



VOLUME 5 – ISSUE 2: TRANSCRIPT

# Featured Cases: Pulmonary Exacerbations: Diagnoses, and Therapeutic Regimens

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

- Describe a general definition of pulmonary exacerbations.
- Define a successful recovery from a pulmonary exacerbation.
- Summarize the key unanswered questions about pulmonary exacerbations.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to Pulmonary Exacerbations in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 5, Issue 1 *eCysticFibrosis Review Newsletter* – [Pulmonary exacerbations: diagnoses, and therapeutic regimens.](#)

### MEET THE AUTHOR



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### Guest Faculty Disclosure

The author has indicated that he does not have financial interests or relationships with a commercial entity.

### Unlabeled/Unapproved Uses

Dr. Flume reports that he will refer to the non-FDA-approved use of macrolides in the treatment of cystic fibrosis.

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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.

**INTENDED AUDIENCE**

This activity has been developed for pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dietitians, nutritionists, nurses, and physical therapists.

**STATEMENT OF NEED**

Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

**Disease-Modifying Therapies**

- Clinicians may be unfamiliar with recently introduced disease-modifying therapies and how they are altering the therapeutic landscape for patients with cystic fibrosis.
- Clinicians may be uncertain how to integrate genotyping into therapeutic decisions and how to communicate with patients and families about the relationship between genotype and therapy

**Nutrition**

- Many clinicians lack strategies to persuade patients to adhere to CF nutritional requirements, resulting in low body weight and nutritional failure in patients with cystic fibrosis.
- Many clinicians remain uncertain how to optimize pancreatic function in patients with cystic fibrosis.

**Treating CF Patients with Inhaled Antibiotics**

- Clinicians lack knowledge about the use of existing and emerging inhaled ABX to treat chronic pulmonary infections.
- Clinicians need more information to make informed decisions about the use of inhaled ABX in combination.
- Clinicians lack information about best practices for scheduling ABX therapy to suppress chronic airway infections.
- Common clinician assumptions about treating pulmonary exacerbations lack supporting evidence.
- CF clinicians are not aware of and/or are not actively advocating inhaled ABX patient-adherence strategies.

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**MR. BOB BUSKER:** Welcome to this eCysticFibrosis Review podcast, the first in our fifth volume of this program. Today's discussion is a follow-up to our newsletter topic: *Pulmonary exacerbations: diagnoses and therapeutic regimens*. Joining us today is that issue's author, Dr. Patrick Flume, Professor of Medicine and Pediatrics, at the Medical University of South Carolina in Charleston.

eCysticFibrosis Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from AbbVie, Gilead Sciences Inc., and Vertex Pharmaceuticals.

Learning objectives for this audio program include:

- Describe a general definition of pulmonary exacerbations.
- Define a successful recovery from a pulmonary exacerbation.
- Summarize the key unanswered questions about pulmonary exacerbations.

Dr. Flume has indicated that he does not have any relevant financial interests or relationships with any commercial entities, and his discussion today will refer to the non-FDA-approved use of macrolides in the treatment of cystic fibrosis, although these agents are in general use and are recommended by the guidelines.

I'm Bob Busker, managing editor of eCysticFibrosis Review. And I want to thank you, Dr. Flume, for joining us today.

**DR. FLUME:** Thank you, it's my pleasure to be here with you today.

**MR. BUSKER:** In your newsletter issue, you reviewed the relevant literature describing the use of antibiotics in pulmonary exacerbations, why some patients don't recover to baseline after a pulmonary exacerbation, and the importance of treating pulmonary exacerbations in mild lung disease. Today I'd like to discuss how some of that new information can translate into practice change in the clinic. So please start us out by describing a patient.

**DR. FLUME:** Let's start with a pediatric case. Our patient is 10 years of age and is homozygous for delta-F508 so is pancreatic-insufficient. He has no history

of pseudomonas, but the clinic has a program of frequently culturing their patients. His last culture was an oropharyngeal swab that grew methicillin-susceptible *Staphylococcus aureus*. His baseline lung function has an FEV1 90% of predicted, and the clinic thinks the patient and his family are pretty adherent to therapy, which in his case includes airways clearance, dornase alfa, and hypertonic saline. We get a call from home, and his mother says her son is having increasing cough and chest congestion and can't keep up with his exercise and athletics as he typically does.

**MR. BUSKER:** My first question is pretty simple: is this a pulmonary exacerbation?

**DR. FLUME:** I think most people would give the short answer and say yes. Although we don't have a specific definition for a pulmonary exacerbation, in general it's when a patient's baseline status is worse. Years ago, the CF Foundation pulled together a consensus conference to come up with their first set of guidelines related to exacerbations, which they defined it as a change in respiratory signs and symptoms from the patient's baseline necessitating treatment with antibiotics and augmented airway clearance.

The FDA would prefer our definition to be based up the patient's presentation, and then once we've made the diagnosis, that would prompt the therapy. If we look at those changes in respiratory signs and symptoms, the most common one we'll see is an increase in coughs, increase in chest congestion, and decrease in exercise tolerance, which is what we're hearing from this patient.

Some additional features that patients might see would be new findings, like crackles, on chest exam. There might be some hemoptysis, a decrease in appetite or weight loss, or a drop in lung function, which would require bringing in the patient for a clinic visit. I think most people, if they know this patient well and hear this description of the patient, are probably comfortable defining this as a pulmonary exacerbation.

**MR. BUSKER:** Assuming this is a pulmonary exacerbation, how would this patient most likely be treated?

**DR. FLUME:** The most common approach to treatment would be instituting antibiotics and ramping up of his airways clearance, much like was stated in those CF guidelines. In terms of airways clearance therapies, most times we'll talk to the patient or parents to make sure they're adherent — in some cases they're not — and getting them to do their therapies. That's the most important step. You might increase the frequency, for example, instead of twice a day, go to three times a day, and then be certain they're also adherent with their chronic therapies, such as in his case dornase or hypertonic saline. But antibiotics would most likely be prescribed for a patient like this, typically based on the knowledge of what he has had in his cultures. Since he has not grown pseudomonas in the past, it's unlikely that an antipseudomonal antibiotic would be selected. Since he's grown methicillin-susceptible *S. aureus*, very likely he'll be prescribed an oral antibiotic, which could be a penicillin, a sulfa drug, or doxycycline to target the methicillin-susceptible *S. aureus*.

**MR. BUSKER:** Let's assume that this patient has had these treatments you've described. How do you know when the exacerbation has resolved?

**DR. FLUME:** That's the critical question: what is the main endpoint when we know the exacerbation has resolved? Various endpoints have been things like a change in symptoms, a change in lung function, getting back to their previous baseline, perhaps a change in quality of life, or time to next exacerbation. But since this patient is being treated based on the worsening of symptoms, it's very likely that we'll look for a resolution of those symptoms, that he gets back to this baseline.

Unfortunately, we don't have any measures that are used routinely in the clinic, although some measures are being evaluated by the FDA to see if they can be validated for use in clinical trials. If we wanted to look at lung function, it would require bringing the patient in before treatment to see if the lung function has changed, and if it has, then trying to get him back to his previous baseline, which we said was about 90% of predicted.

The unfortunate finding, looking at registry data, is that patients often don't get all the way back to their baseline lung function. That's one of the challenges in these kinds of cases where they seem to be young,

are doing well, and we're comfortable treating these patients over the phone without requiring them to come in for a clinic visit. In fact, patients and families may not be willing to come in for clinic visit and would prefer to be treated over the phone because a clinic visit is very inconvenient or they're missing school or work.

I think in this case the patient would probably be treated for 10 to 14 days with antibiotics with either a plan for a subsequent phone call, a conversation to see if he's recovered, or an appointment to the clinic to see if he is in fact back at his baseline lung function for reevaluation.

**MR. BUSKER:** After this patient has been treated and the exacerbation has resolved, what are the next steps? What happens in the longer term?

**DR. FLUME:** When we take care of our patients with exacerbations, we try to look at ways to prevent exacerbations, in part because exacerbations are inconvenient, they're associated with worse morbidity, they may be associated with loss of lung function that doesn't recover, so we'd love to be able to prevent them.

When we think about exacerbations and their causes, some are truly acute events like a viral infection, so in that case we might make sure the patient has been fully immunized, teach them good hygiene, or try to prevent acquisition of other viral infections. In some cases, they may not fully recover because of their chronic regimen or their underlying host response. There's not much we can do to manage the inflammatory response these patients generate, at least not at this point. We can try to reinforce the importance of doing their daily therapies, because some of our patients, their exacerbations are not actually acute events but an accumulation of chronic airway secretions, so perhaps we could do a better job with our chronic therapies and our airways clearance. This becomes an opportune time to reinforce that chronic management.

The one piece I wish we could do a much better job of is documenting these events so we can learn from them to develop our best practices for best way to manage these patients, particularly over the telephone. So we need to know what prompted therapy and what was the outcome.



**MR. BUSKER:** Thank you for that patient and discussion, doctor. And we'll return, with Dr. Patrick Flume from MUSC, in just a moment.

**MS. MEGAN RAMSEY:** Hello, my name is Meghan Ramsay, nurse practitioner and adult clinical coordinator for the Johns Hopkins Cystic Fibrosis Program at the Johns Hopkins University School of Medicine. I am one of the Program Directors of eCysticFibrosis Review. These podcast programs will be provided on a regular basis to enable you to receive additional current, concise, peer-reviewed information through podcasting, a medium that is gaining wide acceptance throughout the medical community. In fact, today there are over 5,000 medical podcasts. To receive credit for this educational activity and to review Hopkins policies please go to our website at [www.ecysticfibrosisreview.org](http://www.ecysticfibrosisreview.org). This podcast is part of eCysticFibrosis Review, a bimonthly email-delivered program available by subscribing. Each issue reviews a current literature on focus topics important to clinicians caring for patients with Cystic Fibrosis.

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**MR. BUSKER:** Welcome back to this eCysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Patrick Flume, professor of medicine and pediatrics at the Medical University of South Carolina in Charleston. Our topic is "Pulmonary exacerbations: diagnoses and therapeutic regimens." We've been discussing how the information Dr. Flume presented in his newsletter issue can be put into practice in the clinic. So please bring us another patient.

**DR. FLUME:** Let's go to another common type of patient we see: an adolescent. We had a 17 year old young man who is also homozygous for delta-508 and thus is pancreatic- insufficient. He's undernourished, has a low body mass index, and unlike our previous patient, he has chronic airways infection with pseudomonas. This is not the first pseudomonas infection; he has grown it on repeated past cultures.

His baseline lung function is an FEV<sub>1</sub> that's 75% of predicted, and you are not so convinced that he's faithful to his treatment regimen. He's on a pretty robust regimen which includes airways clearance, inhaled dornase, inhaled hypertonic saline, inhaled antibiotics, and chronic macrolides. I need to say that macrolides are not indicated by the FDA for the treatment of cystic fibrosis, but we have demonstrated their benefit in patients with cystic fibrosis and they are in our practice guidelines.

So that's a very difficult regimen for a 17 year old to take, so it's not surprising that he may not be fully adherent to therapy. And so again we get a call from home and his mother says he has an increasing cough and sputum production, his appetite's down, and he's not doing his therapies which is consistent with the history we gave. This time you bring him to clinic and repeat his lung function. His FEV<sub>1</sub> now is reduced, it's 55% of predicted which is down from his baseline of 75%, and he's lost some weight, so his body mass index has decreased.

**MR. BUSKER:** How should this patient be treated?

**DR. FLUME:** First, I think everyone will agree that this patient has a pulmonary exacerbation and warrants intervention. The first question is how are you going to treat him, and the second question is where are you going to treat him: are you going to treat him at home or in the hospital?

In terms of how you will treat him, I think antibiotics will be a preferred regimen because he has pseudomonas in his cultures. We have very few options when it comes to oral therapies, generally fluoroquinolones, and very likely he's seen a lot of quinolones given his lung function status.

People might prefer to have a broader choice of antibiotics, which would mean intravenous therapy, although some people use combinations of oral and inhaled, IV and inhaled, and so forth. Since he is

already supposedly on inhaled antibiotics, then to just continue that would probably not be the best approach. I think most people would probably say this is a pretty significant drop in lung function in a young man who is undernourished, so IV therapy would probably be the choice.

Most people would probably give a combination of antibiotics, not necessarily because pseudomonas requires two antibiotics, but because complex infections like we see in cystic fibrosis might be better covered with dual coverage.

The next question is whether we should do this in the hospital or at home. In some cases the decision to hospitalize is because of the acuity of illness. If a patient is too ill, then we want to have them in a greater observed setting, but in other cases we'll bring him into the hospital because we want to be certain they get the therapy they need. It's not just about IV antibiotics, because that can be done reasonably easy at home as well, but it's the other aspects of therapy, airways clearance therapy in particular, but also nutritional management and monitoring for potential CF-related diabetes. I think in this particular case, because you are worried about the patient's adherence to therapy, you'd have little faith that he would actually ramp up to what he needs. He needs IV antibiotics, so I think most people will probably recommend hospitalization and treatment with IV antibiotics as well as the rest of his therapies.

**MR. BUSKER:** Selecting the antibiotics to treat this patient — what would guide your choices?

**DR. FLUME:** As I have already said, most people will probably to use a combination of antibiotics. You have the luxury of knowing his previous cultures, so in many cases people will probably try to choose antibiotics to which that bug would be susceptible. It comes from our classic teaching of microbiology that we need to identify the bug and its susceptibilities because if we don't use that antibiotic, the patient will fare poorly.

But what we've learned in cystic fibrosis is that the information we get from the microbiology lab does not really predict clinical outcome. The easiest example for me to describe that is a patient who has a pathogen that is resistant to the antibiotics you are using, yet the patient improves clinically.

We've tried to understand why that might be the case, and people have talked about synergy testing and so forth, but nothing has really risen to inform us. But what we have learned is that infection in CF patients is far more complex; it's not just the couple of bugs that are identified under standard culture techniques, so when you look at microbiome testing you begin to understand that there may be hundreds of different species down there, but you don't know which are the bugs of interest, which are the bugs that are causing the infection or the exacerbation. Although we're constantly tempted to use susceptibility testing to guide our therapy, we've learned that it's probably a reasonable strategy to use the antibiotic on which you've had success previously.

For example, if six months ago he had been treated with cefepime and tobramycin and did well, that might be a reasonable choice for today. We would perhaps recommend changing those antibiotics if he isn't recovering as you feel he should be, for example he is not getting better from this exacerbation or he seems to be having more frequent exacerbations; those might warrant a change in those antibiotics.

**MR. BUSKER:** The duration of IV antibiotic therapy — what would you expect it to be in a patient like this?

**DR. FLUME:** The million dollar question is what is the optimal duration of IV antibiotics. When you talk to clinicians, they may tell you with great certainty the duration should be 10 days or 14 days. But when you look at what people actually do, you begin to see that a very broad range of antibiotic durations has been used. When we did this analysis for our guidelines a few years ago, we found that the average duration of antibiotics peaked at around 14 days, with another, smaller peak at 21 days, but there was a wide spread around that ranging from two to 32 days.

Our guidelines state we didn't know the optimal duration of therapy. Previous guidelines said the duration should be 10 to 14 days, and perhaps longer if the patient has other features that would suggest that a longer duration is necessary. This is a question we desperately need to answer.

For obvious reasons we would not want to treat for too short a time, because we would expect they would not recover completely or they would have a second exacerbation in a short period of time. There are also

considerable risks of treating too long because of the cost and potential toxicity of these medications, particularly with aminoglycosides that our adult patients use. After years of IV aminoglycosides use, we see toxicity with reduction in hearing and perhaps renal insufficiency. So this is a terribly important question that needs to be answered, and we're trying to do that now with novel approaches to understanding optimal treatment of exacerbations.

**MR. BUSKER:** One more question on this patient, and that's, how would you measure success in treating this patient's exacerbation?

**DR. FLUME:** That's another very important question. Obviously clinicians choose to stop antibiotics at some point where they've decided they have achieved as much as they can from the antibiotics. But some of those patients are being treated for a third week, a fourth week, or longer so we're trying to understand what drives that decision, what makes them want to treat for a longer period of time.

As I mentioned earlier, there are some potential candidates for a clinical endpoint, such as symptoms; returning to baseline, but we don't currently measure that; lung function, we measure it frequently; and we can talk about return to baseline. In our study of exacerbations, one of the things we're asking clinicians to tell us is their target lung function, because we now have data from the registry showing that a considerable portion of patients don't fully recover to their baseline. When that doesn't happen, we are trying to understand why the clinicians chose to stop therapy: is it because baseline is not an achievable goal, they've established a new baseline, or should we have treated for a different period of time?

The other possible endpoint is the time to the next exacerbation. Some data we have looked at suggest that the median time to that next exacerbation is about six months, and that just seems too long to blame on the duration of treatment; it much more likely has something to do with the chronic therapies they use between the exacerbations.

Another potentially effective endpoint is something we'll call early treatment failure. By that I mean the time to the next exacerbation occurs soon after completion, and this is comparable to what has been done in other types of lung infections like ventilator-

associated pneumonia or community-acquired pneumonia, looking at the proportion of patients who require or are treated with antibiotics less than 30 days after the previous completion. We're hoping to learn the relevant endpoints from our observational trial of exacerbation, because that's how we'll learn about optimal treatment of exacerbations.

**MR. BUSKER:** Thank you for sharing your thoughts. Please bring us one more patient.

**DR. FLUME:** Let's go to an adult patient. This is a 27 year old female, also homozygous for delta-F508, thus also pancreatic-insufficient. She, too, has chronic infection with pseudomonas, and her baseline lung function is an FEV<sub>1</sub> that's 55% of predicted. You believe she adheres pretty well to her therapies, which include airways clearance, inhaled dornase, inhaled hypertonic saline, inhaled antibiotics, and oral macrolides. She calls saying she feels she's having signs and symptoms of an exacerbation. She has increasing cough and sputum production, and she also describes coughing up about a quarter cup of bright red blood as part of this event.

**MR. BUSKER:** Would you hospitalize this patient or treat her at home?

**DR. FLUME:** I think everyone would agree that she has a pulmonary exacerbation and we need to treat her. The other interesting aspect here is hemoptysis. When we were trying to put together our guidelines on how to manage complications such as hemoptysis, we very quickly learned there were no published trials that provide evidence for managing hemoptysis. So for those guidelines we prepared a consensus document, obtained from a panel of pediatric and adult physician experts from around North America. None of whom knew who else was in the group, and we used the Delphi approach to get their opinion on these recommendations. One of the questions we asked was, should the patient be treated in the hospital. Of course, the answer we got from them was, it depends on how much blood they're coughing up.

So we had to separate scant hemoptysis, which might be less than 5 cc, a teaspoon of blood, all the way up to massive hemoptysis, which would be defined as more than 250 cc of blood in a day. This patient falls in the moderate range, and generally, the experts felt that amount was better managed in the inpatient setting. The treatment of the exacerbation would be

principally the same; however, the worry was that could this result in even greater bleeding, and so observation would be necessary. So in this case I think most people would recommend hospitalization.

**MR. BUSKER:** With an exacerbation of this magnitude, I think we can assume you're going to use IV antibiotics. But is there a role for aerosolized antibiotics in conjunction with the IV?

**DR. FLUME:** That was a question that we also addressed in our guidelines on exacerbations. Principally we're talking about using inhaled aminoglycosides like tobramycin when you are already using intravenous aminoglycosides. Generally, people would say that intravenous therapy is the gold standard because the drug will go to the site of infection. But we've learned recently looking at MRI scans of lung perfusion, that during exacerbations some areas of the lung have reduced perfusion, so you don't really know where the antibiotic is being delivered intravenously or by the inhaled route.

That lends the idea that maybe there might be some advantage to using inhaled therapy along with intravenous therapy, that you're sort of hitting the infection from both directions and increasing your probability of trying to get drug to where you want it. The problem we had with the guidelines is that there wasn't any evidence that showed that this was more efficacious, there wasn't any evidence to show that it was safer. So when we sat down to design a study and imagine what that study might look like, one of the key questions we faced was timing of dosing. Because when you use an inhaled antibiotic, some of that drug will be absorbed, and when dealing with a drug like an aminoglycoside where you're measuring levels, you're doing pharmacokinetics to help dose your IV therapy, how much drug is being absorbed and will it affect those results.

We did a small study of 20 patients, looking at the effect of timing of the inhaled antibiotics, and we found that if you give the inhaled drug in the latter part of the dosing interval, that is, in the few hours before the next dose is to be delivered, in about 40% to 45% of patients you will change the PK measurements. The patients will absorb enough drug that it might change how you dose intravenously.

We didn't show anything about efficacy or safety, but we did show that if you use inhaled along with IV, you need to understand that pharmacokinetics will change because that will affect how you interpret the levels you get.

**MR. BUSKER:** Besides the antibiotics, are there other therapies you would recommend for this patient?

**DR. FLUME:** Some people are concerned about continuing some of the standard therapies used in these patients, such as airway clearance or chronic therapies including dornase and hypertonic saline, because in a patient with hemoptysis they will aggravate the bleeding. For example, will hypertonic saline make them cough so much that that clot will break free and aggravate additional bleeding? Same for airway clearance therapies. Others would say the problem is inflammation, so you have to treat that underlying process or the bleeding will just keep going. In our guidelines we found that in patients with less hemoptysis, more like scant hemoptysis, there was very little concern about holding off on those therapies, so they would be continued.

In the setting of massive hemoptysis, there was greater concern about inhaled therapies and airway clearance therapies, so the recommendations generally in massive hemoptysis is to hold up on airway clearance therapies, particularly things like vests or IPV, which are more rigorous than the active cycle breathing. And maybe back off with the inhaled therapies.

But in this patient who has moderate hemoptysis, there was no clear recommendation, but the general hint was that people were a little more concerned about hypertonic saline because it was more likely to aggravate the cough.

I think in a patient like this, people are probably willing to continue some of the inhaled therapies like antibiotics and dornase, but far more likely to withhold the hypertonic until the hemoptysis resolves. Other therapies that have been tried, particularly in patients like this, are corticosteroids to try to reduce the inflammation.

When we looked at that question for the guidelines on exacerbations, we again found insufficient information upon which to make a recommendation. There are clearly cases in which patients seem to



improve with corticosteroids, but we don't have enough evidence upon which to make a recommendation for using it as a routine therapy.

**MR. BUSKER:** Thank you for today's cases and discussion, Dr. Flume. I'd like to switch topics now and ask you: In current investigations into pulmonary exacerbations, what are the key areas that are being focused on?

**DR. FLUME:** As I alluded to earlier, exacerbations come with increased morbidity and increased costs, and another key finding is that many of these patients lose lung function from which they don't recover, and we desperately want to try to maintain lung function.

I listed three hypotheses for why patients might not recover their lung function. One could be the etiology of the exacerbation, so there is still a need to know what might be causing exacerbation. We also have to know that not all of our patient's exacerbations are from the same cause. We're trying to understand the phenotype to try to help guide some therapy.

If the etiology of the exacerbation, like viruses, change in bacterial community, allergies, then are there biomarkers that would tell us when that's occurring? But our main goal in those patients would be prevention: how do we prevent those events?

The second major hypothesis is patient factors such as their underlying pulmonary impairment, what chronic therapies they are using, and their host response. Because if we're now developing therapies there, we can try to focus on trying to deal with inflammation perhaps or work on adherence to their chronic therapies.

The third hypothesis is the one we're focusing on in our studies of exacerbations: treatment. Because if we provide inadequate treatment and that's why the patients don't fully recover, that's where we could actually try and work to improve.

One main area of inadequate treatment would be delayed intervention, when the patient's symptoms or issues are developing but we're just starting to late. An approach being looked at in a study called the eICE trial has patients doing closer monitoring at home, which would provide the information to allow the clinician to prompt therapy sooner. We're trying to define optimal treatments, and that's what we're

doing in our STOP trial, the Standardized Treatment of Pulmonary Exacerbations, to try to define clinical endpoints we can use in our first interventional trials.

So there's a lot of exciting work going on in the study of pulmonary exacerbations now.

**MR. BUSKER:** Thank you for sharing those insights, Dr. Flume. To wrap things up, I'd like to revisit our learning objectives in light of today's discussion. So to begin: providing a general definition of pulmonary exacerbations.

**DR. FLUME:** The first definition is a change from baseline in respiratory symptoms. The second is a change in other signs, typically a change in lung function such as FEV1. And the third key one is the presentation with other relevant features such as coughing up blood, or hemoptysis.

**MR. BUSKER:** And our second objective: defining the success of recovery from a pulmonary exacerbation.

**DR. FLUME:** In general, clinicians use two key areas to determine when to stop therapy in treatment of exacerbation. The first is symptom resolution: whatever symptoms were worse, they have now returned to their baseline.

The second is recovery of lost lung function to baseline. Some people will have a standard treatment duration for treating patients.

Those are the endpoints people use when taking care of an individual patient, but other important outcomes include time to the next exacerbation.

**MR. BUSKER:** And finally: the key unanswered questions about pulmonary exacerbations.

**DR. FLUME:** We outline several unanswered questions in our guidelines because we asked them and we didn't find sufficient evidence. But I think we should do better on some key questions. One is the duration of IV antibiotics. The second is defining a role for corticosteroids, and who should get them and when. The third is hospital versus home therapy, what time should be spent in the hospital for optimum management.

**MR. BUSKER:** Dr. Patrick Flume from the Medical University of South Carolina, thank you for participating in this eCystic Fibrosis Review Podcast.

**DR. FLUME:** It was my great pleasure to be here. I do enjoy talking about exacerbations, and I hope that our next conversation I have more answers than I had today.

**MR. BUSKER:** To receive CME credit for this activity, please take the post-test at [www.ecysticfibrosisreview.org/test](http://www.ecysticfibrosisreview.org/test).

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