Featured Cases: New Therapies in Cystic Fibrosis Directed Toward the Basic Defect

Our guest is Steven Rowe, MD, MSPH, from the University of Alabama at Birmingham.

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

- Describe how CFTR modulator therapy fits into the clinical armamentarium of CF lung disease
- Determine which patients are most appropriate for CF modulator treatment
- Describe current research efforts and how to identify patients suitable for referral for consideration in CFTR modulator clinical trials

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to *New Therapies in Cystic Fibrosis Directed Toward the Basic Defect* in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 4, Issue 7 *eCysticFibrosis Review Newsletter – New Therapies in Cystic Fibrosis Directed Toward the Basic Defect*.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

Unlabeled/Unapproved Uses
Dr. Rowe has indicated that he will refer to unlabeled/unapproved uses of ivacaftor, lumacaftor, ataluren, VX-661, N6022, and aminoglycosides.

Guest Faculty Disclosure
Dr. Rowe has indicated that he has received grants/research support from Novartis, PTC Therapeutics, N30 Pharmaceuticals, and Vertex Pharmaceuticals, Incorporated.

Release Date: November 26, 2013
Expiration Date: November 25, 2015

Next Month’s Topic
Behavioral treatment to improve dietary adherence and weight gain in children with cystic fibrosis
CME/CE INFORMATION

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
Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
Podcast: This 0.5 contact hour Educational Activity is provided by The Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 1 contact hours or a total of 6 contact hours for the seven newsletters in this program.

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.

LAUNCH DATE
This program launched on February 28, 2013, and is published monthly; activities expire two years from the date of publication.

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.

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.

There are no fees or prerequisites for this activity.

Estimated time to complete activity: 30 minutes.

DISCLOSURE POLICY
As a provider approved by the Accreditation Council for Continuing Medical Education (ACCMCE), it is the policy of The Johns Hopkins University School of Medicine Office of Continuing Medical Education (OCME) to require signed disclosure of the existence of financial relationships with industry from any individual in a position to control the content of a CME activity sponsored by OCME. Members of the Planning Committee are required to disclose all relationships regardless of their relevance to the content of the activity. Faculty are required to disclose only those relationships that are relevant to their specific presentation. The following relationships have been reported for this activity:

- Michael P. Boyle, MD, FCCP, discloses that he has received grant/research support from Vertex Pharmaceuticals, Inc. and is a consultant to Gilead Sciences, Inc., Novartis, Pharmaxis, Inc., Genentech, Inc., Savara, and Vertex Pharmaceuticals, Inc.

No other planners have indicated that they have any financial interests or relationships with a commercial entity.

Guest Author Disclosures

STATEMENT OF RESPONSIBILITY
The Johns Hopkins University School of Medicine takes responsibility for the content, quality and scientific integrity of this CME 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.

CONFIDENTIALITY DISCLAIMER FOR CME CONFERENCE ATTENDEES
I certify that I am attending a Johns Hopkins University School of Medicine CME activity for accredited training and/or educational purposes.

I understand that while I am attending this activity, I may be exposed to "protected health information," as that term is defined and used in Hopkins policies and in the federal HIPAA privacy regulations (the "Privacy Regulations"). Protected health information is information about a person's health or treatment that identifies the person.

I pledge and agree to use and disclose any of this protected health information only for the training and/or educational purposes of my visit and to keep the information confidential.

I understand that I may direct to the Johns Hopkins Privacy Officer any questions I have about my obligations under this Confidentiality Pledge or under any of the Hopkins policies and procedures and applicable laws and regulations related to confidentiality. The contact information is: Johns Hopkins Privacy Officer, telephone: 410-735-6509, e-mail: HIPAA@jhmi.edu.

"The Office of Continuing Medical Education at The Johns Hopkins University School of Medicine, as provider of this activity, has relayed information with the CME attendees/participants and certifies that the visitor is attending for training, education and/or observation purposes only."

For CME Questions, please contact the CME Office at (410) 955-2959 or e-mail cmeinfo@jhmi.edu. For CME Certificates, please call (410) 502-9634.

The Johns Hopkins University School of Medicine Office of Continuing Medical Education
Turner 20/720 Rutland Avenue
Baltimore, Maryland 21205-2195

Reviewed & Approved by:
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

INTERNET CME POLICY
The Office of Continuing Medical Education (CME) at The Johns Hopkins University School of Medicine is committed to protecting the privacy of its members and customers. The Johns Hopkins University SOM CME 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 will keep your personal and credit information confidential when you participate in a CME Internet-based program. Your information will never be given to anyone outside The Johns Hopkins University School of Medicine’s CME program. CME collects only the information necessary to provide you with the services that you request.

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 School of Medicine 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
PC: Internet Explorer (v6 or greater), or Firefox
MAC: Safari
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 educational grants from Aptalis Pharma, Inc, Gilead Sciences Inc., and Vertex Pharmaceuticals.

Today’s program is a companion piece to our eCysticFibrosis Review newsletter: New Therapies in Cystic Fibrosis Directed Toward the Basic Defect.

Our guest today is that issue’s author, Dr. Steven Rowe, from the University of Alabama at Birmingham.

This activity has been developed for pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dietitians, nutritionists, pharmacists, nurses and nurse practitioners, physical therapists, and others involved in the care of patients with cystic fibrosis.

The Accreditation and Credit Designation Statements can be found at the end of this podcast. For additional information about accreditation, Hopkins policies and expiration dates, and to take the posttest to receive credit online, please go to our website newsletter archive: www.eCysticFibrosisReview.org, and click the Volume 4, Issue 8 podcast link.

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

- Describe how CFTR modulator therapy fits into the clinical armamentarium of CF lung disease
- Determine which patients are most appropriate for CF modulator treatment
- Describe current research efforts and how to identify patients suitable for referral for consideration in CFTR modulator clinical trials

I’m Bob Busker, managing editor of eCysticFibrosis Review. On the line we have with us Dr. Steven Rowe, Associate Professor of Medicine in the Division of Pulmonary, Allergy & Critical Care Medicine, at the University of Alabama at Birmingham.

Dr. Rowe has indicated that he has received grants and/or research support from Novartis, PTC Therapeutics, N30 Pharmaceuticals, and Vertex Pharmaceutical, Incorporated.

He had also indicated that in today’s discussion he will refer to the unlabeled or unapproved uses of ivacaftor, lumacaftor, ataluren, VX-661, N6022, and aminoglycoides.

Dr. Rowe, welcome to this eCysticFibrosis Review Podcast.

DR. ROWE: I’m glad to be with you and discuss this very exciting therapeutic area. I think it’s a real example of the benefits of basic research and personalized approaches to medical care that are coming to fruition.

MR. BUSKER: In your newsletter issue, you reviewed some of the recent advances in therapies that directly address repairing dysfunctions in the CFTR gene. Today I’d like to translate how some of that new information can affect clinical practice. So please Dr. Rowe start us out by describing a patient.

DR. ROWE: Our first case is a 16 year old patient with CF who is heterozygous for the G551D and F508del-CFTR mutations. He has moderate lung disease severity marked by an FEV1 of 60 percent predicted for age and he chronically grows Pseudomonas aeruginosa. He has one to two CF pulmonary exacerbations per year, typically requiring courses of IV antibiotics with two drug therapy.

In the last five years, his disease has been complicated by CF-related diabetes mellitus requiring subcutaneous insulin administered with meals. He had a history of allergic bronchopulmonary aspergillosis that has resolved and for which corticosteroids and itraconazole were once required.

Medications include recombinant human DNase, oral azithromycin, and intermittent inhaled tobramycin, insulin, and pancreatic enzyme replacement therapy.

He has been clinically stable for the last three months and complains of a chronic productive cough that is typical in both severity and character for this individual.
MR. BUSKER: Is this 16 year old patient a candidate for ivacaftor?

DR. ROWE: I think this is a patient in whom ivacaftor should certainly be considered. He meets the FDA indicated label as he harbors at least one copy of the G551D mutation and his lung disease severity doesn’t draw concerns; it’s clearly within the indicated label. In addition, the patient is in the right age group to be considered in that he is age six or over. So given his relatively stable clinical status, I think this is a good candidate for consideration with this patient.

Other things that ought to be considered include concomitant medications. This patient isn’t taking an inducer or inhibitor of CYP3A drugs, so he otherwise appears to be a good candidate.

MR. BUSKER: Let me ask you to clarify something for us. In patients like this should ivacaftor be considered a cure?

DR. ROWE: I think we want to be very careful about how we term these CFTR modulator therapies to our patients. I certainly wouldn’t advocate the use of the term cure for this patient. While we think these CFTR modulator therapies are going to be very effective, and there is good evidence, as reviewed by the phase 3 study by Ramsey and colleagues presented in the newsletter, that these therapies are very effective, they shouldn’t be considered a cure, and all medications for CF right now should be continued, although that should certainly be addressed on an individual basis.

MR. BUSKER: Let’s assume the patient you presented has started on ivacaftor. How would you monitor the effect of his therapy?

DR. ROWE: The therapy should be monitored similarly to those for other routine therapies for CF. The patient has to be seen regularly in CF clinic and his clinical status will be monitored similarly to what is routinely done.

To see if ivacaftor is working for this patient you would look at measurements of lung function by spirometry, clinical symptoms, cough severity, and sputum production. Weight gain is another very important objective measure that was seen to be increased in therapeutic trials with ivacaftor in patients with CF, and another thing to look for is a change in the overall exacerbation frequency.

Each of these effects were observed in the phase 3 trials examining ivacaftor in both the older patients as in the study outlined by Ramsey and colleagues, as well as in younger individuals.

Another test that can be considered to monitor CF patients is the use of sweat chloride. There was a significant improvement in sweat chloride seen in all studies of patients with G551D who were administered ivacaftor, and it’s a very strong indicator of improved CFTR activity. However, there is considerable debate on how this marker can be used in the clinic.

These were reviewed in the newsletter in two papers, one by Durmowicz and colleagues published in Chest, and one by Seliger and colleagues published in the Journal of Cystic Fibrosis, which present two different viewpoints on this issue. While almost all patients had an improvement in sweat chloride in phase 3 testing, not all patients who received ivacaftor have had improvement in their lung function, so in that way it can be an indicator of whether ivacaftor is effective in modulating the CFTR but may not be a marker of clinical benefit.

MR. BUSKER: What potential adverse effects associated with ivacaftor therapy should the clinician be on the lookout for?

DR. ROWE: With all new medications—and this would certainly be one that’s newly available to patients—providers have to be cautious about the use of new medications, and this is certainly one instance where on the whole relatively few patients have been tested with ivacaftor.

In phase 3 testing, again as outlined in the newsletter, ivacaftor was generally well tolerated and the side effects that have been reported were generally consistent with symptoms that patients with CF frequently experience—just cough or changes in sputum, headache, sore throat, things that are associated with respiratory infections.

Liver function tests should be monitored in patients on ivacaftor every three months. One should use caution if there is any change in the liver function test, particularly if they exceed five times the upper limit of normal.
Another area that’s of emerging interest is the effects of ivacaftor and blood glucose instability. This patient has CF related diabetes and takes insulin therapy. There is emerging evidence that ivacaftor can change the effects of insulin or augment insulin release. Those results are still very early and we don’t know the clinical implications of this yet. But certainly recommendation of more intense glucose monitoring at the onset of ivacaftor therapy is warranted.

MR. BUSKER: As a point of clarification, would you recommend that any of the other therapies this patient is on be stopped?

DR. ROWE: Decisions regarding other therapies should be made on an individual basis. Right now there is no evidence that other therapies should be stopped on a global basis. Other therapies were not discontinued in the trials outlined in the newsletter and in those reported to date.

Right now we know that there is no evidence that ivacaftor is going to reverse bronchiectasis and infection is still present. So therapies that are directed, such as antimicrobial therapy or anti-inflammatory therapy should almost certainly be continued until more evidence emerges.

We also don’t expect changes in pancreatic function, and although we don’t fully understand the beneficial effects of ivacaftor and weight gain, there is no indication to stop pancreatic enzymes in patients of this sort.

MR. BUSKER: Thank you for that case and that discussion, bring us another patient.

DR. ROWE: This is a 32 year old patient with CF who is heterozygous for the G542X and F508del-CFTR alleles. He’s been doing well and is clinically stable at this visit. His baseline FEV₁ is 75 percent predicted. Medications include recombinant human DNase, hypertonic saline and intermittent aztreonam lysate for inhalation, in addition to pancreatic enzyme replacement therapy and antacid therapy.

He reports intermittent cough that resembles his baseline symptoms.

MR. BUSKER: Let me start out with the same initial question as before. Is this patient a candidate for ivacaftor?

DR. ROWE: This is not a patient that’s a candidate for ivacaftor.

MR. BUSKER: Why?

DR. ROWE: This patient doesn’t have the G551D allele and other studies, including that reviewed in the newsletter, have shown that ivacaftor is not effective against the F508del allele.

MR. BUSKER: So this patient, as you said, is heterozygous for the G542X and F508del mutations. What are the potential treatment options that can target those basic CFTR defects, and what’s their status in the research pipeline?

DR. ROWE: This patient harbors mutations that are still under therapeutic development. Let’s cover them individually and start with the G542X allele. This is an example of a premature termination codon or a PTC allele, also sometimes called a stop codon or an X mutation. The most advanced therapy in the research pipeline that’s looking at this is the agent ataluren, formerly called PTC124. It’s currently an investigational drug and recently completed phase 3 trials in CF.

As you can read about more in the newsletter, ataluren has had mixed results in clinical trials. In the most recent phase 3 study, the primary endpoint was not met and there was no improvement in lung function in individuals assigned to receive ataluren compared to those who received placebo. This conflicted somewhat with three previous phase 2 studies that had mixed results: two of which had showed efficacy in an open label format, and one did not.

So right now it’s uncertain where ataluren stands in the therapeutic pipeline, and additional communication is ongoing between the sponsors and the regulatory authorities about what to do next.

As with any trial, much information is attempted to be gleaned on the results, and one interesting area that’s been gleaned from this study is that the use ataluren was partially inhibited by the use of the inhaled aminoglycoside tobramycin. So there is more to be learned about that antagonistic effect and whether the benefits of ataluren can be achieved when these inhaled aminoglycosides are not used.
Other therapies are also in earlier stages in the pipeline, and that includes using aminoglycosides or synthetic versions of aminoglycosides or research aminoglycosides that are made more effective for read-through than their antimicrobial activities. Those are advancing through the pipeline in various research studies.

Several investigators are looking at other novel small molecules to try and advance to the clinic that could also be applicable to patients with CF. We’ll look for emerging information with that in the coming year.

**MR. BUSKER:** Can gentamicin or other aminoglycosides be considered useful for treatment?

**DR. ROWE:** Right now there is really no indication for the use of chronic gentamicin or other aminoglycosides. There is evidence in the laboratory that they are effective, but they’re really not suitable agents to use alone long-term. I mentioned that synthetic aminoglycosides that are not yet publicly available are being researched to improve efficacy, but that is not the current standing of gentamicin and other agents. So right now the toxicity of gentamicin and other aminoglycosides for chronic administration don’t warrant the use for treatment for the basic defect.

**MR. BUSKER:** What about agents that are active against the F508del mutation? What can you tell us about their status?

**DR. ROWE:** We mentioned this patient was heterozygous, with the other allele being the F508del CFTR allele. Of course, that’s the most common allele that causes CF.

A number of agents in the research therapeutic pipeline are investigating this population. This includes corrector programs that are currently in development and that includes the agent VX809 or lumacaftor, or VX661, both of which are being developed by Vertex Pharmaceuticals.

Clinical research studies are currently enrolling patients to receive lumacaftor and ivacaftor in combination, if they have two copies of the F508del mutation. Shorter phase 2 studies are evaluating the effect of these agents in patients with one copy of the F508del mutation. So this patient could be suitable for referral to a research center that’s enrolling patients with one copy of the F508del mutation, if he’s clinically stable, interested in research, and of the right age category. As he is an adult he is certainly somebody that could be considered for such a study. Discovery programs are currently underway, programs by N30 Pharmaceuticals looking at agents for the patients with two copies of the F508del mutation, and other companies such as Genzyme, Pfizer, and others are evaluating CFTR corrector agents that do not yet reach.

Another approach that could be considered for patients with a wide variety of CFTR alleles will be gene therapy. Gene therapy is currently being pursued, for instance, in the UK Gene Therapy Consortium, and that would be applicable to a wide variety of CFTR alleles in the applicable population.

**MR. BUSKER:** Let me present a hypothetical situation. This same patient — 32 years old, clinically stable, baseline FEV1 at 75 percent. What if this patient had a different CFTR allele, something that conferred a milder phenotype with partial CFTR activity that could be demonstrated by sweat chloride analysis, say the R117H allele. Give us your thoughts, on that.

**DR. ROWE:** That would certainly enter the patient into a different category of disease. Mutations that confer partial activity are an emerging area of interest, since it’s been shown in the laboratory that ivacaftor can be active against a number of those mutation types. R117H is an example of one of those mutation types where ivacaftor has been shown to be active, and phase 3 clinical studies are currently enrolling patients with the R117H mutation to determine whether ivacaftor has long-term benefit in these people.

Actively enrolling studies are looking for patients with partially active CFTR alleles as conferred by a milder clinical phenotype. One way to measure that, as you mentioned, is sweat chloride analysis, but another way to measure it would be pancreatic sufficiency. Ongoing studies are looking at this patient population as well.

So I think in the next few months or a year, many of these studies will have results available that will help us give firmer indication of which other patients that have partially active CFTR alleles and therefore may be candidates to receive ivacaftor, actually receive clinical benefit.
MR. BUSKER: Thank you. We’ll return, with Dr. Steven Rowe from the University of Alabama, in a just 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 regularly 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 bimonthly email-delivered program available by subscribing. Each issue reviews a current literature on focused topics 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 a thousand of our colleagues have already become subscribers. The topic-focused literature reviews help keep them 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 this eCysticFibrosis Review podcast. I’m Bob Busker, managing editor of the program. Our guest is Dr. Steven Rowe, from the Division of Pulmonary, Allergy & Critical Care Medicine at the University of Alabama at Birmingham, and our topic is New Therapies in Cystic Fibrosis Directed Toward the Basic Defect.

We’ve been looking at how some of the new information Dr. Rowe reviewed in his newsletter issue can be applied in clinical practice. So to continue our discussion: please bring us another patient.

DR. ROWE: This is a 26 year old woman with cystic fibrosis who is homozygous for the F508del CFTR mutation and presents with a progressively deteriorating course. While she was previously hospitalized once or twice annually for CF exacerbations, she’s had three admissions for IV antibiotics in the last six months, and her baseline spirometry has deteriorated from 55 percent predicted FEV₁ while well to 35 percent following her most recent recovery. Currently, her FEV₁ is 29 percent in clinic, and she has had an additional three pounds of weight loss over the last six months, increasing respiratory symptoms including a more frequent cough, worsening sputum production, and dyspnea.

On exam she has crackles, worse in the upper lung fields, and mild expiratory wheezing.

MR. BUSKER: This patient sounds like she’s in a lot of trouble. How do you assess her?

DR. ROWE: I agree, she is certainly having a CF pulmonary exacerbation and a worsening overall course over the last six months. Many of us would characterize this patient as having a rapidly progressive phenotype and an increasing recognized entity that warrants increased medical attention.

Many times this sort of patient has captured a new organism such as a more pathogenic Pseudomonas or a worse organism such as Burkholderia cepacia. In other cases, the patients have a rapidly progressive phenotype of unknown cause. This sort of case requires an aggressive diagnostic evaluation including assessment of laboratory tests, radiographic studies, and sputum culture, to try and identify new organisms, including atypical organisms such as Mycobacteria species. Others would advocate bronchoscopy, and that would certainly be considered in patients who are not responding to initial empirical therapy, in which case a cause of new organisms remains suspected.

This patient should certainly be considered for early referral to a lung transplant center, given her rapidly progressive phenotype and a reassessment of chronic therapies regarding adherence, whether she is...
experiencing side effects, and whether more aggressive chronic therapy can be administered.

**MR. BUSKER:** What can you tell us about the status of F508del-CFTR rescue in this patient?

**DR. ROWE:** This patient is homozygous for the F508del, and correctors are in development, but this is not yet an approved strategy for this patient population. As we talked about in the first case, and also outlined in the eCF Review in a study by Flume and colleagues, ivacaftor monotherapy showed no benefit in this population. And as we also talked about, corrector therapy with one or two agents is not yet approved for these patients.

The patient would also not be a candidate for enrollment in clinical trials because of her rapidly progressive phenotype. Patients have to be clinically stable before a referral can be considered. This is an example of a patient who needs more aggressive clinical therapy rather than enrollment in studies with CFTR modulators that are in development.

**MR. BUSKER:** As you said, this patient would not be a candidate for ongoing clinical trials. But what about compassionate use programs?

**DR. ROWE:** We would certainly want to think about compassionate use programs for patients whose disease is more severe and are eligible for clinical studies and have the right genotype group as this patient does. Right now no compassionate programs are available for patients who are homozygous for the F508del mutation, but pending results of emerging studies, I think that could evolve over time.

So what I would recommend at this point is close monitoring of results as they emerge from clinical studies. You can also pay attention to resources such as [www.clinicaltrials.gov](http://www.clinicaltrials.gov) to look for opening of open label compassionate use programs.

**MR. BUSKER:** Thank you for today’s cases and discussion, Dr. Rowe. I’d like to ask you to look into the future for us now. What advances do you expect in new therapeutic options for addressing the basic defect in cystic fibrosis?

**DR. ROWE:** I think we’re likely to see continued advances in protein repair, and it is likely that new combination approaches to maximize the rescue of CFTR will become a part of a therapeutic approach. For example, patients heterozygous for F508del and a premature termination codon may take a CFTR corrector, an agent to induce translational read-through such as we discussed for aminoglycosides or ataluren, and the CFTR potentiator, all in combination to result in a maximal benefit.

Looking even beyond that, since we’re learning that F508del CFTR has multiple checkpoints, we also are likely to see multiple agents directed towards that individual CFTR mutation, one or more agents to actually increase its expression to the cell surface, followed by the addition of a CFTR potentiator to maximally activate that channel.

I think in the future we’ll see personalized approaches based on the presence of their CFTR mutations and combining multiple agents to maximize the benefit for CFTR activity.

**MR. BUSKER:** Thank you for sharing your thoughts, Dr. Rowe. To wrap things up, I’d like to summarize what we’ve discussed today in light of our learning objectives. So to begin: describing how CFTR modulator therapy fits into the clinical armamentarium for treating CF lung disease.

**DR. ROWE:** I hope you understand that while the clinical availability of CFTR modulators is currently limited to a single end agent directed toward a single CFTR mutation, in this case referring to ivacaftor for patients with a G551D mutation, there’s good reason to believe additional studies could successfully determine that this approach will work for a wider variety of CFTR mutations in patients who harbor them.

Further, because we do not expect these agents to reverse lung injury and they do not return CFTR function to normal levels, existing therapies will be needed to maintain optimal health for patients requiring CFTR modulators.

**MR. BUSKER:** And our second objective: determining which patients would be most appropriate for CF modulator treatment.

**DR. ROWE:** This will remain a personalized approach based on each patient, their genetic mutations, and their age and severity of disease. Key features include whether their CFTR mutation is localized at the cell surface, a premature termination codon, and whether the patient is with one or more copies of the F508del-CFTR mutation.
Key lung function cutoffs are often an FEV\textsubscript{1} of 40 percent predicted for many clinical research studies.

**MR. BUSKER:** And finally: identifying patients suitable for referral for consideration in CFTR modulator clinical trials.

**DR. ROWE:** We expect this topic to be both busy and dynamic, with regular changes based on the emergence of new agents, new populations to test current treatments such as younger ages, different levels of lung function, or the presence of different CFTR mutations.

A few places to monitor for these changes will be www.clinicaltrials.gov, the website from the Cystic Fibrosis Foundation, and information from clinical research networks such as the Therapeutics Development Network or the Clinical Trials Network in Europe.

**MR. BUSKER:** Dr. Steven Rowe from the University of Alabama at Birmingham, thank you for participating in this eCystic Fibrosis Review Podcast.

**DR. ROWE:** I’m happy to be with you and discuss this exciting area.

**MR. BUSKER:** This podcast is presented in conjunction with eCysticFibrosis Review, a peer-reviewed CME and CNE-accredited literature review emailed 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 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 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 0.5 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

For nurses, this 0.5 contact hour educational activity is provided by The Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 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 and The Institute for Johns Hopkins Nursing names 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.

eCysticFibrosis Review is supported by an educational grant from Aptalis Pharma, Inc, Gilead Sciences Inc., and Vertex Pharmaceuticals.

This program is copyrighted, with All Rights Reserved by The Johns Hopkins University School of Medicine.