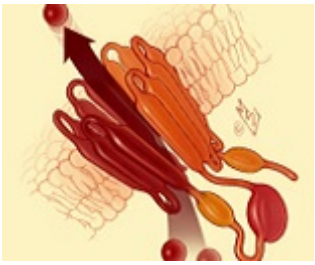
JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eCysticFibrosis Review
Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Vol 7: Supported by educational grants from Gilead Sciences, Inc., Vertex Pharmaceuticals Incorporated, AbbVie, Inc., and Chiesi USA, Inc.



CF Pulmonary Exacerbations: Known Unknowns?

Editor's Note:

With this issue, we launch our seventh volume of eCysticFibrosis Review. We want to thank all our subscribers for your continuing involvement with this program and especially for your assistance in helping us identify the key practice challenges our programs needs to address. Our best to all in 2017.

In this Issue...

Pulmonary exacerbations occur frequently in people with cystic fibrosis (CF) and are associated with loss of lung function, decreased survival, and worsened quality of life. Every year, over 17,000 pulmonary exacerbations treated with intravenous antibiotics are recorded in the Cystic Fibrosis Foundation Patient Registry. However, there is currently insufficient evidence on which to base guidelines for treating exacerbations. Questions about duration, number of antibiotics to use, route of antibiotics administration (oral, IV, or inhaled), or site of treatment (home vs hospital) all remain to be definitively answered. Current practices vary widely for these key treatment decisions that are likely to affect pulmonary exacerbation outcomes. In this issue, Drs. Mark Jennings and Rebecca Dezube from the Johns Hopkins University School of Medicine describe the current evidence that informs our understanding of pulmonary exacerbations and provide perspective to guide approaches to intervention and management.

LEARNING OBJECTIVES

- Explain the significance of pulmonary exacerbations and their impact on the progression of cystic fibrosis lung disease.
- Summarize the current evidence describing risk factors for pulmonary exacerbations and strategies for management.
- Discuss the challenges in investigating pulmonary exacerbations and the current efforts to better understand how best to treat them.

GUEST AUTHORS OF THE MONTH

Commentary & Reviews

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Guest Faculty Disclosure

Drs. Mark Jennings and Rebecca Dezube indicate they have no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation.

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IN THIS ISSUE

COMMENTARY

Perhaps a famous and oft-quoted line of jurisprudence appropriately describes our current understanding of pulmonary exacerbations in cystic fibrosis. The United States Supreme Court Justice Potter Stewart poignantly noted in a 1964 opinion that: “I shall not today attempt further to define . . . [what] I understand to be embraced within that shorthand description; and perhaps I could never succeed in intelligibly doing so. But I know it when I see it.”

In fact, pulmonary exacerbations are a shorthand description for clinically significant events in the lives of people with cystic fibrosis (CF), and although there is no clearly formulated definition of what a pulmonary exacerbation is, patients with CF and their providers alike recognize exacerbations not only by their associated signs and symptoms but also by their impact on the progression of CF lung disease. Pulmonary exacerbations remain a challenge in CF care, and the CF research community is actively engaged in efforts to determine how best to treat these events. It has been well established that pulmonary exacerbations are associated with increased mortality,[1,2] decline in lung function,[3] reduced quality of life,[4] and increased health care use.[5] As discussed in this issue, Valerie Waters and colleagues have demonstrated that a significant proportion of the decline in lung function that patients with CF experience can be attributed to the severe pulmonary exacerbations that punctuate the progression of their disease. In fact, consecutive or more frequent exacerbations appear to have significant impact on the rate of lung function decline. Additionally, DB Sanders and colleagues have shown that 25% of patients who experience a pulmonary exacerbation do not recover to their baseline lung function.

These studies clearly frame the clinical challenge of pulmonary exacerbations and pose the question: Are there risk factors that predict who will not recover from an exacerbation and who is at risk for more frequent exacerbations? VanDevanter and colleagues have shown that previous exacerbations are strongly associated with time to subsequent exacerbations. DB Sanders’ analysis of the Cystic Fibrosis Foundation Patient Registry suggests that longer time to treatment initiation and a larger fall in FEV_1 are associated with failure to recover from an exacerbation. Recent studies have also shown that persistence of pulmonary inflammation in an exacerbation is associated with both failure to recover lung function and increased risk of future exacerbations.

These findings are hypothesis-generating insofar as they suggest ways we might intervene to improve outcomes associated with pulmonary exacerbations. If we could identify exacerbations earlier in their course, or if we could optimize antibiotic treatment, could we effect a clinical outcome, such as lung function recovery or longer time to next exacerbation? The reviewed paper by Stanojevic et al highlights the fact that a majority of pulmonary exacerbations are treated with oral antibiotics. These treatments were associated with milder exacerbations in which lung function did not drop by more than 10% from baseline. Nonetheless, a significant proportion of people treated with oral antibiotics failed to recover to baseline lung function, and in 20% of these "milder" events, lung function did not recover to previous baseline within three months of oral antibiotic therapy. Research has also suggested that shorter courses of IV antibiotic treatment for pulmonary exacerbations increase the risk of treatment failure or retreatment within 30 days.[6] The Cochrane review of the literature in this issue also highlights the lack of evidence supporting the routine use of inhaled antibiotics in the management of pulmonary exacerbations.

As we await the results of prospective analyses of pulmonary exacerbation treatment strategies, the hope is that we will stand poised to not only know an exacerbation when we see it but also to be able to treat and manage it to improve outcomes and mitigate its impact on the course of CF lung disease.

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The Clinical Significance of Exacerbations

Stanojevic S, McDonald A, Waters V, et al. Effect of pulmonary exacerbations treated with oral antibiotics on clinical outcomes in cystic fibrosis. *Thorax* 2016.

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In 2015, nearly 35% of people individuals with cystic fibrosis (CF) in the United States were treated with intravenous (IV) antibiotics for a pulmonary exacerbation (PEx); this percentage has remained largely unchanged over the past decade.[1] While the CF community has known the prevalence of exacerbations for some time, we continue to learn the effects of such events.

In 2010 D.B. Sanders and colleagues conducted a case control study at the University of Washington's pediatric CF center and found that 23% of patients did not recover to baseline lung function.[2] They subsequently expanded this research using the Cystic Fibrosis Foundation Patient Registry (CFFPR).[3] In this second study, they randomly selected one exacerbation (defined as treatment with IV antibiotics) per patient in the registry and used multivariable logistic regression models to identify associations between patient and exacerbation factors and the failure to return to baseline lung function. The authors defined baseline lung function as the best lung function in the six months prior to before the start of an exacerbation, with recovery defined as any FEV_1 in the three months after treatment that was ≥ 90% of the baseline FEV_1. Their study population contained 8,479 patients

individuals with PEx. Of theose, 2,159 (25%) failed to recover to baseline at three months; 19% failed to recover after six months, and 15% had still had not recovered their baseline lung function one year after treatment.

Non-responders to IV therapy were more likely to be female, chronically infected with methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, or multi-drug resistant *Pseudomonas aeruginosa*, and insured by Medicaid, and to have a baseline FEV_1 below 40% predicted and a low body mass index. Factors associated with failure to recover included female gender, pancreatic insufficiency, persistent infection with MRSA, *Pseudomonas aeruginosa*, or *Burkholderia cepacia*, low body mass index, and a diagnosis of allergic bronchopulmonary aspergillosis. Exacerbation-specific factors associated with a failure to recover included a longer time between the prior previous clinic visit and the initiation of treatment, and a greater decline in FEV_1.

Sanders and colleagues note that as a significant proportion of individuals with PEx fail to recover their baseline pulmonary function, such exacerbations represent a critical component in the course of CF lung disease, and that the lifetime decline in FEV_1 may be punctuated rather than gradual. They also note that while causality cannot be determined from their study, their findings support earlier antibiotic intervention.

The study of PEx has largely centered on exacerbations treated with IV antibiotics, in part because this information is more readily available in the CFFPR. In 2016 Stanjoveic and colleagues published their study examining the effect of PEx treated with oral antibiotics on FEV_1 and body mass index — one of only a few studies elucidating the effects of PEx treated with oral antibiotics. In their single-center study of 570 patients, they defined an exacerbation as any clinical event treated with antibiotics for a respiratory cause. The authors constructed mixed-effects models to look at the effect of the number of exacerbations in the prior twelve months for each individual from 2009-2014.

They found that pediatric patients experienced a median of 1.1 exacerbations treated with oral antibiotics per year, compared to 0.8 for adult patients (although the confidence intervals overlapped). In the majority of exacerbations treated with oral antibiotics, lung function had not dropped to below 90% of the baseline at the initiation of antibiotics, which may explain findings that treatment with oral antibiotics results in smaller gains in FEV_1 compared to treatment with IV antibiotics.

The authors report that lung function was significantly decreased if individuals patients had one or more exacerbations treated with oral antibiotics compared to exacerbation-free periods that were exacerbation-free; the association was no longer statistically significant after adjusting for cofactors. However, when examining the cumulative effect of such exacerbations, patients with the greatest number of exacerbations had the steepest rate of decline in FEV_1; there were no significant effects on body mass index.

The authors thus concluded that exacerbations treated with oral antibiotics have both short-term and long-term effects on lung function, and suggest that exacerbations treated with oral antibiotics be incorporated into future clinical trials.

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Factors Predicting Recovery to Baseline and Time to Next Pulmonary Exacerbation

Waters VJ, Stanojevic S, Sonneveld N, et al. Factors associated with response to treatment of pulmonary exacerbations in cystic fibrosis patients. *J Cyst Fibros*. 2015;14(6):755-762.

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VanDevanter DR, Pasta DJ, Konstan MW. Treatment and demographic factors affecting time to next pulmonary exacerbation in cystic fibrosis. *J Cyst Fibros*. 2015;14(6):763-769.

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VanDevanter DR, Morris NJ, Konstan MW. IV-treated pulmonary exacerbations in the prior year: An important independent risk factor for future pulmonary exacerbation in cystic fibrosis. *J Cyst Fibros*. 2016;15(3):372-379.

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Pulmonary exacerbations (PEx) clearly affect the lives of individuals with CF and impact the clinical course of the disease. However, it is not clearly understood why some patients respond to therapy for a PEx and recover to baseline lung function while others do not. Investigators have previously identified female gender, poorer nutritional status, and greater drop in FEV_1 from baseline to PEx as risk factors for failing to recover lung function, but these are not modifiable risk factors at the time of treatment for a PEx.

Waters and colleagues conducted a secondary analysis from a randomized controlled trial of IV antibiotic treatment for a PEx in individuals with CF with chronic *Pseudomonas aeruginosa* infection that was originally conducted in five centers in Canada from 2009-2013 (Clinicaltrials.gov NCT 00786513). The aim of their secondary analysis was to identify factors associated with lung function response to antibiotic treatment of PEx.

Baseline lung function was defined as the last pulmonary function test done when the patient was clinically stable. Spirometry was repeated after 14 days of antibiotic treatment and again at the next follow-up clinic visit when the patient was deemed clinically stable and off IV antibiotic treatment. Response was defined as recovery of > 100% of baseline FEV_1 at day 14 of antibiotic therapy. Maintenance (for those who initially responded at day 14) or recovery (for those who were nonresponders initially) was defined as an FEV_1 > 100% of baseline FEV_1 at the follow-up clinic visit. A total of 70 PEx in 36 patients were analyzed, with 51% of PEx treatment showing a completed response at day fourteen with a FEV_1 > 100% above baseline. Of the 34 who were nonresponders at day 14, 11 had no follow-up, but five recovered 100% of baseline FEV_1 at the clinic follow-up visit. Nonresponders at day 14 had a greater drop in FEV_1 from baseline to day 0 of PEx (- 12.4% vs responders - 5.3%), a lower FEV_1 at time of exacerbation (34% vs 49.8% for responders), a higher serum WBC, and a higher sputum *P. aeruginosa* bacterial density. Factors predicting a response at day 14 of antibiotic therapy included a smaller drop in FEV_1 from baseline to exacerbation (OR 1.09, $P = .04$), as well as a greater decrease in sputum neutrophil elastase (NE) (OR 2.94, $P = .04$).

Given the clinical significance of PEx and association with accelerated lung function loss, reduction of risk of future PEx and time to next PEx have garnered attention as outcomes when looking at PEx treatment. In the study conducted by Waters et al above, subsequent time to next exacerbation was 132 days. Higher CRP and higher NE levels at day 14 were associated with a greater risk of subsequent PEx during the study period.

Using the CF Foundation Patient Registry (CFFPR), VanDeVanter and colleagues looked at risk factors affecting time to next PEx in a cohort of patients followed at the Cleveland, Ohio CF Care center. As reported in their 2015 report, 193 patients had a PEx between January 2010 and September 2014, and 80% of these patients had at least one subsequent PEx for analysis (median time to next PEx was 219 days). Six covariates were associated with future PEx: number of PEx in the prior year (hazard ratio (HR) 25.1 for ³ 3 and 4.4 for one to two prior-year PEx vs none, $P < .0001$), IV treatment duration in weeks (HR 1.2, $P = .0004$), percent of treatment in the hospital (HR 1.1, $P = .0018$), and chronic inhaled aminoglycosides (HR 2.5, $P < .0001$), leukotriene modifiers (HR 1.8, $P = .0031$), and high dose ibuprofen (HR 0.52, $P = .0006$).

The authors then performed a second study (published 2016) analyzing prior-year PEx and the association with future PEx using 13,579 patients in the CFFPR who had a PEx after January 2010. They found similar results: those with 1, 2, 3, or ³ 4 prior-year PEx treated with

IV antibiotics had a HR of 1.6, 2.4, 3.6, and 6.0, respectively, for a future PEx, compared to those without a prior-year PEx.

These findings suggest that a patient's history of PEx is a far more important risk factor associated with time to next PEx than any other available risk factor; therefore, closer attention should be paid to patients with multiple, previous PEx in the prior year.

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Antibiotic Choice for Treatment of Pulmonary Exacerbations

Wagener JS, Rasouliyan L, VanDevanter DR, et al; for the Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Oral, inhaled, and intravenous antibiotic choice for treating pulmonary exacerbations in cystic fibrosis. Pediatr Pulmonol. 2013;48(7):666-673.

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Waters V, Stanojevic S, Atenafu EG et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. Eur Respir J. 2012;40(1):61-66.

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Treatment of PEx usually involves antibiotics, in addition to measures to increase airway clearance and continuation of maintenance medications. However, there is a wide variability and lack of standardized recommendations for PEx secondary to the lack of objective evidence for best practices. Given that most definitions of a PEx are defined by the use of IV antibiotics, data is available (as noted above) for patients who respond or fail to completely respond to IV antibiotic therapy. However, very little data is available on PEx treated with oral and/or inhaled antibiotics. Wagener and colleagues aimed to evaluate the clinical use of all routes of antibiotics for treating PEx and outcomes associated with treatment.

The Epidemiologic Study of Cystic Fibrosis (ESCF) is a multicenter, prospective, longitudinal study of therapy and the natural history of CF. Wagener and colleagues analyzed 18,140 patients enrolled in the ESCF between 2003-2005, defining a PEx as any clinical worsening in pulmonary status in which the clinician decided to initiate new antibiotic therapy. Analysis included antibiotic treatment for the PEx, short-term impact on FEV_1 (FEV_1 30 days before PEx compared to FEV_1 in the 90 days after treatment for PEx), and impact on long-term FEV_1 (highest FEV_1 in the past year compared to the highest FEV_1 within 180 days following PEx onset).

During 2003-2005, 13,194 patients had 45,374 exacerbations. Oral antibiotics were used in 73.2%, inhaled antibiotics in 23.9%, and IV antibiotics in 38.7%, with frequent overlap of more than one route of administration. Forty-four percent were treated with oral antibiotics alone, and 15% were treated with inhaled ± oral antibiotics. Patients under 6 years old were 4.1 times more likely to be treated with non-IV antibiotics than IV antibiotics, while adult patients were slightly more likely to be treated with IV antibiotics.

Degree of lung dysfunction was associated with the likelihood of different routes of antibiotic choice, as PEx occurring in patients $FEV_1 > 100\%$ were four times more likely to receive inhaled and/or oral antibiotics, whereas patients with $FEV_1 < 40\%$ were treated with IV antibiotics more than half the time. Treatment with IV antibiotics was associated with a lower FEV_1 before the PEx compared with non-IV treated PEx (53.6 ± 22.8% vs 71.5 ± 24.1% predicted, $P < .001$). Short term improvement in FEV_1 was greater for PEx treated with IV antibiotics (5.1 ± 12.7%) vs non-IV treated PEx (2.0 ± 11.6% predicted, $P < .001$). The average long-term loss of FEV_1 after treatment for a PEx was 3.8 ± 10.5% predicted, and this loss was similar for both IV and non-IV treated PEx. Lastly, the authors compared patients with a single treated PEx during the three-year study and those without a recorded PEx and found no difference in long-term decline in FEV_1 (- 2.4 ± 9.9% predicted vs - 2.4 ± 10.6% predicted).

In the retrospective study by Waters and colleagues, the authors analyzed the proportion of long-term lung function decline that could be explained by PEx. Among 851 subjects, 415

patients had had at least one PEx; the adjusted annual rate of FEV_1 in those without an exacerbation was 1.2% per year, compared with 2.5% per year in those with an exacerbation. This study also showed the annual rate of FEV_1 decline was greatest in subjects with ≤ 6 months between exacerbations.

In conclusion, these studies demonstrate that the majority of PEx are treated with oral antibiotics, and IV antibiotic treatment for a PEx was more likely to occur in older patients with a lower baseline FEV_1 and/or a greater decline in FEV_1 from baseline.
Although improvement in lung function was noted after any antibiotic treatment, a greater improvement was reported with IV antibiotics. However, this observational study has many implicit biases that would prevent one from concluding that IV antibiotics are superior to oral medication in all instances.

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Studies of Inhaled Antibiotics for Pulmonary Exacerbations

Ryan G, Jahnke N, Remmington T. Inhaled antibiotics for pulmonary exacerbations in cystic fibrosis. *Cochrane Database Syst Rev*. 2012;12: CD008319.

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In 2012, the Cochrane Library conducted a systematic review on the use of inhaled antibiotics instead of or in addition to IV antibiotics for treatment of pulmonary exacerbations. The authors noted that patients had felt this topic was of great importance, with the possible benefits of inhaled antibiotic treatment including decreased toxicity and avoiding the need for IV access. However, despite considerable interest, relatively few trials have examined inhaled antibiotics used instead of or in conjunction with IV antibiotics result in equal or improved clinical outcomes.

The Cochrane Review authors searched the Cochrane Cystic Fibrosis Group's Cystic Fibrosis Register as well as ClinicalTrials.gov and The Australia and New Zealand Clinical Trials Registry. They identified only four completed trials of 167 patients, as well as one study in the Australia and New Zealand Clinical Trials Registry which was ongoing (by Soulsby, registered in 2009 and still listed as recruiting). Two of these studies compared inhaled antibiotics to IV antibiotics, with both published only in abstract form. Cooper et al (1985) compared inhaled tobramycin and inhaled carbenicillin to IV tobramycin and IV ticarcillin.[1] Shatunov et al (2001) compared inhaled ceftazidime to IV ceftazidime.[2] Cooper found no significant difference in improvement in FEV_1 between the inhaled and IV antibiotic treatment groups (FEV_1 in the inhaled therapy group improved from 42 percent predicted to 55 percent predicted, and the IV group improved from 39 percent predicted to 42 percent predicted); Shatunov did not provide spirometric results.

Two additional studies, both published in full, reported on the use of inhaled antibiotics in addition to IV antibiotics. Both were published in the 1980s. Stephens and colleagues reported a study of inhaled tobramycin combined with salbutamol plus IV tobramycin and IV ticarcillin vs IV tobramycin and IV ticarcillin alone.[3] Outcomes included eradication of *Pseudomonas aeruginosa* in addition to pulmonary function testing. Schaad and colleagues reported a study of inhaled amikacin plus IV ceftazidime plus IV amikacin vs IV ceftazidiem and IV amikacin alone; the primary outcome was eradication of *P. aeruginosa*.[4] Both groups of authors concluded that the addition of inhaled therapy to IV therapy increased eradication rates of *P. aeruginosa* but did not improve clinical outcomes.

The authors of this Cochrane review concluded that they had found "no high level evidence to inform the use of inhaled antibiotics for exacerbations."

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