



VOLUME 2 – ISSUE 10: TRANSCRIPT

Featured Cases: Guidelines: State-of-the-Art Treatment for CF Lung Disease

At the conclusion of this activity, participants will demonstrate the ability to:

- Describe the assessment process for infants diagnosed with cystic fibrosis,
- Explain the use of chronic daily therapies for adolescents with CF, and
- Discuss the treatment of pulmonary exacerbations in adult CF patients.

This audio activity has been developed for clinicians caring for patients with issues related to cystic fibrosis. You can also read the **companion newsletter**. Dr. Flume will help expand our understanding of how the guidelines treating lung disease affects the treatment of cystic fibrosis, with the discussion some typical case scenarios.

Unlabeled/Unapproved Uses

The author indicates in this presentation that there will be discussion of the off-label use of azithromycin to treat patients with CF.

MEET THE AUTHORS



Patrick A. Flume, MD

Professor of Medicine and Pediatrics
Medical University of South Carolina
Charleston, South Carolina

Guest Faculty Disclosure

Patrick A. Flume, MD discloses that he receives grants and research support from Boehringer Ingelheim, Gilead, Mpex, Pharmaxis and Vertex.

Release Date	Expiration Date	Next Issue
September 14, 2010	September 13, 2012	August 10, 2010

PROGRAM DIRECTORS

Michael P. Boyle, MD, FCCP
Associate Professor of Medicine
Director, Adult Cystic Fibrosis Program
The Johns Hopkins University
Baltimore, MD

Peter J. Mogayzel, Jr., MD, PhD
Associate Professor of Pediatrics
Director, Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

Donna W. Peeler, RN, BSN
Pediatric Clinical Coordinator
Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

Meghan Ramsay, MS, CRNP
Pediatric Clinical Coordinator
Adult Clinical Coordinator
Cystic Fibrosis Center
The Johns Hopkins University
Baltimore, MD

ACCREDITATION STATEMENTS

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

The Institute for Johns Hopkins Nursing and the American Nurses Credentialing Center do not endorse the use of any commercial products discussed or displayed in conjunction with this educational activity.

CREDIT DESIGNATIONS**Physicians**

Podcast: The Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.75 *AMA PRA Category 1 Credit(s)*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurses

Podcast: 0.50 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.50 contact hours or a total of 3.0 contact hours for the six podcasts in this program.

To obtain contact hours, you must complete this Education Activity and post-test before September 13, 2012.

Allied Health

Podcast: the Johns Hopkins University has approved this activity for 0.75 contact hours for non-physicians.

Respiratory Therapists

For United States: [Visit this page](#) to confirm that your state will accept the CE Credits gained through this program.

For Canada: [Visit this page](#) to confirm that your province will accept the CE Credits gained through this program.

There are no prerequisites to participate in the activity.

INTENDED AUDIENCE

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

LAUNCH DATE

This program launched on March 9, 2010, and is published monthly; activities expire two years from the date of broadcast, ending in March 8, 2012.

SUCCESSFUL COMPLETION

To take the post-test for eCysticFibrosis Review you will need to visit [the Johns Hopkins University School of Medicine's CME website](#) and [the Institute for Johns Hopkins Nursing](#). If you have already registered for other Hopkins CE programs at these sites, simply enter the requested information when prompted.

Otherwise, complete the registration form to begin the testing process. A passing grade of 70% or higher on the post-test/evaluation is required to receive CE credit.

STATEMENT OF RESPONSIBILITY

The Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing take responsibility for the content, quality and scientific integrity of this CME/CE activity.

INTERNET CME/CE POLICY

The Office of Continuing Medical Education (CME) at the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing are committed to protect the privacy of its members and customers. The Johns Hopkins University maintains its Internet site as an information resource and service for physicians, other health professionals and the public.

Continuing Medical Education at the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing will keep your personal and credit information confidential when you participate in a CE Internet-based program. Your information will never be given to anyone outside the Johns Hopkins University program. CE collects only the information necessary to provide you with the service you request.

FACULTY DISCLOSURE

As a provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of Johns Hopkins University School of Medicine to require the disclosure of the existence of any relevant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

- **Michael P. Boyle, MD, FCCPD** discloses that he has received grant/research support Vertex Pharmaceuticals, Inc.
- **Peter J. Mogayzel, Jr, MD, PhD** discloses that he has no financial relationship with commercial supporters.
- **Meghan Ramsay, MS, CRNP** discloses that she has no financial relationship with commercial supporters.
- **Donna W. Peeler, RN** discloses that she has no financial relationship with commercial supporters.

DISCLAIMER STATEMENT

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only. Use of Johns Hopkins University name implies review of educational format design and approach. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K Modem or better, Windows Media Player 9.0 or later, 128 MB of RAM, monitor settings: high color at 800 x 600 pixels, sound card and speakers, Adobe Acrobat Reader.

MR. BOB BUSKER: Welcome to this eCysticFibrosis Review podcast. eCysticFibrosis Review is presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by an educational grant from Genentech, Eurand Pharmaceuticals, Vertex Pharmaceuticals, Axcan Pharma, and Gilead Sciences Medical Affairs.

Today's program is a companion activity to our August 2010 eCystic Fibrosis Review newsletter topic: Guidelines: State of the Art Treatment for CF Lung Disease. Our guest is Doctor Patrick Flume, from the Medical University of South Carolina in Charleston.

This activity has been developed for physicians, nurses, respiratory therapists, dieticians, and physical therapists caring for patients with cystic fibrosis. There are no fees or prerequisites for this activity. The Accreditation and Credit Designation Statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies, expiration dates, and to take the post-test to receive credit on-line, please go to our website newsletter archive, www.ecysticfibrosisreview.org, and click on the September 2010 podcast link.

Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:

- Describe the assessment process for infants diagnosed with cystic fibrosis,
- Explain the use of chronic daily therapies for adolescents with CF, and
- Discuss the treatment of pulmonary exacerbations in adult CF patients.

I'm **BOB BUSKER**, managing editor of eCysticFibrosis Review. On the line we have with us our August newsletter issue's author, Doctor Patrick A. Flume is a Professor of Medicine and Pediatrics, and Director of the Cystic Fibrosis Center at the Medical University of South Carolina. Doctor Flume has disclosed that he has received funds for grants or research support from Boehringer Ingelheim, Gilead, Mpex, Pharmaxis, and Vertex.

His presentation today will include discussion of the off-label use of azithromycin to treat patients with CF.

Doctor Flume — welcome to this e-cystic fibrosis review Podcast.

DR. FLUME: Thank you, I'm happy to be here.

MR. BUSKER: To increase our understanding of how the various guidelines can help clinicians provide better patient care, we've asked Dr. Flume to discuss some typical case scenarios. So if you would, doctor — bring us our first case.

DR. FLUME: The patient is a six-week old infant who was diagnosed with cystic fibrosis by newborn screening. He had an elevated immunoreactive trypsinogen test and was found to be homozygous for delta-F508, the most common mutation in CF. The parents state that the infant has no respiratory symptoms and is feeding well. He has frequent foul smelling stools, his examination is essentially normal with his weight and length at the 50th percentile.

MR. BUSKER: In the newsletter issue, you reviewed the most recent guidelines for the management of infants with CF. Your comments on how they apply here?

DR. FLUME: So the CF Foundation recently supported the development of some guidelines for the management of infants with cystic fibrosis, and one of the critical points is that by doing newborn screening we expect to identify infants who otherwise appear totally healthy to the parents. So for many of these families this diagnosis is going to be a surprise.

So one of the major steps for these families is to be able to provide them with an adequate amount of time and education to prepare them for learning about CF and what to expect in the care of their child, and this is best performed at a CF center.

And so one of the key recommendations out of these guidelines were that these children should be referred to a CF center to be seen within 24 to 72 hours of the diagnosis. At that center we can provide the information in the most clear, most structured format for the families, both verbal as well as the developing materials, and to steer them towards what they need

to be looking for and what they should anticipate as we evaluate this child as they grow up.

MR. BUSKER: And the approach to evaluating these babies at the time of diagnosis?

DR. FLUME: The critical goals for the child are to maintain normal growth and development as well as delay the onset of pulmonary disease. And so one of the critical issues is the evaluation of nutritional status and implementation of proper treatment of these infants, and this is a child growing at a time with very high metabolic needs, and we also know from studies that the better the nutrition in the infant, the better their lung health will be later in life. So nutrition is really a key early in life.

Many of these children with CF will have pancreatic insufficiency, that is they won't make or produce sufficient digestive enzymes to digest the food that they eat. Pancreatic insufficiency might be present in about 60 percent of infants who are diagnosed with newborn screening, but in that first year, maybe as many as 90 percent of kids will be diagnosed with pancreatic insufficiency.

So we start off with a very high sensitivity to look for this diagnosis, and this diagnosis can be made by evaluating the stool, looking at how well they digest fat so we can collect the stool and look at fat, or we can do a test where we look for digestive enzymes in the stool, simple, straightforward test, but those results are not going to be available immediately and so for many of those kids we would want to introduce therapy early on.

Certainly if a child has obvious features of pancreatic insufficiency with frequent stools, failure to grow, foul smelling stools, as in, for example, this child that I presented, we also know that there are certain gene mutations which are clearly associated with pancreatic function, and in the guidelines there is a very nice table listing those common mutations and whether they are associated with pancreatic insufficiency or whether they would be expected to have normal pancreatic function.

So, for example, our child has two copies of the most common mutations. It is associated with pancreatic insufficiency, and the guidelines would suggest that this child should be started on digestive enzymes.

The guidelines also provide recommendation on how to start digestive enzymes in these children with the recommendation that we start with about 2,000 to 5,000 units of lipase with each feeding. And as the child grows, this would need to be adjusted to make sure they have adequate calories and digestive enzyme.

The assessment of the nutritional status is terribly important and it's why we have a dietician present as part of the team, we monitor weight gain and if there is insufficient weight gain there are a number of steps that can be implemented to try and improve their performance, perhaps by increasing calories, or adjusting medications to enhance the activity of the digestive enzymes or even work on behavioral issues to try and improve their growth calorie intake.

There were several other recommendations about other types of nutrients and I just want to comment on one of those, and that is the importance of salt replacement. These kids lose large amounts of salt through their sweat, and although there is salt in human milk or infant formulas, it's usually not sufficient to provide the salt that CF children need. And so there are recommendations for how much salt to supplement. For example, an eighth of a teaspoon of table salt each day starting at diagnosis and as the child grows you would increase that to perhaps a quarter teaspoon of table salt daily when they get to be six months of age.

MR. BUSKER: Now we know that a major goal in CF care is the prevention of lung disease, because that's going to be one of the chief morbidities that these kids will face. What do the guidelines advise as to therapeutic options?

DR. FLUME: One of the challenges that we have is that although we know that there is evidence of disease very early in life, there's not a lot of research done on therapies early in life to try and prevent that. And so what we end up doing is using many of the therapies that effective in our older kids and using them to our advantage in the infant.

So in terms of preventive measures, one thing everyone does agree on, and that is to limit the exposure to tobacco smoke. So we believe that cigarette smoke exposure is harmful to children with CF and so we are very stern in our discussions with families about secondhand smoke exposure.

The second recommendation comes with the use of airway clearance therapy, and the clearance of secretions that collect in the lower airway is abnormal in terms of how it gets out of the lungs. And so we use airway clearance therapies as a basic treatment to rid these airways of these secretions and infection that develops down in the lower airways.

In our airway clearance guidelines, we made the recommendation that airway clearance therapies should be used for all patients with CF, and even though we don't have strong data that proves their benefit in infants, we were very convinced that it should be used in these kids because the pathophysiology of disease is going on from the very beginning. And although we can't prove that there's great benefit in these therapies in these kids, there is also very little harm. And so we encourage the parents to begin airway clearance therapies as early in life as possible.

There are fewer options of airway clearance therapies in the kids, and usually that is going to be percussion and postural drainage, and we teach the families how to perform this. One of the key recommendations is that the child should not be put in the head down position to try and prevent reflux of stomach contents up the esophagus, as that might get down into the lungs.

And the other major problem that occurs in kids with CF is the development of airways infection, which we believe accelerates the progression of disease. And so we have a strategy of trying to be very aggressive at treating infections, and because these kids may become infected and yet not have any symptoms, the guidelines have now recommended that we take a very aggressive approach to culturing our patients more often.

For the young kids and the infants, these would be typically done by a swab of the oropharynx, although there have been studies looking at the benefit of bronchoscopy, or going down into the lower airways to collect secretions. Those data are suggesting that's not necessary. And so the guidelines have recommended getting oropharyngeal cultures in our kids at their quarterly visits, and certainly more often if they become symptomatic.

MR. BUSKER: Dr. Flume, let's assume that cultures are taken, and they're positive for *Pseudomonas*. What should happen then?

DR. FLUME: So the CF community is very key to chronic infection in the airways, and *Pseudomonas aeruginosa* has obviously been a very important pathogen, and we know a great deal about it and its association with more rapid progression of disease. And so we take a very aggressive approach to trying to treat it. So we look for it and if the organisms are there, we would try and treat that.

Now I want to note that we do not recommend chronic prophylaxis with antibiotics to prevent the selection of infection, so we don't start our kids on antibiotics in the absence of infection. But if a person now has a positive culture, we would then use antibiotics to try and eradicate that infection.

MR. BUSKER: Talk to us, if you would, about eradication strategies.

DR. FLUME: So there are a number of approaches that have been used to try and eradicate the early infection and this might include oral antibiotics, inhaled, or even intravenous antibiotics. We have recent data from the ELITE trial performed in Europe, and the EPIC trial performed in the United States, looking at these strategies. And although they are not necessarily defining the optimal method of eradication therapy, what they have shown us is that four weeks of aerosolized antibiotics in these studies using inhaled tobramycin, actually resulted in making the patient culture negative, suggesting eradication of the organism in 90 percent of patients.

MR. BUSKER: What about that other 10 percent? What do the guidelines suggest if eradication fails and the subsequent culture is still positive?

DR. FLUME: So, obviously, some patients are not going to respond and they will have persistence of bacterium in their cultures and this may represent what we would describe as chronic infection, and that you are not going to be able to eradicate that bug. And so in those patients, the guidelines recommend a strategy of suppressive antibiotic therapy and that's typically done by using aerosol antibiotics to suppress the burden, there are a number of bugs present in the airways, to try and prevent progression of disease or exacerbations of infection.

MR. BUSKER: A bit earlier you mentioned the role of the dietician on the CF care team. What about the primary care provider?

DR. FLUME: So the primary care provider plays a critical role, for most of these patients the CF center is not assuming total care of the patient. So you want to include the primary care provider as a member of that team. And so what's critical is that they maintain communication, that they are letting each other know what is going on.

But in those infant care guidelines there is a very nice table that they have included which lists CF specific issues that would be important for the primary care providers. And I won't go through all of them, but some of the key points that we have already discussed, one is that infants with CF do need supplemental salt and that they need to know how much to be contributing if that becomes a part of their daily routine.

The second is that we no longer have the expectation that CF kids should be short or thin. We have high standards for our kids, we want them at or above the 50th percentile, and we look at weight for length. Another way of putting that is that we would like to see our kids being slightly chubby. So we don't want to accept what they may have been in the past.

So we encourage a high fat diet, including the use of whole milk, a good way to get those calories in, and then perhaps the most important piece of information to convey is that life expectancy is steadily increasing. And so we want to maintain a high standard, high expectations for our kids, but to accomplish that we need to be doing daily preventive care. And so we want them to be reinforcing those daily therapies that we're encouraging our kids to do.

MR. BUSKER: That's information that certainly seems like it needs to be communicated to the parents, as well.

DR. FLUME: Absolutely. The parents are key members of the team. Everybody should have the same goals in mind.

MR. BUSKER: We've talked about infants, Dr. Flume — let's move on to older children in our next case.

DR. FLUME: So the next case is an 18 year old female with cystic fibrosis who has just graduated from high school and she plans to go away for college in the fall. She has a daily cough and sputum production, but there is no change from her usual symptoms. For therapy her parents perform chest physiotherapy and

she uses aerosolized dornase alfa. She has pancreatic insufficiency for which she takes digestive enzymes. She appears well, her body mass index is 18.5, and her FEV1 is 75 percent of predicted.

Her sputum grows *Pseudomonas aeruginosa*, and the culture for *Mycobacteria* is negative.

MR. BUSKER: So here we have a late adolescent who's on daily therapies for her lungs. What do you make of her current airway clearance therapy?

DR. FLUME: So an important point here is that she's going off to college, and she is going to need to have a therapy that she can do herself. Currently, her parents are performing her chest physiotherapy, but they are not going to go to college with her presumably and so she needs an alternate therapy.

In our airway clearance therapy guideline, we recommended not only that patients should do therapy every day, we also made the statement that no one therapy has been demonstrated to be superior to any others. Now that is not the same as suggesting that they are all equivalent, it just merely means that no study has demonstrated superiority.

So what we try to do is to find a therapy which works best for that individual patient. And some of the therapies that are available are — can be done by a person by themselves. So, for example, and oscillating vest, high frequency chest compression, is a device that a person could use, the same with intrapulmonary percussive ventilation or IPV.

There are handheld devices like an Acapella or a flutter, or other what we call PEP therapy devices that could be used, these are very portable. And we also in the guidelines emphasized exercise, not only as an adjunct to airway clearance, but certainly all the other benefits of exercise.

So one of the steps that we use in our center is with all of our patients we introduce them to every mode of airway clearance so they can see which therapy might work best for their situation.

MR. BUSKER: What about her chronic pulmonary medications? Are there any changes that should be made there?

DR. FLUME: So in the guidelines for chronic medications to maintain lung health, there were

several medications that have been recommended for routine use. Many of these, she would be a good candidate. Currently she is using dornase alfa, but she has *Pseudomonas* present in her cultures and could perhaps use inhaled antibiotics.

Currently available would be inhaled tobramycin, and recently inhaled aztreonam was approved. Hypertonic saline up to concentrations of 7 percent have been recommended. Macrolides, such as azithromycin, as daily therapy to reduce the inflammation, particularly if they don't have Mycobacteria present in their cultures, as she does not. And then inhaled bronchodilators.

Now she is only doing one of those therapies, that being the dornase alfa, but a couple of things are worrisome to me. And that is her body mass index is 18.5 and we might wish her to be a bit more than that, with the previous guidelines recommending a target of perhaps 22 for females, and her lung function of 25 percent of predicted is not normal.

So one strategy might be to test her with each of these other therapies to see if they add any additional benefit, although she doesn't really complain of symptoms, it may be that she could feel even better with the new therapies or realize a further improvement in her lung function.

MR. BUSKER: About bronchodilation agents — should this patient be on inhaled steroids?

DR. FLUME: So bronchodilators were recommended for our patients in our guidelines; however, we put in some caveats about which of those patients should be on bronchodilators. And actually, inhaled steroids, although they are commonly used in cystic fibrosis, much like they are in patients with asthma or COPD, we actually gave steroids a de-recommendation as a routine therapy.

What that means is that we are not recommending steroids, either oral or inhaled, as a chronic routine therapy for cystic fibrosis patients unless, of course, they have asthma or allergic bronchopulmonary *Aspergillo*sis, or ABPA. We made this recommendations because although steroids do help reduce the inflammation in the airways, there were other untoward side effects when using systemic or oral steroids, certainly in kids, affecting their growth. But recent studies have also shown no additional benefit to inhaled steroids.

So although inhaled steroids don't appear to be harmful, they didn't add any benefit, and that's why we gave the de-recommendation. But again, a caveat, that does not apply if the patient has either asthma or ABPA.

MR. BUSKER: I'd like to go into more detail on some of the things you just mentioned. Let's start with ABPA — talk to us, if you would, about how to assess a patient like this for *Aspergillo*sis.

DR. FLUME: So ABPA is an allergic response to a common fungus, or *Aspergillus*. And we do have specific criteria to establish that diagnosis. These patients not only have the bronchiectasis, but they may also have an elevated IgE, or an antibody that is elevated typically in allergies. They'll have antibodies specific to *Aspergillus*, that will be elevated, and finally a skin test to *Aspergillus*, much like you would do any other kind of allergy tests, they'll respond very quickly to it.

Those are tests that we routinely do in our patients to assess for ABPA, and we recommend that you assess all of your patients for ABPA because it occurs in perhaps 8 to 10 percent of patients.

MR. BUSKER: You also mentioned asthma.

DR. FLUME: Now, asthma is a more difficult diagnosis to make in cystic fibrosis patients because it generally is associated with wheezing and CF patients often wheeze. They may show reactivity, meaning their pulmonary function tests might improve with the use of inhaled bronchodilator, but that happens in CF all the time and doesn't mean that a patient has asthma. So it makes it a little more tricky to make that diagnosis. So the guidelines recommended assessing patients for ABPA and in terms of making a decision about using bronchodilators, that you might do pulmonary function testing before and after bronchodilator, and if they demonstrate reactivity, then yes, include bronchodilators as part of their routine therapy.

MR. BUSKER: Now with this patient — she's a young woman, she's leaving home for the first time — what else should the clinician be concerned about?

DR. FLUME: This is a critical time her life. Adolescence is a difficult time for everybody, and more so if they have a chronic condition like cystic fibrosis. So what we need to work towards is

development of independence, but yet to maintain that seriousness about the importance of doing daily therapy.

So we focus on things like adherence to treatment. It's hard to take medications, it is hard to do therapies, particularly airway clearance and aerosol therapies which take additional time. And so it is very important to try and establish a routine.

So one strategy of doing this with patients is a strategy of motivational interviewing to try and find out what works for that particular patient and build on that to try and support them. We do not take a hostile approach, we are not their parent, we do not yell and scream at our patients. We try and encourage to motivate, to help understand what they perceive is working for them and to find some way to make this work in their life.

Going off to college, there will be lots of exciting things to do, lots of new friends, peer groups, they may be shy about sharing their health condition and we have got to help them be open and comfortable with that and try and find strategies that would work for them.

MR. BUSKER: And we'll return in a moment — with Doctor Patrick Flume from the Medical University of South Carolina.

MS. MEGAN RAMSEY: Hello, I'm Megan Ramsey, nurse practitioner and clinical coordinator for adults at 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. This podcast is part of eCysticFibrosis Review, a bi-monthly, e-mailed delivered program, available by subscribing. Each issue reviews current literature on focused topics that are important to clinicians caring for patients with cystic fibrosis.

Continuing education credit for each newsletter and each podcast is provided by the Johns Hopkins University School of Medicine for physicians, and by the Institute for Johns Hopkins Nursing for nurses. Subscription to eCysticFibrosis Review is provided without charge, and nearly 1,000 of our colleagues have already become subscribers. The topic-focused literature reviews help them keep up to date on issues critical to maintaining the quality of care for their patients.

For more information, to register to receive eCysticFibrosis Review without charge, and to access back issues, please go to www.ecysticfibrosisreview.org.

MR. BUSKER: Welcome back to our September 2010 eCystic Fibrosis Review podcast.

I'm Bob Busker, managing editor of the program. Our guest is Doctor Patrick Flume from the Medical University of South Carolina. And our topic is — Guidelines: State of the Art Treatment for CF Lung Disease. We've looked at case scenarios that illustrate how the most recent guidelines can help clinicians improve patient care for infants and adolescents. So now, Dr. Flume, let's talk about adults.

DR. FLUME: Our third case is an adult male with CF who presents to the clinic feeling worse. He describes an increase in cough and an increase in sputum production. His sputum is dark green but there is no hemoptysis. There is no fever or sweats, but his appetite is decreased and he believes that he has lost weight.

On exam, he has indeed lost weight, with a BMI of 20.5, which is down from his baseline of 22. He has crackles in both upper lung zones and there is no wheezing. His spirometry reveals an FEV₁ of 60 percent of predicted, which is down from his baseline of 70 percent of predicted.

MR. BUSKER: Your initial impressions of this patient, Dr. Flume?

DR. FLUME: This patient has what we would call a pulmonary exacerbation of CF. These are frequent events, they occur in about a third of the patient visits to the adult clinic. They occur with greater frequency in patients as they get older or have more advanced disease.

MR. BUSKER: Now Dr. Flume, you were the lead author of the recently published clinical practice guidelines for treating pulmonary exacerbations. Is there any definition that differentiates an exacerbation from other presentations?

DR. FLUME: The definition of an exacerbation is something that is elusive to us. We all have a general agreement as to what an exacerbation is, generally it's an increase in symptoms, and much like this gentlemen, worsening cough, increase in sputum. He has systemic symptoms where he's lost his appetite and now he's losing weight, and other objective measures such as a drop in lung function.

And although we don't have a clear definition of exacerbation, this is a clear example that everyone would agree is a patient with an exacerbation that needs intervention.

MR. BUSKER: What might cause an exacerbation to occur?

DR. FLUME: In most cases where a patient presents with an exacerbation, we don't have an idea of what caused it, what prompted this worsening of symptoms. There have been many suggestions as to what causes an exacerbation, some of which are acute events, and others may be that it's really just a chronic progression of their underlying disease that has finally reached a critical threshold where the patient develops symptoms.

Examples of acute events might be an acute infection, so perhaps even a viral infection that now has increased the inflammation of the airways and revved up the bacterial infection. Or it may be that they've acquired a new bacterium, that now a new *Pseudomonas* or a *Staph* has reached the airways and is causing an increase in inflammation.

And then there are some who have suggested that there are changes that occur with the bacteria present in the airways, something happens that they now morph into a more inflammatory inciting infection, and that's what's prompted the exacerbations.

But other suggestions of non-infective acute changes range from esophageal reflux, or even an aspiration down into the lower airways, and that causes them inflammation that exacerbates their symptoms.

MR. BUSKER: In the case of bacterial infections, what do the guidelines advise regarding antibiotics?

DR. FLUME: Antibiotics have become a principal aspect of an exacerbation, whether it's because of a new bacterial infection, or because they have the chronic bacterial infection, that may be exacerbated. Antibiotics are often used to try and improve their symptoms.

The antibiotics are typically targeted towards the bugs that we think are present in the lower airways, so obviously *Pseudomonas* becomes a prominent choice, but they may be targeted to other bugs present in the cultures that we have grown previously. And then we deliver the antibiotics by whatever method is appropriate, which might mean oral for some infections, but IV are commonly used for exacerbations which seem to be a bit more serious. And even the use of inhaled antibiotics in some of our patients.

So the decision of how to treat is often based upon the perceived severity of the exacerbation, and perhaps the response that the patient has had before. Perhaps you've tried oral antibiotics that weren't successful, and you've jumped to intravenous antibiotics.

The antibiotics are often selected not merely on what bugs are present in the airways, some people try to base it on the susceptibilities that you get from culture data, although there is not a good correlation between the susceptibility you get in the micro lab and the response to antibiotics.

So a general strategy is to use what worked last time. And oftentimes patients will do well with that approach. If they don't do well then perhaps we change it.

Now a common strategy for treatment of *Pseudomonas* with IV antibiotics is to use two drugs. That has been sort of a standard approach for many, many years, although the literature does not support the need for two drugs. The guidelines on treatment of exacerbations was unwilling to stray from tradition or standard of care, because although we have data that suggests that two drugs are better than one, we also can't say that one drug is just as good as two.

So we chose to stick to the standard of care with the recommendation that this is something that should be studied in the future.

And then the other critical question which could not be answered in our guidelines was how long to treat. The duration of antibiotics, oftentimes patients are treated with approximately two weeks of antibiotics, but this is based more upon past experience or just the perception that they need to be treated for a longer period of time and not because of clinical trials that have demonstrated the proper duration.

And the guidelines also stated that this would be a very important question to figure out in our patients, that we ought to be able to know what the proper duration of antibiotics would be for our patients.

MR. BUSKER: For the patient you described, Dr. Flume, what other therapies would be recommended?

DR. FLUME: So the guidelines reviewed several of the common therapies that are typically used in treatment of exacerbations. And, of course, one of the discouraging parts was that we didn't find a lot of published literature, and so for many of our recommendations we had to state that there was insufficient evidence in which we would need to investigate further.

We did feel comfortable suggesting that airway clearance therapies and any chronic medications should be continued in those patients, that there was no reason to stop any of those medications.

Now one caveat to that is for those patients who are on aerosolized tobramycin as routine therapy, and you are going to use intravenous tobramycin as part of your treatment, we don't have evidence as to whether one should continue aerosolized therapy while they're on IV. There certainly are no data to suggest that it's more efficacious, that it actually works better, in fact, we don't have any data that suggests that it is more harmful, but it might affect how you dose your IV medications depending upon when you aerosolize the drug. And that is a study that should be done to make sure that it's not altering your calculation of dosing in your patients.

We also looked at the possibility of steroids, there were just a couple of small studies that hinted that there might be some effect, but we, in the end we didn't have any sufficient evidence to say yea or nay, whether steroids would be an appropriate treatment of an exacerbation.

MR. BUSKER: I think we've got time for one more case — so if you would, Dr. Flume.

DR. FLUME: I chose to be very simple with this approach and this is an adult female with cystic fibrosis who now presents with complaints of hemoptysis, or coughing up of blood. She quantifies it as about 200 ccs of bright red blood in the last 24 hours.

MR. BUSKER: A patient who's coughing up blood — does she need to be in the hospital?

DR. FLUME: So hemoptysis is a very common symptoms. Many patients will cough up a little bit of blood now and then and most of them, they don't actually tell us that this is happening. In the registry we track how often they cough up a lot of blood, and massive hemoptysis occurs in about 4 percent of patients in their lifetime. Or to put that into perspective, about 1 in 115 patients a year are going to have massive hemoptysis.

So when we set about the guidelines on complications, we didn't have studies that would guide us into proper treatment, and so we did this with a consensus approach using Adelphi technique of asking experts their opinion on how to manage various problems.

And each were blinded to others' response so they wouldn't be biased in terms of their answers. And so we asked them should these patients be admitted to the hospital, and for definition purposes, we described scant hemoptysis as less than 5 ccs of blood, mild to moderate hemoptysis between 5 and 240 ccs, and massive being more than 240 ccs. So we've picked a patient who is in that moderate range, not quite all the way up to massive.

So when we asked our experts, our panel of experts about who should be admitted to the hospital, a patient with scant hemoptysis they did not think needed to be admitted to the hospital and they had very good consensus with that response.

In terms of if they have massive hemoptysis, all of them suggested the patient should be admitted to the hospital with perfect consensus. But in that mild to moderate range, they were right smack in the middle of the fence about who needed to be admitted.

So in this patient who is leaning more towards that massive hemoptysis, this is a patient who most likely needs to be admitted to the hospital for further intervention.

MR. BUSKER: About those further interventions: bronchial artery embolization — is this patient a candidate for that?

DR. FLUME: So the general approach to treatment of hemoptysis includes treatment of an exacerbation with antibiotics and such. But some patients need to go on to further intervention, and embolization of the bronchial arteries is one approach to acutely stop the bleeding.

So we asked our panel of experts what they thought, you know, who should go onto embolization. And this was a little bit tricky in getting a response, because it wasn't so connected to the amount of blood, as it was to the stability of the patient.

So for one example, they did not recommend embolization for people with scant or even mild hemoptysis. So we're talking about those patients with massive hemoptysis, but their feeling was that if the patient is clinically stable and they are no longer coughing up blood, that generally speaking they did not need to take those patients for embolization. So on a scale of zero to ten they gave that about a four, but there was still a pretty broad range of response.

But in those patients who are clinically unstable, meaning they continue to cough up blood, they might even be hypotensive, they might have some respiratory compromise, they were very clear those patients should go to embolization. Again, on a scale of zero to ten, that got a nine with a very good consensus.

So I think their interpretation of this patient would be not yet. If she shows any signs of instability, that might be different, but at the front I didn't describe her as being unstable.

MR. BUSKER: The recommendations for airway clearance therapies — tell us about those and how they would apply to this patient.

DR. FLUME: So I had mentioned that these patients are typically treated as if they were having exacerbation, which includes not just IV antibiotics,

but even aerosol therapies, their chronic therapies, and airway clearance. And we were concerned about how people should treat these patients for fear that it might exacerbate the bleeding, that it might loosen the blood clot.

And so when we asked them about airway clearance therapies, in general, if the patient has massive hemoptysis, the panel was pretty consistent, scoring very high that airway clearance therapies should be withheld, with median scores up around 8.5 to 9.0 out of 10.0.

Now having said that, they gave a little bit lower scores to those therapies which might be perceived as being kinder or gentler, such as active cycle breathing or oscillating PEP, like with the Acapella or flutter. And they didn't have the same degree of consensus.

And in those patients with mild to moderate hemoptysis, they were right smack in the middle giving everything about a five out of ten as to whether one should withhold airway clearance therapies, with only some consensus.

So I think in general with this particular patient, they probably with withhold airway clearance, if they wanted to do airway clearance, they would use something a little bit gentler such as oscillating PEP or active cycle breathing.

MR. BUSKER: In that same vein, tell us about using aerosol medications in this patient.

DR. FLUME: We typically use aerosol therapies for our patients, again, bronchodilators, hypertonic saline, antibiotics, dornase alfa, and we asked our experts whether those should be withheld in the patient with hemoptysis. And for massive hemoptysis, in general the answer was kind of again in the middle. They were not very good consensus with median scores of about 4 to 5 out of 10.

The one exception to that rule was with hypertonic saline. They scored that actually a little bit higher, about an 8 out of 10, with the perception that hypertonic saline is perhaps a little more irritating to the airways and might induce cough, and therefore exacerbate more bleeding. And so it would be probable that this patient would continue on inhaled therapy with the exception of hypertonic saline.

In those patients with more milder hemoptysis, in general, the committee was, the panel was not so concerned about stopping aerosol therapies, with the one exception again being hypertonic saline, giving about a 5 out of 10, but some folks rated it as high as an 8.

So in this particular patient, she probably would have been, had the hypertonic saline held as part of her therapy.

MR. BUSKER: Dr. Flume, take the final word, please, on the development of these guidelines.

DR. FLUME: An important part of development of guidelines is the recognition that these reflect our current knowledge and understanding. And as time goes forward, we will learn new things and these guidelines, therefore, need to be reviewed and perhaps changed to reflect our current or future knowledge of treatment of patients.

And so one of the things that you have to do is, when you develop guidelines, is first make sure you've got your questions correct, and make sure you've included all the parties who are most important. So that includes not just doctors, but, for example, in our guidelines we included nursing, and pharmacy, and respiratory therapy, and physical therapy, but also patients and families. You have got to include everybody who has a role in this.

We also then set the precedent that we would review these guidelines every three to five years to make sure that nothing else needs to be changed. And so, for example, we published our guidelines on chronic therapies, chronic medications, to maintain lung health in 2007, it's time for us to review again to see what new medications have entered the market, what additional data, would those change our guidelines. And some may not, but then, you know, some may actually result in critical changes in those recommendations.

And so these should be considered living documents that need to be reviewed periodically, and then distributed to everybody involved.

MR. BUSKER: Dr. Patrick Flume — from the Medical University of South Carolina — thank you for participating in this e-Cystic Fibrosis Review Podcast.

DR. FLUME: Thank you for having me. I hope that this is useful for everyone. We feel very strongly about the guidelines. We hope that we have done it correctly and that people understand they are important and how best to make use of them. They should be a useful tool for the clinician, the patient and the family to use together. Thank you.

MR. BUSKER: This podcast is presented in conjunction with eCysticFibrosis Review, a peer-reviewed CE-accredited literature review e-mailed monthly to clinicians treating patients with cystic fibrosis.

This activity has been planned and implemented in accordance with the essential areas and policies of the Accreditation Council for Continuing Medical Education, with a joint sponsorship of the Johns Hopkins University School of Medicine, and the Institute for Johns Hopkins Nursing.

The Johns Hopkins University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education, to provide continuing medical education to physicians. For physicians, the Johns Hopkins University School of Medicine designates this educational activity for a maximum of 0.75 *AMA PRA Category 1 Credits*[™]. Physicians should only claim credit commensurate with the extent of their participation in the activity.

For nurses, this 0.50 contact hour educational activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.50 contact hours.

This educational resource is provided without charge, but registration is required. To register to receive eCysticFibrosis Review via e-mail, please go to our website, www.ecysticfibrosisreview.org.

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of The Johns Hopkins University School of Medicine name implies review of educational format, design, and approach. Please review the complete prescribing information of specific drugs, combination of drugs, or use of medical equipment — including indications, contraindications, warnings

and adverse effects — before administering therapy to patients. Thank you for listening.

Thank you for listening, eCystic Fibrosis Review is supported by an educational grant from Genentech, Eurand Pharmaceuticals, Vertex Pharmaceuticals, Axcan Pharma, and Gilead Sciences Medical Affairs.

This program is copyrighted, with all rights reserved by the Johns Hopkins University School of Medicine.