



VOLUME 7 - ISSUE 2

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Weighing the Options in Managing Exacerbations

Our guest authors are Mark T. Jennings, MD, MHS and Rebecca Dezube, MD from the Johns Hopkins University School of Medicine in Baltimore, MD

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

- Describe the significance of pulmonary exacerbations and the impact they have on the progression of CF lung disease.
- Summarize the current evidence of risk factors for pulmonary exacerbations and strategies for management.
- Discuss the challenges in investigating pulmonary exacerbations and the current efforts to better understand exacerbations and how best to treat them.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of the Weighing the Options in Managing Exacerbations. This program is a follow up to the Volume 7, Issue 1 eCysticFibrosis Review newsletter—CF Pulmonary Exacerbations: Known Unknowns?

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The authors indicate there will be no off-label or unapproved uses of any drugs or products

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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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Podcast Transcript

BOB BUSKER: Welcome to this eCysticFibrosis Review podcast.

I'm Bob Busker, managing editor of the program. Our discussion today is a follow-up to our newsletter on **Pulmonary Exacerbations in Patients with Cystic Fibrosis**. With us today, from the Johns Hopkins University School of Medicine, are that issue's authors, Dr. Mark Jennings, Instructor of Medicine, and Dr. Rebecca Dezube, Postdoctoral Fellow in the Division of Pulmonary and Critical Care Medicine.

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Learning objectives for today's audio program include:

- Describe the significance of pulmonary exacerbations and the impact they have on the progression of CF 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 exacerbations and how best to treat them.

Our guests have indicated they have no financial interests or relationships with any commercial entity whose products or services are relevant to the content of this presentation. They have both indicated that there will be no references to the unlabeled or unapproved use of any drugs or products.

Dr. Jennings, Dr. Dezube, thank you both for joining us today.

DR. MARK JENNINGS: Thank you, Bob, it's a pleasure to be here today.

DR. REBECCA DEZUBE: Thank you very much.

MR. BUSKER: In your newsletter issue, doctors, you presented a wide-ranging review of what's currently known about pulmonary exacerbations in patients with CF. What I'd like to do today is discuss how that information can translate into improved clinical practice. So start us off, if you would please, Dr. Jennings, with a patient scenario.

DR. JENNINGS: Sean is a 17 year old male with cystic fibrosis. He is homozygous for the F508-del mutation and his baseline lung function represented by FEV₁ percent predicted is 85 percent. His sputum cultures have previously been positive for *Pseudomonas aeruginosa* despite attempted eradication three years ago. He presents to clinic today after having completed a two week course of oral antibiotics with ciprofloxacin.

He had previously called the clinic complaining of increased cough and sputum production. He was instructed to increase his airway clearance in conjunction with the oral antibiotic. Despite these measures, he states that his cough continues to be worse than normal. He is bringing up a large amount of sputum every day.

Over the last week he states that his energy level has been low. Pulmonary function testing performed today demonstrates an FEV₁ of 60 percent predicted. Sean is clearly frustrated and disappointed. Moreover, he indicates that he is alarmed by the drop in his lung function.

MR. BUSKER: So would you consider this patient's case a clear example of a pulmonary exacerbation?

DR. JENNINGS: There's no clear definition of a CF pulmonary exacerbation; however, this case illustrates many of the signs and symptoms that are encountered with an exacerbation: changing or increasing symptoms such as worsening cough and sputum, decreased energy level, drop in lung function as measured by FEV₁ percent predicted. There are likely a number of different causes of pulmonary exacerbations, but despite these different causes, exacerbations usually manifest in similar ways.

In terms of managing exacerbations, understanding the cause is not as important as what the response is. This scenario is a common one, in which a patient with mild lung disease reports a change in symptoms. Increasing airway clearance is almost always encouraged in the context of such symptoms and very often oral antibiotics are used as a first-line treatment in such a case.

MR. BUSKER: What about the change in this patient's lung function? That drop from baseline was what, 25 points? Is this degree of lung function loss common with a pulmonary exacerbation?

DR. JENNINGS: This is a great question and leads us to one of the key points to understand about pulmonary exacerbations in cystic fibrosis. We know that patients with CF experience a loss of lung function over the course of their disease; however, it is clear that a significant portion of this lung function loss can be attributed to pulmonary exacerbations.

In this sense, patients' lung function loss is not necessarily linear or gradual; rather, they experience a significant drop in lung function in the context of an exacerbation, and unfortunately many do not recover. These drops in lung function punctuate the decline of lung function that defines the progression of CF lung disease.

Phoebe Sanders and colleagues in one of the articles reviewed in the newsletter showed that 25% of patients who experience a pulmonary exacerbation do not recover to their baseline lung function.

MR. BUSKER: What should be done to avoid this loss of lung function from becoming permanent? Dr. Dezube?

DR. DEZUBE: This loss of lung function and the concern that patients will not recover to their previous baseline is what warrants a timely and aggressive response to a pulmonary exacerbation. Research has shown that the degree of lung function loss and the time to treatment initiation are associated with failure to recover lung function. We interpret these data to mean that in addition to increasing airway clearance, antibiotics should be started as soon as possible in response to an exacerbation.

In this scenario, the patient continues to have symptoms, and his lung function is significantly below his baseline, despite a course of oral antibiotics. We know that a majority of pulmonary exacerbations are treated with oral antibiotics. Oftentimes these are exacerbations that are considered milder in nature. Nonetheless, research demonstrates that even in exacerbations treated with oral antibiotic, a significant proportion of patients do not recover to their baseline lung function.

MR. BUSKER: Anything to add, Dr. Jennings?

DR. JENNINGS: Yes, In addition to drop in lung function and time to treatment initiation, we know that infection with methicillin-resistant *Staph. aureus*, *Pseudomonas aeruginosa* and multidrug resistant pseudomonas, as well as low body mass index, female gender, pancreatic insufficiency, and baseline lung function less than FEV₁ of 40 percent predicted also predict failure to respond to treatment of exacerbations.

MR. BUSKER: In a situation like this, where the patient has not effectively responded to a two-week course of oral ciprofloxacin, what's the next step in management? Dr. Jennings?

DR. JENNINGS: As we discussed, it is very common that in a patient with mild lung disease, the initial treatment is a course of oral antibiotics. In this example, Sean has clearly not improved with this therapy, and the persistence of his symptoms and the degree of his drop in lung function warrant more aggressive treatment. The CF Foundation has published guidelines that address management of pulmonary exacerbations. In this situation we would start him on a course of IV

antibiotics. Rebecca, do you have anything to add?

DR. DEZUBE: Sure, there's a fair amount of variability in the choice and duration of IV antibiotic therapy, and when you look at differences amongst CF caregivers and care centers, antibiotics are selected based on known infection. In the case of *Pseudomonas aeruginosa*, two antipseudomonal antibiotics are conventionally given concurrently with one of these antibiotics is tobramycin if patient tolerance and allergy profiles allow. Anything else, Mark?

DR. JENNINGS: Yeah, there are not currently great data as to what the optimal duration of IV antibiotics is for an exacerbation. In practice, patients are often treated for two weeks, with subsequent clinical follow-up. Valerie Waters in one of the articles included in our newsletter, has investigated responses to treatment with IV antibiotics. She looked at responses to 14 days of IV antibiotic treatment of exacerbations in patients with chronic *Pseudomonas aeruginosa*. Fifty-one percent of subjects showed recovery of lung function at day number 14 of IV antibiotics.

In her analysis, subjects who had a greater drop in lung function at the time of their exacerbation, a higher white blood cell count, and a higher sputum density of *Pseudomonas aeruginosa* were less likely to improve with IV antibiotic therapy. Factors that predicted a response at day 14 of IV antibiotics included less of a drop in FEV₁ and a greater decrease in sputum neutrophil elastase, which is a marker of inflammation.

DR. DEZUBE: I just want to add also that whenever we are evaluating a patient that is not responding to treatment of an exacerbation, it is also important to think about other possible reasons why they are not improving. Are antibiotics being dosed correctly with appropriate therapeutic and serum levels? Do we have current culture data? Do we know if any new infections are contributing to this exacerbation? For example, is there new MRSA or new *Burkholderia cepacia*? Could nontuberculous mycobacterial infection be present? Could a noninfectious cause such as ABPA, or allergic bronchopulmonary aspergillosis, be contributing to the symptoms of the exacerbation? These are some of the things that we must investigate to determine why a patient's exacerbation may be nonresponsive to our traditional antibiotics.

MR. BUSKER: Thank you for that case and discussion. And we'll return, with Dr. Mark Jennings and Dr. Rebecca Dezube from Johns Hopkins in just a moment.

MR. BUSKER: This is Bob Busker; I'm the managing editor of eCysticFibrosis Review.

eCysticFibrosis Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to pulmonologists, gastroenterologists, infectious disease specialists, pediatricians, respiratory therapists, dietitians, nutritionists, nurses, and physical therapists.

Bimonthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new information into practice in the clinic.

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I'd also like to tell you about the CF Family Day Meeting Builder. This is a one-stop shop to help you create patient and caregiver education and Family Day meetings. To find out more, please visit www.CFFamilyDay.org.

MR. BUSKER: Welcome back to this eCysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guests are Dr. Mark Jennings and Dr. Rebecca Dezube from the Johns Hopkins University School of Medicine. We've been discussing Pulmonary Exacerbations in Cystic Fibrosis — and specifically how some of the information our guests presented in their newsletter issue can impact clinical practice. So to continue, — let me ask you to bring us another patient scenario, if you would please, Dr. Jennings.

DR. JENNINGS: Sure. Heather is a 22 year old female with cystic fibrosis. Her baseline lung function as measured by FEV₁ percent predicted is 37%. She has chronic *Pseudomonas aeruginosa* and MRSA infection. She presents to clinic today with complaints of increasing cough and sputum production. Her energy level is way below her baseline. She is worried that she got sick after attending a recent family gathering where a few of her relatives had cold symptoms.

In clinic her FEV₁ is 30 percent predicted. She is not surprised to hear the recommendation that she start a course of IV

antibiotics. She has had three hospitalizations for IV antibiotic treatment of a pulmonary exacerbation in the past 12 months.

MR. BUSKER: Dr. Dezube, the frequency with which this patient is experiencing pulmonary exacerbations — why is she at greater risk? What does the evidence say?

DR. DEZUBE: There is some evidence that provides reasons why some patients are at risk for pulmonary exacerbations. Phoebe Sanders and colleagues, in an article that we reviewed in the newsletter, showed that there are characteristics that are associated with a failure to respond to IV antibiotic treatment of exacerbations: specifically, female gender, chronic infection with MRSA or *Pseudomonas aeruginosa*, Medicaid insurance, baseline FEV₁ less than 40 percent predicted, and low body mass index. We have also stressed that prolonged time to initiate treatment of an exacerbation and the degree of lung function decline associated with an exacerbation predicts failure to recover.

MR. BUSKER: Dr. Jennings, what about her risk of future exacerbations? Again what's the evidence say?

DR. JENNINGS: In terms of risk of future exacerbations one variable that stands out is history of prior pulmonary exacerbations. VanDevanter and colleagues in one of the articles reviewed in the newsletter, have shown that the number of exacerbations in the prior year is strongly associated with increasing risk of future exacerbations.

In an analysis of the CF Center in Cleveland, Ohio, they noted that for patients with three or more exacerbations in the prior year they were 25 times more likely to experience a subsequent exacerbation. There we similar findings when using the CF Foundation Patient Registry, patients' history of pulmonary exacerbations the most important factor in terms of risk of a future exacerbation.

It is also notable that in studies performed by Walters and colleagues, again in one of the articles reviewed in the newsletter they found that in patients being treated with IV antibiotics for a pulmonary exacerbation, those who had elevated markers of inflammation, higher C reactive protein and neutrophil elastase at day 14 of treatment were at greater risk of developing a subsequent exacerbation.

In this scenario, the fact that Heather has already had three exacerbations in the past year predict that she is at high risk for suffering another exacerbation.

MR. BUSKER: The best way to treat a pulmonary exacerbation — Dr. Dezube?

DR. DEZUBE: That's a great question. Unfortunately, there is not a clear answer. When we treat pulmonary exacerbations, we usually recommend increasing airway clearance techniques and therapies in addition to prescribing antibiotics. There is tremendous variability in how antibiotics are used in the management of pulmonary exacerbations.

To date, there is not sufficient data to recommend a specific approach or treatment algorithm. Do you have any other thoughts, Mark?

DR. JENNINGS: Yes, The CF community has relied on observational data regarding different approaches to antibiotic therapy for exacerbations. These data are difficult to interpret, they are inherently clouded by what we call indication bias.

For example, we know that pediatric patients less than 6 years of age are four times more likely to be treated with oral antibiotics compared to IV antibiotics. Conversely, older or adult patients are more likely to be treated with IV antibiotics. Patients with an FEV₁ greater than 100% are also four times more likely to be treated with oral antibiotics, whereas patients with an FEV₁ less than 40% or with a greater decline in lung function from their baseline are more often treated with IV antibiotics.

Clearly, the type of antibiotic treatment that is used is related to severity of CF lung disease and the severity of a given exacerbation. Thus, it is difficult to say that one type of treatment is better than another based on the particular outcome.

There are data indicate that delaying antibiotic treatment will lead to worse outcomes in terms of lung function recovery. Therefore, one of the most important points about exacerbation management is the early initiation of antibiotics. Do you have any other thoughts, Rebecca?

DR. DEZUBE: Well, I think the CF community is eagerly awaiting data from prospective, randomized, clinical trials that are actively engaged in investigating the efficacy of different antibiotic regimens for pulmonary exacerbations.

DR. JENNINGS: I agree.

MR. BUSKER: Let me ask you Dr. Dezube, the length of treatment with IV antibiotics — does how long the IV treatment continues matter?

DR. DEZUBE: Again this is a great question, but the answer is not clear. In fact, the best answer is maybe. Research has shown that shorter courses of IV antibiotics are associated with a treatment failure or a need for retreatment of an exacerbation within 30 days.

Conventionally, pulmonary exacerbations are treated with a 14-day course of antibiotic, but we don't have sufficient data to suggest that a particular course of therapy is better than an alternative. Nor do we know if there is a one-size-fits-all approach that would be effective for patients with CF.

MR. BUSKER: Thank you for that case and discussion, doctors. We've got time for one more patient, so if you would, please, Dr. Dezube.

DR. DEZUBE: Sure. Julia is a 34 year old woman with cystic fibrosis. She is homozygous for the delta-F508 mutation with a baseline function of FEV₁ of 70 percent predicted. Over the past two years her sputum cultures have grown *Pseudomonas aeruginosa* and methicillin resistant *Staphylococcus aureus*. Her chronic medication regimen includes lumacaftor/ivacaftor therapy, daily dornase alfa and hypertonic saline, daily oral azithromycin and inhaled tobramycin which she takes for 28 days at a time alternating with a month off of therapy, in addition to pancreatic enzymes and CF multivitamins. She has an allergy to doxycycline. She is married with a 2 year old son, and works as a kindergarten teacher.

Julia calls her CF clinic to report three days of increased cough productive of green sputum. She also feels more dyspneic than usual. Her son has a cold. Many of her students have also been out sick.

MR. BUSKER: So my initial question is: Is this patient experiencing a pulmonary exacerbation?

DR. DEZUBE: Well I think a lot of us clinically would say that the patient has a lot of signs and symptoms of an exacerbation, but one of the biggest challenges is, as Dr. Jennings has already alluded to, is that there is no standardized definition of a pulmonary exacerbation. Many research studies define exacerbations as the use of intravenous antibiotics, either at home or in a hospital. This data is more readily available in the CF Foundation Patient Registry, but other studies have shown that the majority of exacerbations are treated with oral antibiotics, unless they are not captured by the CF Foundation Patient Registry.

Other definitions of exacerbations include changes in therapy, such as the addition or alternation of any intravenous, oral, or inhaled medications for any number of pulmonary or generalized signs and symptoms. Which is interesting because that might mean that if we gave this patient antibiotics, she would be having an exacerbation, but if we do not treat her she would not be having an exacerbation.

In this scenario, she called with changes in symptoms. We don't have any pulmonary function tests, and thus we have to base our decision on whether or not she's having exacerbation on subjective rather than objective data.

MR. BUSKER: So that decision really becomes a choice based on each clinician's knowledge and experience. All right, Dr. Dezube — let's assume for this discussion that your patient is experiencing an exacerbation. What potential treatment options would you consider for her?

DR. DEZUBE: Well broadly speaking, the treatment options would include either oral, intravenous, or inhaled antibiotics in addition to airway clearance therapy, as Dr. Jennings has previously mentioned. However, in a survey of CF providers who are given 28 clinical cases of exacerbations, providers demonstrated substantial variation in treatment practices between and even within US CF centers. There wasn't a single patient scenario in which all the providers said they would treat the

patient the same way.

The CF Foundation has published guidelines for the management of exacerbations, but they found insufficient evidence to recommend the number of antibiotics to use, the duration of antibiotics, the location of antibiotics, whether they should be at home or in the hospital, or whether systemic corticosteroids should be added to the treatment regimen.

Specifically looking at inhaled antibiotics, the Cochrane Review, in an article that we reviewed in the newsletter, concluded that there is no strong data to guide the use of inhaled antibiotics in the treatment of pulmonary exacerbations.

So I think there remains a lot that we don't know about the management of exacerbations

DR. JENNINGS: And let me add that although there's a lot of uncertainty with how we approach exacerbations, the CF community is hopeful that a lot of the ongoing research is going to answer some of these questions and provide guidance moving forward as to what might be best practice with regards to treatment strategies and treatment durations.

MR. BUSKER: Thank you for that case and discussion doctors. I'd like to move to a more general topic now and ask Dr. Dezube, if you would please, to review for us the recent efforts to better understand exacerbations.

DR. DEZUBE Sure, one of the recent studies that has been presented at the 2015 North American Cystic Fibrosis Conference, was called the Pilot Observational Study to Determine the Feasibility of a Standardized Treatment of Pulmonary Exacerbations in Patients with Cystic Fibrosis, or STOP-OB. This was an observational study designed to understand current treatment practices related to pulmonary exacerbations. The patients that were included in the study were 12 and over admitted for pulmonary exacerbation. There were 218 patients at 10 CF centers. Their inclusion criteria was that patients had to have a planned inpatient stay of at least five days with intravenous antibiotics.

When the physicians were surveyed they reported that their primary treatment objective in 53% of the patients was recovery of lung function, and in 45% of the patients was improvement of symptoms. Forty-six percent of the patients reported having a protocolized treatment duration. At CF centers with a treatment protocol, the mean plan duration of antibiotic therapy was 13.8 days. A majority of the physicians said they would be willing to enroll their patients in a trial of differing durations: 70% would enroll their patients in a trial which looked at 10 days, 85% said they'd be willing to enroll their patients in a trial that looked at 14 days, 85% said they'd be willing to let a trial specify the antibiotics, 81% said they'd be willing to let a trial specify other treatments, but physicians and providers were not willing to look at treatment courses for less than seven days, only 28% of providers said they would agree to enroll their patients in the trial that looked at that.

Of the patients that were in the STOP-OB study, most of them had had symptoms for more than one week before admission, and nearly half had been treated as an outpatient with oral antibiotics before beginning IV therapy.

The researchers also surveyed the providers to ask what their goal improvement in FEV₁ was for these patients, and they found that the mean targeted improvement was 16 percentage points higher than the admission FEV₁, although this was actually only 4.7 percentage points higher than the best FEV₁ in the prior six months, and actually half a percentage point lower than the best FEV₁ in the prior year.

MR. BUSKER: Continuing in a similar vein, Dr. Jennings — let me ask you to review for us the ongoing efforts to better understand the treatment of pulmonary exacerbations.

DR. JENNINGS: Sure. Most of the efforts right now fall under a study that's being sponsored by the CF Foundation, it's called the Standardized Treatment of Pulmonary Exacerbations 2 study, the STOP-2 study. This is a study that really builds on the results of the STOP-OB study that Rebecca just discussed. And the STOP-2 study is designed to evaluate the efficacy and safety of different durations of IV antibiotic treatment, either given in the hospital or at home for an exacerbation.

Now specifically, the study is looking to assess the noninferiority of 10 days of IV antibiotics vs 14 days of IV antibiotic treatment among patients who are determined to have what they describe as "early, robust improvement in their lung function." The study is also looking to assess the superiority of 21 days of treatment vs 14 days of treatment among subjects who do not meet a preset definition of early, robust improvement.

The primary outcome of this study is the absolute change in lung function and is measured by FEV₁ percent predicted from

the start of treatment to 14 days after the end of treatment. The researchers are also looking at the secondary outcomes, including change in weight and symptoms scores during the time that they're treated.

Interestingly, the treating physicians at the study sites will largely determine the specific antibiotics that are used. The STOP-2 study started enrolling patients in the summer of 2016, and the goal is to enroll 880 adult patients through the year 2019 at multiple CF centers across the country.

MR. BUSKER: Thank you for sharing your insights, doctors. I'd like to wrap things up now by reviewing today's discussion in light of our learning objectives. So to begin: the significance of pulmonary exacerbations and the impact they have on the progression of CF lung disease. Dr. Dezube?

DR. DEZUBE: Pulmonary exacerbations are significant contributors to the progression of CF lung disease. They contribute to a decline in lung function, and patients are at risk for not recovering the lung function that is lost in the context of an exacerbation. Pulmonary exacerbations require timely and aggressive management.

MR. BUSKER: And our second learning objective: the current evidence describing risk factors for pulmonary exacerbations and strategies for management. Dr. Jennings?

DR. JENNINGS: The main risk factor for pulmonary exacerbations is the patient's history of previous exacerbations. Research has demonstrated that more frequent exacerbations in the past place a patient at greater risk for a subsequent exacerbation. And although there are many questions that we're hoping to answer with regards to management of pulmonary exacerbations, we do know that optimal management requires prompt initiation of targeted antibiotic therapy.

MR. BUSKER: And finally, Dr. Dezube: the challenges in investigating pulmonary exacerbations and the current efforts to better understand exacerbations and how to treat them.

DR. DEZUBE: The biggest challenges in investigating pulmonary exacerbations include the lack of a standardized definition of an exacerbation, as well as the wide variety in practice patterns in treatment exacerbations. Ongoing research efforts are, however, in place to study a standardized duration of IV antibiotic therapy.

MR. BUSKER: From the Johns Hopkins University School of Medicine — Dr. Rebecca Dezube, Dr. Mark Jennings — thank you both for participating in this eCysticFibrosis Review Podcast.

DR. JENNINGS: Thank you, Bob, it was our pleasure.

DR. DEZUBE: Thanks for having us. This was great.

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