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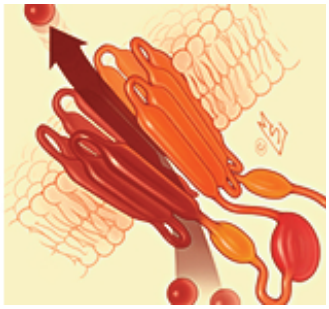

VOLUME 5 — ISSUE 12: TRANSCRIPT

Featured Cases: Benefits of CFTR Modification Beyond FEV_1 Improvement

Our guest author is Christopher Goss, MD from the University of Washington Medical Center in Seattle, Washington.

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

- Describe the effects of CFTR modulation on nutritional status.
- Evaluate the observational data supporting the impact of CFTR modulation on chronic infection in CF.
- Summarize the newer advances in our understanding of the pathophysiology of CF and how CFTR modulation may impact this process.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to the effects of CFTR modification targets in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 5, Issue 11 *eCysticFibrosis Review Newsletter* — Benefits of CFTR Modification Beyond FEV1 Improvement.

MEET THE AUTHOR

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Guest Faculty Disclosure
Dr. Christopher Goss reports that he has research grant funding from Vertex Pharmaceuticals Inc. In addition he has received honorarium from Gilead Sciences and L. Hoffman – La Roche Ltd.

Unlabeled/Unapproved Uses
Dr. Christopher Goss has reports that the activity will not contain any discussion of off-label or unapproved drugs or products.

Release Date
September 30, 2015

Expiration Date
September 29, 2017

CME/CE INFORMATION ⇩ PROGRAM BEGINS BELOW

ACCREDITATION STATEMENTS
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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, dieticians, 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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Estimated time to complete activity: 30 minutes.

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HARDWARE & SOFTWARE REQUIREMENTS
PC: Internet Explorer (v6 or greater), or Firefox
MAC: Safari

MR. BOB BUSKER: Welcome to this *e*CysticFibrosis Review podcast.

Our program today is a follow-up to our newsletter topic: "Benefits of CFTR Modification Beyond FEV_1 Improvement." With us is that issue's author: Dr. Christopher Goss, professor in the Division of Pulmonary and Critical Care Medicine, and professor of pediatrics at the University of Washington in Seattle.

*e*CysticFibrosis 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:

- Describe the effects of CFTR modulation on nutritional status
- Evaluate the observational data supporting the impact of CFTR modulation on chronic infection in CF
- Summarize the newer advances in understanding of the pathophysiology of CF and how CFTR modulation may impact this process.

Dr. Goss has disclosed that he has received research grant funding from Vertex Pharmaceuticals Inc. In addition, he has received honoraria from Gilead Sciences and L. Hoffman–La Roche Ltd. His presentation today will not reference the off-label or unapproved use of any drugs or products, with the exception of ataluren.

Dr. Goss, welcome to this *e*CysticFibrosis Review Podcast.

DR. CHRISTOPHER GOSS: Well thank you very much for inviting me to talk today.

MR. BUSKER: In your newsletter issue, doctor, you reviewed some of the key studies on the effects of CFTR modification — in the clinical trials, in real world usage, and in on-going research. What I'd like to do today is talk about how that information can translate into actual practice in the clinic. So start us out, if you would doctor, with a patient scenario.

DR. GOSS: The patient is a 26 year old female with cystic fibrosis with the following mutations in her CFTR gene: delta-F508 and G551D. Thus, she is heterozygous for the gating mutation G551D. Her FEV_1 is 55% predicted, and her body mass index is 19 kg/m2. She has struggled to maintain her weight with pancreatic enzymes and a high calorie diet for years. The highest her body mass index has ever been is 20 kg/m2. The CF Foundation nutritional guidelines recommend a body mass index of BMI for women above 22 kg/m2. She has now started treatment with the FDA approved agent ivacaftor.

MR. BUSKER: Her FEV_1 is currently 55%. Based on the information you presented in your newsletter issue, what might this patient expect to be the impact of ivacaftor therapy on her lung function?

DR. GOSS: If she is like the average patient in the phase 3 clinical trial with ivacaftor, she will gain 10.4% of her FEV_1 over 6 months. Importantly, similar effects were seen on FEV_1 gain in an observational study after patients not previously in a clinical trial started on the drug. So we feel this is probably an accurate reflection of how the drug works in the general population.

MR. BUSKER: And what is the expected impact of ivacaftor therapy on her nutritional status?

DR. GOSS: If she is like an average patient in the phase 3 trial with ivacaftor, she will gain about 2.7 kg over six months. Importantly, similar effects on weight gain were also seen in observational study after patients not previously in the clinical trial program started ivacaftor. So the results were really generalizable to the overall population of patients with the G551D mutation. Such a degree of weight gain has not been seen with any other drug therapy trial in CF.

MR. BUSKER: Do the data provide any insight into the mechanism of the weight gain seen with ivacaftor treatment?

DR. GOSS: Recent research suggests that the weight gain may be attributable to changes in the gut pH seen with treatment with ivacaftor. In CF, the proximal bowel pH is lower, or more acidic, than it should be compared to people without CF. Ivacaftor appears to activate channels that permit bicarbonate to be

secreted into the proximal small bowel and correct this abnormality, thus allowing pancreatic enzymes to function more normally.

MR. BUSKER: We know how important it is to manage patient expectations with any therapy, and in particular with these CFTR modifiers and correctors. So as the treating clinician, what would you tell the patient about what we've just been discussing?

DR. GOSS: That's a great question. What I try to tell patients is that although the average patient in the clinical trial improved both weight and lung function, some patients did not. It's important to know that lack of improvement in lung function doesn't indicate lack of clinical benefit. When the studies were reevaluated, those who had large improvements in sweat chloride didn't necessarily have large improvements in lung function, but on average they can anticipate lower rates of pulmonary exacerbation and improved quality of life, but some of the important endpoints like weight and nutritional status and lung function may vary by patient. So we need to caution them to expect that the results of the trial suggest average improvement, not what each patient can anticipate.

MR. BUSKER: Going back to the patient you described: How long has she been on ivacaftor therapy?

DR. GOSS: She's now been on the therapy for nine months and has been tolerating it extremely well.

MR. BUSKER: And in those nine months, what has she shown in lung function, nutritional status, and exacerbation frequency?

DR. GOSS: In the nine months since she's been on the therapy, she's had an improvement of her lung function of about 8%, which she was very happy with, and more important, she had a rapid improvement in her weight, gaining over 3 kilograms. What was even more startling, she had a tremendous, tremendous drop in her rate of exacerbation. She has not had a pulmonary exacerbation since starting the therapy after having on average two to four a year in the prior three years. So it has markedly improved her quality of life.

MR. BUSKER: Thank you. And we'll return, with Dr. Christopher Goss from the University of Washington 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 *e*CysticFibrosis 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 *e*CysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Christopher Goss from the Division of Pulmonary and Critical Care Medicine at the University of Washington in Seattle. And we're talking about the "Benefits of CFTR Modification Beyond FEV_1 Improvement." So let's continue with another patient scenario.

DR. GOSS: This is a 30 year old male with cystic fibrosis with the following mutations in his CFTR gene: delta-F508 and G551D, and thus he is heterozygous of the gating mutation G551D. He has a FEV_1 72% of predicted. *P. aeruginosa* has grown in his sputum each time it's been cultured for the last five years. He's also had both mucoid and nonmucoid isolates of *Pseudomonas* in his sputum. He has now been treated with the FDA approved agent ivacaftor for the last year, and he's noticed marked improvement in his cough and sputum production and a significant improvement in his FEV_1% predicted.

MR. BUSKER: Provide us a frame of reference. How does his improvement match what was seen in the clinical trials of ivacaftor?

DR. GOSS: This patient had improvement very similar to what has been observed in a phase 3 clinical trial program, notably the marked reduction in cough, change in sputum production, and improvement in lung function as measured by FEV_1. So he has really in many ways mirrored the results of the phase 3 program.

MR. BUSKER: Were any unexpected effects of ivacaftor therapy noted in this patient?

DR. GOSS: One thing is quite unusual in this patient. He seems not to have had *Pseudomonas* in his follow-up cultures. He has had *Pseudomonas* in every culture over the last five years, and he appears to be no longer positive for *P. aeruginosa*. This corresponds to some new data that suggests patients with single or two CFTR mutations for G551D that are treated with ivacaftor can have sputum cultures that are no longer positive for *P. aeruginosa*, as was noted in an observational study that was done after the approval of ivacaftor.

This feature, the fact the drug has been shown to be associated with loss of mucoid and nonmucoid isolates of *P. aeruginosa*, is quite intriguing. It's unclear whether this is a true loss of lower airway chronic infection or just a change in our ability to detect lower airway infection. The patients certainly cough less and have markedly reduced amount of sputum production as this patient did, so that may change our ability to detect these bacteria. But it is an intriguing result.

MR. BUSKER: We've been focusing on *Pseudomonas* — which is important because that's the most common pathogen infecting CF patients. But has ivacaftor therapy been associated with any other changes in the microbiology of patients' sputum?

DR. GOSS: That's an interesting question, and the observational study did, indeed, find changes in other microbiology. Importantly, *Aspergillus*, which is commonly cultured from CF sputum, has been noted to be cultured less frequently after initiation of ivacaftor. *Aspergillus* is a fungus that's commonly found in our environment and it's seen in the sputum cultures of patients with cystic fibrosis. It's unclear if this represents true changes in lower airway infection and colonization with *Aspergillus*, or our ability to detect it based on changes in sputum production and cough.

Other common infections in CF were also evaluated, but they did not change. These included organisms like *S. aureus*, methicillin-resistant *S. aureus*, *H. influenza*, and *B. cepacia* complex.

MR. BUSKER: Do any of these new data elucidate the causes of lung disease in patients with CF?

DR. GOSS: That's a great question. I think there are some new and quite exciting data about the early stages of CF lung disease, and they come from recent animal models in cystic fibrosis. The group at the University of Iowa has created a pig with cystic fibrosis, and they've been able to fairly definitively show that there may be two key defects in host defense in small piglets that have CF.

The first defect, which is quite interesting, is that they seem to have an alkalinization of the fluid that lines the large airways. In the setting of CFTR-deficient pigs — these are pigs with no CFTR — the fluid is more acidic than it should be. That could lead to inactivating the small molecules called antimicrobial peptides that help humans kill bacteria that land in the lung. With this more acidic environment, they seem not to be able to kill the bacteria that enter the lung spontaneously when piglets are born and also when they're living.

Second, there may be an important defect in how mucus is released from the mucous glands. They term this "tethering the mucus to the mucous gland." In the pigs that are deficient in CFTR, the mucus doesn't release from the gland but causes a long tethering phenomenon that can create pontoons of mucus that don't move with the normal mucociliary clearance. The new data really suggest that there may be two important host defects in CF, at least in the CF pig: impaired bacterial destruction because of mucus tethering and impaired bacteria destruction because the airway lining fluid pH becomes too acidic. They did a nice job of outlining this in their animal models, suggesting that these may be the earliest defects that lead to CF lung disease.

One of the big questions that came up with these findings in the animal models is whether the defects could be corrected. The investigators did an interesting experiment normalizing the pH of the airway fluid, which normalized the CF pig's lining fluid's ability to kill bacteria. This suggests that potentially modifying CFTR or activating CFTR

could change the host defect in a way that would kill bacteria that have not been vulnerable otherwise.

This very intriguing finding suggests that there may be alternative effects of these medications that we have yet to fully understand.

MR. BUSKER: We know the data isn't there yet, but please speculate about how these findings may apply to human patients with CF.

DR. GOSS: I think it has two important implications. The first is, could we prevent early infection in CF lung disease in children by merely correcting their CFTR defect. That question is unanswered, but I think it's very intriguing. Clearly, having bacteria in your lungs as a young child is part of the integral process of airway inflammation and destruction that lead to bronchiectasis in CF. The second aspect is, could we use these drugs to modify the current infection of patients with existing lung disease. This is still unanswered, but some of the data we talked about today suggest that maybe these drugs do have a host effect that can change the bacterial colonization in these patients.

Those are two important questions that have yet to be answered but could be very intriguing. By correcting CFTR can we reverse some of the chronic infections in these patients that we historically haven't been able to get rid of.

MR. BUSKER: I want to go back to that finding of a more acidic pH in the lungs. What investigations have been done to normalize the pH in the fluid lining of the airways — with or without using a CFTR modifier?

DR. GOSS: Some preliminary investigations have used a common alkalizer, bicarbonate, to see if it could change the airway pH. Preliminary investigations of nebulizing bicarbonate have not demonstrated any benefit, so that approach I think is not appropriate.

It still remains to be seen whether ivacaftor and similar drugs are indeed alkalizing the airway lining fluid of patients with CF who are treated with these drugs. I think the hope is that these drugs will change the pH of the lining fluid and potentially alter their microbiology.

MR. BUSKER: Interesting discussion, thank you. And now please bring us one more patient scenario.

DR. GOSS: This patient is a 44 year old female who has cystic fibrosis with the following mutations in her CFTR gene which is delta-F508 homozygous, so she has two delta-F508 gene defects. This is the most common mutation in patients with cystic fibrosis. She has a FEV_1 of 35% of predicted, which is severely reduced. She does airway clearance twice a day with nebulized hypertonic saline, which is 70% sodium chloride solution, and she also inhales nebulized Pulmozyme at 2.5 mg once a day. She uses both the hypertonic saline and the Pulmozyme, since their clinical benefit has been demonstrated in CF in phase 3 trials. She also exercises regularly for part of her care.

MR. BUSKER: So this patient — homozygous for F508-del, with an FEV_1 that's pretty low at 35%, and doing everything right to treat it. But now ivacaftor has not been shown to be effective in patients homozygous for F508-del — what are the possible treatments for this patient?

DR. GOSS: That's correct, ivacaftor has not been shown to be helpful in patients who have two delta-F508 mutations. However, I believe the era of CFTR modulation therapy is here for such patients. We are increasingly looking to mutation-specific therapies. And as of May 2015, a phase 3 study of ivacaftor combined with another agent called lumacaftor was published in the *New England Journal of Medicine* showing statistically significant improvement in lung function and also statistically significant and large effect on reducing the rate of pulmonary exacerbations.

I think this is a very interesting era for patients with CF, and a number of drugs in the pipeline are moving forward to target every single gene defect by classification now seen in CF.

MR. BUSKER: I want to note to our listeners that the combination of ivacaftor with lumacaftor was recently FDA approved specifically for patients ages 12 and older who have two copies of the F508del mutation.

DR. GOSS: That's correct.

MR. BUSKER: Based on your knowledge of the ongoing research, what are some of the other

nonpulmonary benefits of CFTR modulation that will likely be investigated?

DR. GOSS: I think there's a lot of potential. CF is a multisystemic disease that affects the pancreas, the gut, and well beyond the respiratory tract. Some intriguing evidence from case reports suggests that use of CFTR modulation, specifically ivacaftor, may reverse some of the defects that were thought to be irreversible. There have been reports that treatment with ivacaftor could improve pancreatic function in a patient with pancreatic insufficiency, which is felt to be irreversible; and the other phenomenon that's been noted in small case series is improvement in glucose modulation with insulin. Both pancreatic insufficiency and CF related diabetes are important complications of the disease that have big effects on the patient's health. So if these drugs could modulate those secondary effects of CF, it would be quite an important finding. These are some of the potential avenues that we have to investigate to look for what I term "off-target effects" of these agents.

It's important to know that the new combination therapy, ivacaftor and lumacaftor, has not clearly demonstrated some of the suggested effects on microbiology that ivacaftor had alone, although the studies were not designed specifically to look at the effects of these drugs on microbiology. I think data will be forthcoming on whether the combination does or doesn't affect the host interaction with bacteria.

It's important to emphasize that what I've talked about today included patients with gating mutations, those with G551D, and then those who are homozygous for del-F508. But I haven't talked about stop mutations, mutations where the CFTR is truncated during readthrough. One agent, ataluren, is currently in phase 3 trials with hopes it will be beneficial for those with stop mutations, and we anxiously await the results of that trial.

MR. BUSKER: Thank you for your insights. Let's wrap things up by reviewing today's discussion in light of our learning objectives. So to begin: the effects of CFTR modulation on nutritional status.

DR. GOSS: The podcast discusses how CFTR modulation can change the pH in the proximal small bowel, increasing the pH to more closely approximate a normal non-CF pH. The information likely explains the significant weight gains seen in the clinical trials and observational studies of ivacaftor. This novel CFTR modulated drug is now approved by the FDA.

MR. BUSKER: Our second learning objective: the impact of CFTR modulation on chronic infection in CF.

DR. GOSS: Recent observational data suggests that drugs that modulate CFTR can affect rates of chronic infection in CF. The podcast notes a case that highlights the potential for a subset of patients who no longer have *P. aeruginosa* or *Aspergillus* cultured from their sputum after treatment with ivacaftor.

MR. BUSKER: Finally: what the newer data are showing about the pathophysiology of CF and how CFTR modulation can affect this process.

DR. GOSS: The podcast discusses some of the novel data from the CF pig model that may really shed light into how patients with CF develop chronic lower airway infections. These include the two primary defects that were noted: the acidification of the airway lining fluid in the CF pig and the tethering of mucus from the mucous glands. These defects could explain the airway injury that we see in patients with CF from childhood through adulthood: the development of bronchiectasis.

MR. BUSKER: Dr. Christopher Goss, from the University of Washington, thank you for participating in this *e*Cystic Fibrosis Review podcast.

DR. GOSS: It's been a real pleasure spending time with you today talking about these new advances, and I want to thank you and your audience for this opportunity to participate.

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 *e*CysticFibrosis 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.
There are no fees or prerequisites for this activity.

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