



VOLUME 5 – ISSUE 10: TRANSCRIPT

Featured Cases: The Effects of CFTR-Modifying Therapies

Our guest author is Stuart Elborn, MD from the Queen’s University in Belfast, Northern Ireland.

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

- Explain the relevance of specific mutations in people with CF to new therapies currently available.
- Identify which patients are suitable for CFTR-modifying therapies based on mutation class.
- Summarize the known risks and benefits of CFTR modification therapy.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to the effects of CFTR-modifying therapies in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 5, Issue 9 *eCysticFibrosis Review Newsletter* — [The Effects of CFTR-modifying therapies.](#)

MEET THE AUTHOR



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Guest Faculty Disclosure

Dr. Elborn has disclosed that he has served as a consultant for Vertex and Boehringer Ingelheim, and has received research support from Vertex, Gilead, and Novartis.

Unlabeled/Unapproved Uses

Dr. Stuart Elborn indicated that his discussion today will include the potential off-label or unapproved uses of inhaled colistin, lumacaftor, ivacaftor, and ataluren.

Release Date
August 20, 2015

Expiration Date
August 19, 2017

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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.

Today's program is a follow-up to our newsletter topic "CFTR-modifying therapies." Our guest today is that issue's author, Dr. Stuart Elborn, Professor of Respiratory Medicine at the Queen's University in Belfast, Northern Ireland.

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

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

- Explain the relevance of specific mutations in people with CF to new therapies currently available.
- Identify which patients are suitable for CFTR-modifying therapies based on mutation class.
- Summarize the known risks and benefits of CFTR modification therapy.

Dr. Elborn has disclosed that he has served as a consultant for Vertex and Boehringer Ingelheim, and has received research support from Vertex, Gilead, and Novartis. He has indicated that his discussion today will include the potential off-label or unapproved uses of inhaled colistin, lumacaftor, ivacaftor, and ataluren.

MR. BUSKER: Dr. Elborn, welcome to this eCysticFibrosis Review Podcast.

DR. STUART ELBORN: Thank you very much. I'm pleased to be participating in this and looking forward to describing some of the clinical endpoints of corrector and potentiating therapies today.

MR. BUSKER: In your Newsletter issue, Dr. Elborn, you reviewed key research into the effects of CFTR modifiers in patients with Class III gating mutations like G551D, as well as the trials describing the use of ivacaftor and lumacaftor in combination to treat the Class II F508del mutation. Today I'd like to discuss how that information can affect clinical practice. So please start by describing a patient situation.

DR. ELBORN: The first patient is a 14-year-old teenager who has one G551D mutation and Y563N mutation. This young lady is pancreatic-insufficient but has reasonably good lung function with an FEV₁ of 80 percent predicted. She has good height and width centiles, between the 75th and 90th. She has a chronic cough, though she has had no admissions to hospitals since 2007 for pulmonary exacerbation. She was started on ivacaftor when it became available in May 2013.

MR. BUSKER: She appears to have been in relatively good health when she began ivacaftor therapy. Tell us about her progress during treatment.

DR. ELBORN: She made a number of significant improvements in what might be considered important clinical outcome measures. Let's start with her sweat chloride, which was just below 100 mol/L before starting ivacaftor and after 12 months of ivacaftor treatment had reduced to just above 40 mol/L. This is within the range described in both the STRIVE and ENVISION studies. Along with the improvement in sweat chloride, she also had an improvement in width, moving from the 80th centile to the 100th centile. Her lung function also improved. Her FEV₁ started around 80 percent predicted, but during the subsequent 12 months, it was maintained at 100 percent predicted.

In our clinic we've also been following the measurement of lung clearance index at using the multiple-breath washout method using SF₆ as the washout gas. This methodology is being used in a number of clinical trials and increasingly is being used in clinics. It is a more sensitive measure of lung function, particularly in children and young adults with cystic fibrosis who have a relatively well-preserved FEV₁. Indeed, at zero months, this young lady's lung clearance index was 10 units, which is significantly greater than you'd expect in a healthy person of this age, in whom you would expect a value of around 6 units.

Treatment with ivacaftor was associated with a reduction in lung clearance index from 10 to 8, bringing it toward normal, giving us a signal of additional value to the FEV₁ (which at just over 80 percent predicted is technically within the normal range). However, the lung clearance index tells us that there is significant lung disease here, and the

treatment with ivacaftor has resulted in an improvement in the physiology associated with lung clearance index, which is better ventilation homogeneity in the small airways.

The measurements we undertook following treatment with ivacaftor in this young lady indicate a very useful improvement in a number of physiological parameters that we would routinely monitor in patients receiving this therapy.

MR. BUSKER: What about her quality of life? Has that improved as well?

DR. ELBORN: These laboratory responses are very important, but what's even more important is how the patient feels and what lifestyle changes result from the treatment that have benefitted her lung function.

The patient reports that she now feels in excellent health. Her cough has gone away, and this is confirmed by her mom, who was really tuned into her cough but now has said that she's had to go into the bedroom in the morning to make sure that her daughter was awake, because she had been used to hearing the coughing. The girl is also now going out running regularly and can run now 3 km to 4 km very comfortably. So ivacaftor treatment in this patient has resulted in a significant change in symptoms and also some lifestyle changes that allow her to exercise and do some things that previously she would've not been inclined to do.

These things are very hard to measure in clinical trials, but in our experience in patients with a G551D gene mutation who receive ivacaftor, this treatment really has a highly positive impact on their lives and transforms many patients' lifestyles and their ability to do things they've been previously unable to do.

MR. BUSKER: A lot of our listeners may not be familiar with MBW/LCI, the multiple breath washout/lung clearance index you mentioned, so please summarize it for us, please.

DR. ELBORN: Certainly, multiple breath washout assesses small airway function by determining the ventilation in homogeneity or the variability of ventilation in diseased small airways. The patient inhales a very small concentration of an inert gas such as SF₆ and then breathes out into another circuit, and you measure the clearance of that gas from a steady

state. This has been shown to be very closely related to the small airways disease, particularly in a disease such as cystic fibrosis. It's also been shown to be more sensitive than traditional spirometry measurement such as FEV₁.

The measurement from this test is the lung clearance index, and it is calculated as the number of lung turnovers or tidal volumes required to reduce the storing concentration of the inert gas to 1/40th. That comes from a historical, traditional physiology set of experiments done during the 1950s and '60s, when this test was originally developed. The innovation is that you can now do this test much more straightforwardly with fairly simple equipment that can be used in any clinical context.

MR. BUSKER: Is this measurement being used more frequently in clinical trials?

DR. ELBORN: A number of studies in cystic fibrosis in the last five years have used lung clearance index as an endpoint, and it's been shown to be very sensitive. In particular, in the study of ivacaftor in patients with very mild lung disease, lung clearance index was shown to be an excellent endpoint demonstrating efficacy in a small crossover study. I think this method will be used more frequently in clinics and also will become a frequent measurement in clinical trials involving people with cystic fibrosis.

MR. BUSKER: Thank you for that explanation. And we'll return, with Dr. Stuart Elborn, from the Queen's University in Belfast, 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.

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. 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.

MR. BUSKER: Welcome back to this eCysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guest today is Dr. Stuart Elborn, professor at the School of Medicine at the Queen's University in Belfast. And our topic is "CFTR-modifying therapies."

We've been discussing how some of the new information Dr. Elborn presented in his newsletter issue can be applied in the clinic. Please bring us another patient scenario, Dr. Elborn.

DR. ELBORN: Thank you. The next patient has been a very challenging case for us and I think illustrates some of the future challenges we may have in patients who are receiving a potentiator or corrector and potentiator therapy in CF.

This patient is a 32-year-old female who has one R117H mutation and an A60X on the other chromosome. She has moderate to severe lung disease and is pancreatic insufficient. She has been infected with *Stenotrophomonas maltophilia* somewhat intermittently but has consistently cultured a fungus called *Scedosporium*, and about five years ago isolated a *Mycobacterium avium-intracellulare*, which cleared without any further therapy. Her long-term therapy over the last few years was inhaled colistin, dorase alfa, and pancreatic enzyme replacement therapy.

This lady agreed to participate in the CONDUCT trial.

MR. BUSKER: You discussed the CONDUCT trial in your newsletter issue. Just to refresh: this was a trial of ivacaftor in patients with at least one R117H Class IV mutation.

DR. ELBORN: Yes. CONDUCT was a relatively small study of patients with this particular mutation, which has just been published.

The patient started on the clinical trial and then continued in the open label extension, and her swap from the randomized, controlled part of the trial to the open label resulted in an improvement of her FEV₁ from 40 percent predicted at baseline to 64 percent predicted, suggesting that she probably had been on placebo in the randomized, controlled trial part of this study, and when she moved from placebo to open label ivacaftor therapy she had a significant improvement in FEV₁. In parallel, her width increased and the frequency of pulmonary exacerbations dropped, and her symptoms generally improved.

This young lady already had one child but was feeling so well on ivacaftor treatment that she asked us if she could proceed to having a second child. After a considerable discussion with the patient and our CF team and discussions with the manufacturer of ivacaftor, we agreed that she could proceed to have a second child, but to do that the safest approach would be to withdraw from the clinical trial and stop ivacaftor treatments. There still is extremely limited data on the effect of ivacaftor on pregnancy. The toxicology studies before licensing don't suggest that there's any teratogenic effect. At this time she'd been on the open label treatment for just over six months.

When she stopped her ivacaftor treatment, she lost 4 kilos over the subsequent two months, and her lung function dropped within two weeks to 42 percent predicted, close to her baseline prior to entering the study. She also had an increase in the frequency of pulmonary exacerbations. After her third exacerbation in four months, she felt so unwell compared to when she was on ivacaftor treatment, she asked if she could rejoin the clinical trial. This was not possible because she'd withdrawn from the clinical trial, but because of her previous excellent response, we had an agreement with the manufacturer that she could receive the drug on a patient access scheme.

She was recommended to go on ivacaftor and had an improvement in FEV₁ from 40 percent predicted up to 61 percent predicted, regained the weight loss with an increase in width to 3 kilos. In the following six months she's had significantly fewer symptoms and no further pulmonary exacerbations. Indeed, this past winter she was able to enjoy a skiing holiday.

MR. BUSKER: Can we assume that when she went back on ivacaftor therapy that she was not pregnant and no longer intended to get pregnant?

DR. ELBORN: She made a clear decision not to proceed with trying to become pregnant to have a second child, partly because she was so unwell, and we also advised her with the frequency of exacerbations and the weight loss, her chances of becoming pregnant were almost certainly reduced. So she made a very clear decision with her partner and with the CF team that she no longer wished to become pregnant and restarted on birth control and then restarted her ivacaftor treatment.

MR. BUSKER: This patient showed a very pronounced response to ivacaftor when she received it in the open label part of the study, as well as when she resumed therapy. How did her responses align with the overall results of the CONDUCT study?

DR. ELBORN: I think this patient is a good example of the patients who responded in the CONDUCT trial. CONDUCT was undertaken in patients with a wide range of lung function, from moderate to severe lung disease to very mild lung disease, and in a range of ages. The study overall did not meet its primary endpoints. The FEV₁ in the whole population studied did not increase significantly, but patients who were over 18 years of age and patients who had 5T polymorphism on intron 8 were more likely to respond. This patient meets both of those criteria: she's over 18, she has more severe lung disease, and she also has a 5T variant, so I think this patient illustrates very well which patients who have an R117H mutation are most likely to respond to ivacaftor.

MR. BUSKER: What can you tell us about the issues this patient faced in deciding to withdraw from the open label trial and how she felt after she stopped her ivacaftor therapy?

DR. ELBORN: This was quite a challenging and quite emotional series of conversations with this lady with cystic fibrosis. She was very committed and very keen to have a second child, driven I think by normal maternal desires to perhaps having a second sibling for a single child. And I think also she was feeling so well when she was on open label ivacaftor, she felt, I could do this, having another child is something that is possible for me now because of the improved

symptoms and improved lung function following the open label extension on ivacaftor.

However, she hadn't anticipated how much her symptoms would revert to the time before she was on ivacaftor treatment and the impact the exacerbations would have on her age with reduced lung function. So she really did change during the time that she stopped ivacaftor to try to become pregnant to protect the child from any teratogenic effects of ivacaftor, and she realized during that time that she really wasn't well enough to proceed with a pregnancy.

She was really quite distressed that she had decided to stop, even though at the time we had talked to her in considerable detail. So she was very pleased to be able to return to active treatment through the patient access scheme, and her physiology and her symptoms improved very quickly.

I think this illustrates that ivacaftor therapy has to be taken regularly. You can't stop and start it, because stopping for a couple of weeks is likely to be associated with a deterioration in physiology and also a return of symptoms.

MR. BUSKER: The physician's responsibility to stress the importance of continued adherence to ivacaftor therapy seems to be one of the critical takeaways from this case. Would you agree?

DR. ELBORN: Yes, I think so. This treatment needs to be taken regularly. We don't know exactly the length of time from stopping it — for example, FEV₁ would drop — but it's certainly within the first two weeks of stopping treatment. So I think it does illustrate that taking this treatment regularly is really important.

MR. BUSKER: Thank you for that case and discussion, Dr. Elborn. Please bring us one more patient scenario.

DR. ELBORN: This is an interesting and I think quite challenging patient scenario to discuss with you. This is a 29-year-old male with cystic fibrosis who had a history of very frequent pulmonary exacerbations. He was discussing assisted fertility with us when we informed him that he would be eligible to participate in the STRIVE study. STRIVE is the pivotal randomized, controlled trial in patients with at least one G551D mutation, comparing ivacaftor treatment to placebo. This is the pivotal trial for licensing of ivacaftor in patients with G551D and remains the

key study in developing potentiated therapy in patients with cystic fibrosis.

Prior to starting the study, his FEV₁ was 70 percent predicted, and during the randomized controlled trial part of STRIVE, his FEV₁ increased to 90 percent predicted. He then continued on an open label extension and subsequently was prescribed ivacaftor when it became available for patients in the UK. On treatment with ivacaftor, he has maintained his FEV₁ at 90 percent predicted.

This young man also had a history of anxiety and depression, in part as a consequence of his concerns over his long-term future with cystic fibrosis. For example, he had made a conscious decision to not do some things in life because he wasn't sure he would be well enough or would have a significant long-term future. He was also under review with our psychology team to give him support with some of the psychological symptoms associated with coming to terms with a condition where he might have a limited lifespan.

He had around two pulmonary exacerbations per year prior to ivacaftor therapy, but since starting therapy on the clinical trial and subsequently he has not had any further exacerbations requiring intravenous antibiotics.

So this young man deferred assisted fertility in order to participate in the clinical trial, and was now feeling so well he revisited that issue with us. He asked whether he could, while on ivacaftor, proceed to have assisted fertility treatments with sperm aspiration from him and an IVF procedure with eggs from his partner. We agreed to do this, but again, in consultation with the drug manufacturers, we suggested that the best way to do this would be to have a one-month drug holiday and toward the end of that one-month drug holiday to undertake the sperm aspiration procedure.

So he stopped his ivacaftor and his FEV₁ dropped by 15 percent predicted within the first two weeks of stopping treatment. His procedure was undertaken successfully during his month off ivacaftor, and on return to treatment his symptoms improved and his lung function returned to 90 percent predicted. And the good news for this young man is after two cycles of IVF he has recently become the father of a healthy young son.

MR. BUSKER: Between the STRIVE study, the open-label extension, and his prescription after UK approval, this patient has been on ivacaftor for quite some time. Has he encountered any major side effects or complications from the treatment?

DR. ELBORN: No, he has been really very well on ivacaftor, and he's had no significant symptomatic side effects. We've been monitoring things such as his liver function tests, and there have been no specific problems with these tests or any other tests that might indicate toxicity from ivacaftor treatment. He remains very well and is particularly pleased that he's now gone four years without a course of IVs, indicating this reduction in pulmonary exacerbations, and he is also pleased that his lung function has been maintained at 90 percent predicted.

MR. BUSKER: Going beyond this specific patient, in the other clinical trials, as well as in the real world use of ivacaftor, what side effects or complications have been reported?

DR. ELBORN: No major side effects have been reported with ivacaftor treatment. Some patients report some headache and symptoms suggestive of sinus congestion in the first week to month after starting ivacaftor treatment, but those symptoms fell down pretty quickly.

There have been some concerns just around liver function tests (LFT), but this is quite a tricky area in people with CF because CF is associated with some underlying liver disease in many patients, and probably 30 percent to 40 percent of patients will have abnormal transaminases, but this can be somewhat intermittent. So during the trials we were very concerned when we saw any changes in liver function tests, but our conclusion has been that the drug itself was not the cause of any LFT abnormalities but it was much more likely to be the underlying liver disease associated with cystic fibrosis.

However, I think we do have to be very vigilant with monitoring patients on treatment with ivacaftor. Relatively few patients worldwide have had this treatment, so it's important that we look out for very infrequent side effects that might potentially occur with therapies such as ivacaftor. So pharmacovigilance and carefully monitoring patients on a new therapy such as this remain very important for the CF team.

MR. BUSKER: Thank you for today's cases and discussion, doctor. I'd like to shift gears now and ask you to look to the future for us. What CFTR-modifying therapeutic advances might be on the horizon?

DR. ELBORN: This is an area of a lot of active research, both preclinical and clinical trial research. For example, combination therapy with ivacaftor and lumacaftor has now been trialed in patients who are homozygous F508del, and that study has shown an improvement in FEV₁ and a reduction in pulmonary exacerbations. The results were not quite so dramatic as those seen in the STRIVE and ENVISION studies but do show a significant benefit of combination therapy in that large group of patients with CF who are homozygous for F508del.

Also recently, the results of the UK gene therapy study have been presented at the European Cystic Fibrosis Society meeting, and they suggest a maintenance of lung function in patients treated with gene therapy compared to deterioration in lung function in patients treated with placebo. Again, this is not a very dramatic improvement, and the patients didn't improve over baseline, but it does suggest that the gene therapy is worth pursuing. A number of different gene-based approaches are now being trialed in patients with CF, particularly those who are homozygous for the F508del mutation.

I think the future is very positive for developing new and potentially even more effective therapies directed at specific mutations. This approach has now been called "precision medicine," and developing precise therapies around the CF mutations I think bodes well for future effective treatment of this condition.

MR. BUSKER: Thank you for sharing your thoughts. Let's wrap things up by reviewing today's discussion in light of our learning objectives. So to begin: the relevance of specific mutations in people with CF to new therapies currently available.

DR. ELBORN: Ivacaftor is an appropriate therapy for people with G551D mutation and also for some other so-called Class III or gating mutations. It has also been approved for patients with the R117H mutation in the USA but not yet in any other countries.

So ivacaftor is an effective treatment for specific mutations that have been shown to be responsive in clinical trials.

MR. BUSKER: And our second learning objective: identifying which patients are suitable for CFTR-modifying therapies based on mutation class.

DR. ELBORN: It's very important that every person with cystic fibrosis knows which mutations they have, and the CF team should clearly communicate this information to them. This is important because therapies are likely to be directed at particular mutations, and so both the patient and the CF team need to be aware which mutations a particular patient carries.

MR. BUSKER: And finally: the known risks and benefits of CFTR modification therapy.

DR. ELBORN: The data so far indicates that ivacaftor treatment is safe, without serious side effects. The efficacy of treatment is quite significant in people with a G551D or other gating mutations. The therapy significantly improves lung function, reduces pulmonary exacerbations, but also in many of these patients therapy has been transformative in terms of their lifestyle, their aspirations, and their sense of hope for the future.

The effect of ivacaftor in patients with R117H mutation has a lower FEV₁ response, but overall has been considered to be sufficient to approve its use at least in one country.

MR. BUSKER: Dr. Stuart Elborn from the Queen's University in Northern Ireland, thank you for participating in this eCystic Fibrosis review podcast.

DR. ELBORN: Thank you very much for allowing me to discuss these innovative treatments that are making a very significant impact on the quality of life and outcomes in people with cystic fibrosis. These therapies are a major landmark in the treatment of cystic fibrosis, and also speak to our wider optimism that, by understanding the genetics and pathophysiology of disease, we can deliver effective treatments, even in rare diseases such as cystic fibrosis.

MR. BUSKER: Well said, doctor. Thank you.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ecysticfibrosisreview.org/test.

This podcast is presented in conjunction with eCysticFibrosis Review, a peer-reviewed CME/CE credit, emailed monthly to clinicians treating patients with Cystic Fibrosis.

This activity has been developed for the CF Care Team, including 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.

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eCysticFibrosis Review is supported by educational grants from AbbVie, Gilead Sciences Inc., and Vertex Pharmaceuticals.

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