exacerbations play in the lives of patients with CF, relatively little work has been done to provide high quality evidence to guide treatment. Flume and colleagues performed a careful systematic review of the evidence for many aspects of acute pulmonary exacerbation management in CF. They found the evidence woefully lacking and could only give a solid recommendation to continuing chronic care during the treatment of a pulmonary exacerbation and performing airway clearance. Evidence supporting the use of dual antibiotic coverage (2 classes of antibiotics) to treat exacerbations in the setting of *Pseudomonas aeruginosa*—a commonly recommended approach—had little high quality supporting data. Nor was there quality data to support the standard 2-week course of therapy. These questions need to be addressed by the CF community, particularly given the increasingly robust data regarding chronic therapies. We can no longer relegate exacerbations to the sideline in the fight to improve the life expectancy and quality of life of patients with CF.

One of the topics partly addressed in the systematic review related to the value of synergy testing as a complementary tool for susceptibility testing. Recent data comparing synergy testing to standard susceptibility testing when choosing antibiotics to treat exacerbations showed that synergy testing provided no benefit. A novel approach to susceptibility testing (based on growth of P. aeruginosa in a biofilm rather than as a planktonic form) has since been evaluated. Retrospective analyses had suggested that growing these organisms as biofilms (a condition potentially more likely to mirror the CF lung) would point to different antibiotic combinations not previously considered.⁶ Unfortunately, in the study by Moskowitz and colleagues reviewed in this issue, there appeared to be no clear benefit to using antimicrobial susceptibility patterns based on P. aeruginosa grown in a biofilm. This finding may be in part due to conclusions noted in the work by Mowat and colleagues, which outlined the phenotypic variability of an epidemic strain within individual patients with CF. A number of the phenotypic characteristics were based on antimicrobial susceptibility: thus, as our current susceptibility testing does not directly address such diversity, this phenotypic diversity may explain why clinical response to antibiotics does not correlate well with sputum organism antimicrobial susceptibility testing.

Acute pulmonary exacerbations remain a key clinical event in CF lung disease. The studies highlighted in this review emphasize the clinical importance of these events, the lack of high quality data to guide management decisions, and the evolution of important findings regarding the complexity of chronic lung infections in CF.

Commentary References

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RECOVERY TO BASELINE PULMONARY FUNCTION AFTER EXACERBATION

Sanders DB, Bittner RC, Rosenfeld M, Hoffman LR, Redding GJ, Goss CH. **Failure to** recover to baseline pulmonary function after cystic fibrosis pulmonary exacerbation. *Am J Respir Crit Care Med.* 2010 Sep 1;182(5):627-632

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The objective of this study was to use the Cystic Fibrosis Foundation (CFF) Patient Registry to assess the rate of recovery of baseline lung function after an acute pulmonary exacerbation in patients with cystic fibrosis (CF). The investigators had previously found in a single center pediatric study that 23.1% of children in their cohort did not recover to baseline forced expiratory volume in one second (FEV₁) (baseline was defined as an FEV₁ greater than or equal to 95% of the best FEV₁ during the 6 months prior to treatment). For this investigation, the investigators evaluated subjects in the CFF Patient Registry from 2003–2006. They randomly selected one pulmonary exacerbation treated with intravenous antibiotics per patient and compared the best FEV₁ in the 3 months after treatment with the best FEV₁ in the 6 months before treatment. Recovery to baseline was defined as any FEV₁ in the 3 months after treatment that was greater than or equal to 90% of the baseline FEV₁. This more generous definition was chosen given reported week-to-week FEV₁ variability when patients with CF are well. The investigators also assessed clinical predictors of those subjects who failed to respond to antibiotics for acute exacerbation, as well as performing a number of sensitivity analyses to assess the robustness of their results.

One of the key findings of the study was that of the 8,479 evaluable subjects (those with lung function assessment in the pre-specified time windows) with pulmonary exacerbations, a total

of 2,159 (25%) failed to recover to baseline FEV_1 within the 3 months after treatment. Further, at 6 months after antibiotic treatment, 75% of these subjects had still not recovered to baseline lung function. In a multivariable regression model, the following characteristics were associated with failure to recover: insured by Medicaid, undernourished, female, pancreatic insufficient, persistently infected with *P. aeruginosa, Burkholderia cepacia* complex, or methicillin-resistant *Staphylococcus aureus* (MRSA), and allergic bronchopulmonary aspergillosis (ABPA). Interestingly, having mild pulmonary impairment (FEV₁ between 60 and 79% predicted) and treatment at a large CF center (caring for more than 150 patients) were associated with a decreased risk of failing to recover to baseline.

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The key findings of this paper raise the possibility that a significant proportion of patients fail to recover after treatment of an acute pulmonary exacerbation, and that pulmonary exacerbation may play a central role in lung function decline in CF. There are important limitations of such a retrospective cohort study in that data collection and entry are not standardized, and a pulmonary exacerbation was defined by the use of IV antibiotics or the selection of a "pulmonary exacerbation" as the indication for hospitalization on the CFF Patient Registry encounter form—thus milder exacerbations treated without the use of intravenous antibiotics were not studied. Despite these limitations, this study points to a potential "low hanging" fruit to improve lung function in CF, by providing a better understanding what the mechanism might be to explain this failure to recover.

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EXACERBATION FREQUENCY AND LUNG FUNCTION DECLINE

de Boer K, Vandemheen KL, Tullis E, Doucette S, Fergusson D, Freitag A, Paterson N, Jackson M, Lougheed MD, Kumar V, Aaron SD. **Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis.** *Thorax.* 2011 Aug;66(8):680-685

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The authors tested the hypothesis that frequency of pulmonary exacerbation would be associated with accelerated lung function decline and decreased time to death or lung transplantation in adults with CF. Their theory is that airway inflammation induced by exacerbation could lead to more local airway injury and subsequent lung function decline. This 3 year prospective cohort study, conducted in Ontario, Canada from 2005 to 2008, was designed to determine the impact of infection with transmissible strains of *Pseudomonas aeruginosa*. The cohort included 446 adult patients with CF who could spontaneously produce sputum. Pulmonary exacerbations were defined as acute or subacute worsening of respiratory symptoms treated with either oral or intravenous antibiotics. Subjects in the cohort were evaluated at baseline and then annually for 3 years. The authors defined 3 groups a *priori*: <1 exacerbation per year; 1 to 2 exacerbations per year; and >2 exacerbations per year. They employed a number of analytic methods to assess the impact of exacerbation frequency, including the time to 5% decline of the subjects' FEV₁ % predicted relative to their baseline lung function.

Of the 446 enrolled patients, 140 had less than 1 exacerbation per year, 160 had 1 to 2 exacerbations per year, and 146 had greater than 2 exacerbations per year during the study period. Full 3 year follow-up was not available for 101 patients (more with fewer than 1 exacerbation per year). The investigators found that the mean decline from baseline FEV₁ %predicted was 4.85% (95% CI: 8.01% to 1.69%) for patients with less than 1 exacerbation per year compared to 5.44% (95% CI: 8.33% to 2.55%) for patients with 1 to 2 exacerbations per year, and 6.49% (95% CI: 10.10% to 2.91%) for patients with greater than 2 exacerbations per year. Comparison of these rates did not reach statistical significance (p=0.36). However, patients with greater than 2 exacerbations per year did experience a more rapid progression to 5% decline in FEV₁% predicted from baseline compared with patients with less than 1 exacerbation per year [adjusted HR 1.55 (95% CI 1.10 to 2.18, p=0.01)] and an increased risk of death or lung transplant compared with patients with less than 1 exacerbation/year [adjusted HR 4.05 (95% CI 1.15 to 14.28, p=0.03)]. Patients with 2 or more exacerbations also had a higher risk of death compared with those with less than 1 exacerbation per year. Similar findings were noted when evaluating only those with treatment with intravenous antibiotics for exacerbation.

The authors have provided data supporting the relevance of pulmonary exacerbation on both the clinical outcomes of time to 5% reduction in lung function and time to death or lung transplant. Although pulmonary exacerbation rates have been incorporated into previously published prediction models of survival in CF, these prior studies were not based on carefully collected data in a prospective cohort design. The findings from this study add additional data to support the contention that pulmonary exacerbations are integrally involved in the evolution of CF lung disease.



DATA SUPPORTING TREATMENT APPROACHES TO ACUTE EXACERBATIONS

Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, Marshall BC; Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med.* 2009 Nov 1;180(9):802-808

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While acute pulmonary exacerbations are important and common clinical events in the lives of patients with CF, data supporting a number of the key approaches to treatment—including choice of antibiotics—have been poorly studied. The authors undertook a formal systematic review addressing a series of questions related to treatment of pulmonary exacerbations in CF. For each question the evidence was evaluated using the US Preventive Services Task Force grading scheme to weigh the quality of evidence and the potential harms and benefits. The key questions included: site of treatment (inpatient vs. outpatient), continuation of chronic therapies during exacerbation, number of antibiotics employed, choice of antibiotics, duration of antibiotic treatment, use of synergy testing, and use of corticosteroids for the treatment of an acute pulmonary exacerbation. The reviews included English-language reports of controlled trials found in PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE databases.

Only two questions (continuation of chronic therapies and use of airway clearance) achieved a grade of "B" for the treatment of an acute pulmonary exacerbation. Synergy testing received a "D" recommendation and thus could not be recommended in routine care. Use of daily compared to every 8 hour dosing of intravenous aminoglycosides received a grade of "C" (moderate certainty of a small benefit). The remainder of the key questions that address the fundamental management of CF pulmonary exacerbation (site of care, choice of antibiotics, duration of antibiotics and number of antibiotics) all were found to have insufficient evidence to make a recommendation. There was also insufficient evidence to support the use of 1 antibiotic over 2 for acute exacerbations or to support the treatment of an exacerbation with nome intravenous antibiotics and that home therapy may nevertheless be appropriate for selected patients with CF.

This systematic review was instrumental in pointing out the gaps in knowledge in the treatment of a very common event in the lives of patients with CF. The only therapies to get a "B" or higher recommendation (defined as high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial) were continuation of chronic therapies and use of airway clearance. With improved survival in CF, we must move to improve our evidence that supports the optimal treatment of a pulmonary exacerbation.

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BIOFILM TESTING TO SELECT ANTIBIOTICS FOR AIRWAY INFECTION

Moskowitz SM, Emerson JC, McNamara S, Shell RD, Orenstein DM, Rosenbluth D, Katz MF, Ahrens R, Hornick D, Joseph PM, Gibson RL, Aitken ML, Benton WW, Burns JL. **Randomized trial of biofilm testing to select antibiotics for cystic fibrosis airway infection.** *Pediatr Pulmonol.* 2011 Feb;46(2):184-192.

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A majority of patients with CF become infected with *Pseudomonas aeruginosa*. Recent advances in basic and translational science have noted that *Pseudomonas aeruginosa* can grow in biofilms—colonies of bacteria protected from the environment and host by an extracellular matrix—making the organisms more resistant to antibiotics. More recent data have also found that the results of conventional antibiotic susceptibility of sputum bacterial isolates correlate poorly to clinical response to antibiotics. In this report, the authors hypothesized that biofilm testing would more accurately reflect the susceptibilities of bacteria infecting CF airways. They conducted a multicenter randomized clinical trial to assess the efficacy and safety of using biofilm susceptibility testing of *Pseudomonas aeruginosa* sputum isolates to guide antibiotic regimens for chronic airway infections in stable patients with CF 14 years and older. Thirty-nine subjects were randomized to either biofilm susceptibility testing or conventional susceptibility testing, followed by 14 days of 2 antibiotics based on the 2 different susceptibility testing results.

Biofilm and conventional testing of *P. aeruginosa* isolates at screening indicated that most agents were less active against organisms grown in a biofilm compared to those grown using conventional testing (planktonic growth). Meropenem was most active against biofilms, while piperacillin/tazobactam and meropenem were most active against planktonic organisms. Almost half of all regimens in either group contained meropenem (52%) and ciprofloxacin (49%). More importantly, the observed agreement between drug class combinations selected by biofilm susceptibility and by conventional susceptibility testing methods was 49%. Sputum quantitative cultures and lung function response were similar in each group. Both groups noted a drop in quantitative cultures of *P. aeruginosa* (roughly -3.0 log in each group) and a rise in mean lung function (120ml -180ml). There were no differences in the adverse event rate between groups.

Although this study is a relatively small negative study, it did provide some key findings and insight into susceptibility testing in CF. Clinicians in the United States often use conventional susceptibility to guide antibiotic choice in CF experiencing an acute pulmonary exacerbation. Prior retrospective analyses had suggested that biofilm based susceptibility methods would lead to improved clinical outcomes. However, in this carefully done prospective randomized clinical trial of biofilm susceptibility testing compared to conventional susceptibility, the antibiotic choices were remarkably similar between the groups, pointing out that biofilm susceptibility testing is not clearly better than conventional testing. Further, clinicians must still ask whether conventional susceptibility testing results.

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PHENOTYPIC DIVERSITY IN AN EPIDEMIC STRAIN OF PSEUDOMONAS AERUGINOSA

Mowat E, Paterson S, Fothergill JL, Wright EA, Ledson MJ, Walshaw MJ, Brockhurst MA, Winstanley C. *Pseudomonas aeruginosa* population diversity and turnover in cystic fibrosis chronic infections. *Am J Respir Crit Care Med.* 2011 Jun 15;183(12):1674-1679

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The authors evaluated 40 isolates from each sputum of 10 CF subjects infected with the Liverpool Epidemic Strain (LES), with each subject contributing 43 sputum samples at various times (clinically stable, pre-exacerbation, intra-exacerbation during antibiotic treatment and post exacerbation). The investigators performed 15 different assays (11 phenotypic features and 4 genotypic traits) on each isolate. The goal was to understand the diversity and dynamics of *P. aeruginosa* in subjects chronically infected with the LES *P. aeruginosa*.

The researchers found that *P. aeruginosa* within each sputum specimen had tremendous diversity, with a total of 398 distinct haplotypes identified, as well as a rapid turnover of the haplotype through time. Antimicrobial susceptibilities to commonly used antibiotics varied between and within patient samples. Isolates that produced excessive pyocyanin production were more common in samples during exacerbation compared to when patients were stable, potentially explaining the increased virulence of the LES isolates in clinical care. Interestingly,

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The most striking finding of this study was the phenotypic variation in respect to antibiotic resistance from LES isolates within the same patient. They also found that approximately half of the diversity found in the study as a whole could be attributed to phenotypic diversity between isolates within samples. This result may explain the lack of clinical correlation to standard susceptibility testing in CF for the management of pulmonary exacerbation. Additional work in this area will be required before the implications on treatment are fully understood.

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