



VOLUME 5 – ISSUE 6: TRANSCRIPT

Featured Cases: Improving Digestive Capabilities in Nutritionally Compromised Patients with CF

Our guest author is Dr. Steven Freedman of Boston’s Beth Israel Deaconess Medical Center and Harvard Medical School in Boston.

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

- Explain exocrine pancreatic insufficiency with its effects on nutritional status.
- Describe strategies to improve nutritional status in patients with pancreatic insufficiency.
- Identify patients with inadequate response to pancreatic enzyme replacement therapy.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to pancreatic enzymes in the format of case-study scenarios for the clinical practice. This program is a follow up to Volume 5, Issue 5 *eCysticFibrosis Review Newsletter* – [Improving Digestive Capabilities in Nutritionally Comprised Patients with CF](#).

MEET THE AUTHOR



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Guest Faculty Disclosure

Dr. Freedman has indicated that he has served as a consultant and received grant funding from Alcresta.

Unlabeled/Unapproved Uses

Dr. Freedman has indicated that there will be no reference to unlabeled or unapproved uses of drugs or products.

Release Date

April 16, 2015

Expiration Date

April 15, 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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Reviewed & Approved by:
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

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PC: Internet Explorer (v6 or greater), or Firefox
MAC: Safari

MR. BOB BUSKER: Welcome to this eCysticFibrosis Review podcast.

Today's program is a follow-up to our newsletter topic: *Improving digestive capabilities in nutritionally compromised patients with CF*. Joining us today is that issue's author: Dr. Steven Freedman, Chief of the Division of Translational Research and Director of the Pancreas Center at Boston's Beth Israel Deaconess Medical Center, and Professor of Medicine at Harvard Medical School.

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

Learning objectives for this audio program include:

- Explain exocrine pancreatic insufficiency with its effects on nutritional status.
- Describe strategies to improve nutritional status in patients with pancreatic insufficiency.
- Identify patients with inadequate response to pancreatic enzyme replacement therapy.

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Dr. Freedman has indicated that there will be no reference to unlabeled or unapproved uses of drugs or products.

I'm Bob Busker, managing editor of eCysticFibrosis. Thank you, Dr. Freedman, for joining us today.

DR. FREEDMAN: Thank you so much, it's a pleasure to be part of this.

MR. BUSKER: Your newsletter issue, Dr. Freedman, presented recent findings about how early malnutrition impacts cystic fibrosis co-morbidities and mortality, the importance of early testing for pancreatic insufficiency, and how intestinal abnormalities can limit the effects of PERT. Today I'd like to focus on how that information can be applied in clinical practice. So if you would, doctor, please start us off by describing a patient situation.

DR. FREEDMAN: A 6 month old infant with CF diagnosed through newborn screening had a fecal

elastase of 120 micrograms per gram of stool at 3 months of age, however, she's not gaining weight as expected.

MR. BUSKER: Let me start off with a very basic question, doctor: from a diagnostic perspective, is this patient pancreatic insufficient?

DR. FREEDMAN: So that's a great question. Fecal elastase values greater than 200 micrograms per gram of stool is normal. Values less than 100 micrograms per gram of stool is considered abnormal, and it's a gray zone between 100 and 200. So this patient would technically not be absolutely pancreatic insufficient.

What's important, based on a recent article by O'Sullivan and colleagues in *Journal of Pediatrics*, as reviewed in the newsletter, is that a single fecal elastase value may not be sufficient to truly diagnose exocrine pancreatic insufficiency. So it's important to have a follow-up by at least 9 months of age, and in this case sooner if this patient with CF is not gaining weight.

It's important to remember that other factors contribute to poor nutritional outcome, and that includes intestinal abnormalities. We know that loss of normal CFTR gene function not only affects the pancreas, but also has an impact on intestinal epithelial cells and thus can affect the ability of an infant to absorb those critical nutrients.

In addition, as I'll discuss a little bit later, it's important to rule out other potential factors that result in increased energy demand such as an occult lung infection or other abnormality.

MR. BUSKER: So should this patient be receiving PERT and if so what would her ideal dosing be?

DR. FREEDMAN: It's clear that newborn screening is having many important outcomes in patients with CF, in part because of earlier strategy to improve nutritional outcome. As to whether she should receive PERT based on this fecal elastase, it's not unreasonable to begin PERT and also to repeat fecal elastase to be sure that she is truly exocrine pancreatic insufficient.

A recent article by Haupt and colleagues in *Journal of Pediatrics*, as referenced in our newsletter, shows that in fact it can be difficult to achieve the optimal dosing of pancreatic enzymes. However, another article reinforces what recently we published in the literature that, in fact, if you can improve nutritional outcomes, that this has many long-term benefits on both morbidities, including lung disease, as well as mortality.

MR. BUSKER: So, doctor, this baby is only 6 months old. Is it really so important to optimize nutritional status so early in infancy?

DR. FREEDMAN: Ever since the first description of cystic fibrosis by Dorothy Anderson, we know that pancreatic enzyme replacement therapy is truly lifesaving. There are now several papers that have shown that appropriate nutritional status, especially as early as 4 years, and perhaps earlier back to newborn screening, has long-term ramifications.

We know from the article by Yen, et al., in *Journal of Pediatrics*, that is in our newsletter, that if you look at weight for age at age 4, that if you are less than 10th percentile, then you will have more pulmonary exacerbations, impaired glucose tolerance tests, increased risk for CF related diabetes, and a shorter survival. If instead you are at the highest percentile, 50th or greater, that these patients had improved lung function, fewer exacerbations with a better survival. This, in conjunction with several other recent articles, all illustrate that the sooner appropriate nutrition can be provided, and that includes ability to absorb and importantly grow as expected, that these patients will have better health outcomes. We can't be sure whether or not the patients that tend to grow better, maybe they just have milder disease, but when you control for multiple factors, including for the CFTR gene mutation, there is still a clear impact of better nutrition on long-term outcomes.

MR. BUSKER: Thank you, doctor. And we'll return, with Dr. Steven Freedman from Beth Israel Deaconess and Harvard Medical School, 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

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MR. BUSKER: Welcome back to this eCysticFibrosis Review podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Steven Freedman, from Harvard Medical School and Beth Israel Deaconess Medical Center, in Boston. And our topic is *Improving digestive capabilities in nutritionally compromised patients with CF*.

We've been looking at how some of the new information Dr. Freedman discussed in his newsletter issue can be applied in the clinic. So if you would, Doctor, please bring us another patient situation.

DR. FREEDMAN: A 17 year old girl with cystic fibrosis just started her first year of college. She had been doing remarkably well with minimal lung disease, few pulmonary exacerbations, with stable weight; however, at college, 3 months into her first semester she begins to develop weight loss and calls you.

MR. BUSKER: Doctor, the possible causes of this patient's weight loss — I suspect there's a fairly long list, but which are the most likely?

DR. FREEDMAN: There are several possibilities, the first and usually foremost is noncompliance with pancreatic enzyme replacement therapy, in part because of the burden of the number of capsules an individual has to take, especially at college around your friends and colleagues, it's not unusual that patients don't want to take what's been recommended.

In addition, because of body habitus and their perception of what they look like, especially women with CF, it's not unusual that they will scale back the amount of pancreatic enzyme capsules that they're taking in order to lose weight and fit in more with their friends.

In addition, there's a number of other GI comorbidities that needs to be considered in a patient with weight loss in this setting. First is potentially lactose intolerance, so unrelated to CF. Another one is celiac disease which occurs in approximately 1 percent of the population in the United States. There is a suggestion that in fact celiac disease may be more frequent in patients with CF.

Another possibility includes small intestinal bacterial overgrowth. Breath tests generally are not very sensitive or accurate in patients who have known lung disease, including from CF, and therefore based on symptoms, occasionally empirical trials of an antibiotic might be warranted.

Another possible cause includes inflammatory bowel disease. There are earlier publications to suggest that Crohn's disease may be more common in patients with cystic fibrosis, and thus in the right clinical context a further evaluation may be needed.

It could be changes in exercise activity, again, going away to college, perhaps more exercise, and that might be associated with developing weight loss.

Lastly, careful diet history is important to see whether or not there are specific dietary changes that might have led to weight loss. Not infrequently it's difficult to maintain 100 grams of fat consumption per day which is the standard recommended dietary fat intake for patients with CF.

MR. BUSKER: Is it possible her weight loss might suggest worsening lung disease or possibly an occult infection?

DR. FREEDMAN: Absolutely. Anyone who's losing weight who has cystic fibrosis needs to be further evaluated. We know that having any type of infection increases energy demands and can be associated with weight loss, and careful history as well as potentially further testing needs to be done.

There was a wonderful review back in 2000 by Paul Pencharz¹ and Peter Durie on the pathogenesis of malnutrition in cystic fibrosis and its treatment. And what they did is they broke down the pathogenesis of energy and balance in CF into three areas. The first is pancreatic intestinal or biliary abnormalities as a result of loss of normal function of CFTR. And this leads to increased losses. So whether it's pancreatic insufficiency, whether it's an intestinal defect, the lack of appropriate absorption or changes in bile salt secretion affecting micelle formation, all of this leads to increased losses from the gut. The second aspect is that perhaps as a result of loss of CFTR that there is a cellular defect that results in increased resting energy expenditure and it's driving increased need.

And the third area is decreased intake, this can be iatrogenic, this can be psychogenic, this could be from GI symptoms, so anorexia, nausea, vomiting. We know overall that energy deficits, irrespective of the three areas I just went through, these energy deficits are magnified in the setting of any catabolic process, catabolic process being an infection, especially lung disease. And as a result of exacerbation of the lung disease in CF, increased use of respiratory muscles, immune dysfunction, and all of this, drives increased energy expenditure and hence can lead to weight loss if not appropriately diagnosed and effectively treated.

MR. BUSKER: With all that said, Doctor Freedman: what would your next steps with this patient be?

DR. FREEDMAN: I would have a frank conversation with her, at first ask her in a nonthreatening way is she being compliant with pancreatic enzyme replacement therapy, acknowledging the difficulties in taking so many capsules with each meal and that you're here to help her and not be confrontational. Based on her response to that then you should talk about the importance of maintaining pancreatic enzyme replacement therapy at the doses you

recommended if she is not able to be compliant. But what's important is to have this conversation where you are in a partnership with her as opposed to just telling her what the dosing should be. You can emphasize why weight loss can have such a deleterious effect overall on her CF, putting her at risk of pulmonary exacerbations and infection, affecting many other aspects potentially of CF including potentially long-term outcomes.

If she's compliant, I would then explore could this be something related to diet, lactose intolerance? Does she have symptoms of small intestinal bacterial overgrowth, of bloating, abdominal distention, perhaps looser stools? Could she have celiac disease, if that's not clear then a TTG/IGA blood test should be obtained. And then if she is still not better then probably she does need to be seen and evaluated in your office.

As I mentioned earlier, it's important to go through diet to see if she is able to be compliant with consumption of 100 grams of fat per day, especially living away at college it may not be so feasible to maintain those dietary recommendations.

Lastly, it's possible that she could have certain types of infections, whether it's bacterial or possibly Giardia, but generally that presents with loose stool in the setting of weight loss.

MR. BUSKER: Doctor Freedman, let me ask you to focus on the reasons behind the sometimes inadequate response to PERT therapy. In talking about this patient, for example, you noted that the first thing to investigate when a patient is losing weight, or failing to gain weight, is PERT compliance. Now we know that the pill burden of a PERT regimen is difficult for many patients. So my question to you is: do you feel that compliance is the primary reason for the lack of response in some patients taking PERT? Or is it something else?

DR. FREEDMAN: That's a great question, it's actually more than compliance, all currently FDA approved pancreatic enzymes are porcine based. Unfortunately, these are not as effective as our own human endogenous pancreatic enzymes. In addition to the pancreatic enzyme replacement therapy not being very effective, there's a number of other factors specific to the CF gut that's a problem.

First of all, we know that the pH optimum generally has to be 6 or greater for the enteric coating of these porcine pancreatic enzymes to be dissolved. A paper by Gelfond and associates in *Digestive Disease Sciences*, which is discussed in our newsletter, shows that in fact alkalization is impaired in the proximal small intestine of patients with CF based on pH capsule studies. In addition, we know that this lack of alkalization of the proximal intestine in patients with CF affects bile salts being able to form effective micelle that would result in decreased fat absorption.

In addition, we know that this lack of alkalization also decreases mucous unfolding leading to increased viscosity affecting mucosal integrity, nutrient assimilation, and also predisposes the small intestinal bacterial overgrowth. As a result, in addition to the issue of compliance, both these relatively ineffective porcine pancreatic enzymes, as well as the milieu in the gut with this lack of alkalization, altogether is the perfect storm. As a result there's limited effective digestion of what's taken in from the diet, and then in conjunction with the CFTR related intestinal defects, there's lack of effective absorption, together frequently results in the malnutrition that's so characteristic of patients with CF.

MR. BUSKER: What can you tell us about the ongoing research to address these issues?

DR. FREEDMAN: This can be divided into three groups, the first is research on new enzymes. Ideally we would want enzymes that are active across a wide range of pH and thus not affected by the lack of alkalization that occurs in the intestine in the setting of CF. We also want enzymes ideally that aren't dependent on bile salts for maximal activity. We would want them not to be affected by hydration status. Generally microbial-based pancreatic enzymes, including proteases and lipase, would fit that bill. These are generally active over a wide pH range, do not need an enteric coating to maintain stability, and are not generally dependent on bile salts.

There have been extensive studies on a combination of microbial-based lipase, protease, and amylase, further testing is ongoing. In addition, microbial enzymes, by being more effective, would also mitigate the pill burden that's so problematic in CF. It would be ideal if instead of taking 5 to 9 capsules with each main meal, and 2 to 4 as an example with each snack,

if 1 or 2 capsules would be sufficient and be more effective than what is currently available.

In the second category there's now research that's begun on ex vivo pancreatic enzyme digestion. The notion here is could we have essentially an ex vivo exocrine pancreas, a pancreas on a stick, that would allow us to dissolve fats and perhaps protein in any kind of liquid meal outside the body, hence predigesting, so that no enzyme has to be taken by mouth.

There's currently ongoing research studies for this type of ex vivo pancreatic enzyme that are again based on microbial-based lipases. This potentially would be of enormous benefit, especially in patients who are receiving tube feedings in the setting of severe CF malnutrition. Currently there are no FDA approved pancreatic enzymes that can be effectively given or mixed with the enteral substrate given as a tube feed. Not unusually, patients are told to take pancreatic enzyme capsules before a tube feed is begun and then after, but we know that that's probably not very effective. Studies are about to begin looking at whether an ex vivo cartridge with microbial immobilized lipase would allow more efficient digestion of a tube feed, and hence improve nutritional outcome.

The third group is whether or not we can provide better nutritional choices. Up till now the recommendation have been to have patients with CF consume 100 grams of fat per day. We know that 100 gram fat diet per day is associated with better outcomes compared to a low fat diet; however, it's now time to focus on the types of fat.

For example, we know that omega-6 or N-6 fatty acids are pro-inflammatory, while N-9 and especially N-3 fatty acids are anti-inflammatory. Thus the types of fat, not just the amount of fat, may have important outcomes in the morbidity and perhaps even the mortality in patients with CF. In addition, as highlighted in the article by Groleau and colleagues in *Journal of Cystic Fibrosis* discussed in our eNewsletter, a 12 month study of a supplementation called Lymxsorb which is the lysophosphatidylcholine rich structured lipid matrix, did increase caloric intake in the patients. Thus, it may be that very specific nutritional additive may truly impact the health of our patients.

But what's interesting and exciting about that study was that simply increasing caloric intake by 114 calories per day improved growth, as well as resting energy expenditure, and also perhaps had other nutritional impacts. Thus, on the horizon we're going to see changes in all these three spheres that ultimately may improve nutrition and hopefully will increase the health and longevity of our patients with CF.

MR. BUSKER: Doctor, thank you for sharing those insights, as well as for today's cases and discussion. I'd like to wrap things up now by reviewing the key points of our podcast in light of our learning objectives. So to begin: assessing exocrine pancreatic insufficiency and its effects on nutritional status.

DR. FREEDMAN: The first question is does someone truly have exocrine pancreatic insufficiency. I talked about how an initial fecal elastase, especially in an infant in the first 3 to 6 months of life, may not be truly diagnostic. That fecal elastase values can fluctuate during infancy and that it is important to have follow-up values.

The second point is that once you diagnose exocrine pancreatic insufficiency, you want to diagnose this as early as possible and intervene at that point. As I discussed, the sooner you appropriately nutritionally replete someone, the better the long-term outcome, both morbidities and mortality.

You also want to treat effectively. You want to treat with the appropriate dose of PERT and control symptoms and prevent weight loss.

MR. BUSKER: And our second objective: strategies to improve nutritional status in patients with pancreatic insufficiency.

DR. FREEDMAN: So it's a combination of both proper PERT dosing, effectively supplementing calories in addition to the 100 grams of fat per day, and lastly, addressing other causes of malnutrition that potentially are leading to weight loss or preventing appropriate weight gain.

MR. BUSKER: And finally: the reasons for inadequate response to pancreatic enzyme replacement therapy.

DR. FREEDMAN: We know that this is multi-factorial. Porcine pancreatic enzymes are not as effective as our own native enzymes. In addition, as a result of CF related alterations in pH of the duodenum, bile salt abnormalities, abnormalities affecting the intestinal epithelial cells, that patient tends to suffer from malnutrition.

MR. BUSKER: Dr. Steven Freedman, from the Harvard Medical School — thank you for participating in this eCystic Fibrosis Review Podcast

DR. FREEDMAN: Thank you so much, it's truly been a pleasure to be part of this.

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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REFERENCE

1. Pencharz P and Durie P. Pathogenesis of malnutrition in CF and its treatment. *Clin Nutrition* 2000; 19: 387-394