OFFICEPERSPECTIVES: Using More Than Gut Instinct to Diagnose and Treat Exocrine Pancreatic Insufficiency

Transcript

David C. Whitcomb, MD, PhD: Exocrine pancreatic insufficiency or EPI is seen in a wide variety of diseases and conditions. With some diseases, such as cystic fibrosis or, obviously, total pancreatectomy, a patient will certainly have EPI. But in many other instances, there may be overlapping diseases or confusion with suspicious of a disease, and this becomes very difficult to diagnose. Pancreatic insufficiency is not a single disease entity. And in fact, it's determined by a combination of several factors. First, it's the physiologic reserve of the pancreas, how much enzymes can it actually produce. Secondly, it's the consistency of the meal, both in the size and in the content. And there's also adaptation that is possible by the intestine, to make up for some of the inadequacies of the pancreas. Though these have to be considered together, and varies from meal to meal.

The issue of adequate nutrition is important in adults, and it's especially important in children, where malnutrition can really affect their development and survival in diseases such as cystic fibrosis. So this program is designed to help you understand many of the questions surrounding the diagnosis and the treatment of exocrine pancreatic insufficiency to better support your patients on an ongoing basis. All of us work with pediatric and adult patients with EPI, and over the next several minutes we will look at some of the concerns and issues that we all face when it comes to work-up, differential diagnosis, treatment, comorbidities, nutritional compliance and more.

Steven D. Freedman, MD, PhD: Dave, thank you for that wonderful introduction. I'm Steve Freedman, I'm director of our Pancreas Center at Beth Israel Deaconess Medical Center in Boston, Massachusetts. I'm also at Boston Children's Hospital, where I help in the adult Cystic Fibrosis Center. My specialty is on exocrine pancreatic diseases, and especially related to exocrine pancreatic insufficiency, in both children and adults.

Ashley M. Salamone, MSN, CRNP: I'm Ashley Salamone, I'm a nurse practitioner at Johns Hopkins, in the division of Gastroenterology and Hepatology. I see mostly, adult patients, but those with recurring acute pancreatitis, Pancreatitis patients who are postsurgical resections, such as with Whipple or just old pancreatectomy, gastric bypass. Certainly see a plethora of patients with type 2 diabetes, celiac disease, and even inflammatory bowel disease.

Dr. Whitcomb: I'm Dr. David Whitcomb from the University of Pittsburgh. I focus primarily on adult patients, and on all patients with complex genetic diseases. My practice is focused on the nutrition component of our division, mostly inpatients, working with difficult pancreatic resections, surgical complications, patients with short gut, and other types of diseases that make digestion and absorption of food difficult.

Dr. Freedman: So why is it important to focus and diagnose exocrine pancreatic insufficiency in our patients? And there's a number of important aspects here. First, as Dave mentioned earlier, it's critical in the growth of children. In fact, in cystic fibrosis, prior to the advent of pancreatic enzyme replacement therapy, children with CF would generally die within the first 6 months of age. And thus, pancreatic enzyme therapy has been lifesaving in patients who have cystic fibrosis. So it plays a critical role in achieving normal growth, or as normal as possible, in these children with pancreatic disease.

It's also important in trying to normalize digestion and absorption of the nutrients that we take in. It's also critical in alleviating the symptoms related to exocrine pancreatic insufficiency, and in a bit, I think we'll end up talking about the bloating, the steatorrhea, the gas that can be typically associated with exocrine pancreatic insufficiency in individuals. Also critical in diagnosing EPI, so that we can prevent the malnutrition-related morbidity and mortality. And the morbidity can be related to malabsorption of the fat soluble vitamins such as A, D, E and K. And thus for example, coagulopathy, and especially the bone disease related to vitamin D malabsorption.

And lastly, if you diagnose EPI it's important that you then help try to prevent progression of the underlying exocrine pancreatic disease that may be present. There's also a number of articles that show that in fact, diabetes mellitus, whether it's type 1 or type 2, is associated with exocrine pancreatic insufficiency. A lot of these studies are based on doing fecal elastase testing, and showing that perhaps up to 25 to 50% of patients, where they have type 1 or type 2 diabetes mellitus, they have underlying exocrine pancreatic insufficiency to varying degrees. And obviously it's important that this get diagnosed and appropriately treated.

Dave, do you want to talk about the differential diagnosis of this condition?

Dr. Whitcomb: So, in general, there are a few things that are probably most important. The first one is pancreatic diseases themselves, and other ones are syndromes that involve the pancreas. And Steve mentioned diabetes, which is an area of a lot of interest and research now, and really, an area for education. So the major pancreatic diseases that we think about when we think about pancreatic insufficiency is obviously cystic fibrosis. And this is a disease where there's a genetic defect in the calcium and bicarbonate channel in the pancreatic duct, so that, even in utero, the duct cannot flush the digestive enzymes out of the pancreas, and injury and inflammation begins in utero. And often, by the first year of life, the pancreas is completely replaced by scar tissue and destroyed. And so obviously, pancreatic enzymes are critical for life of these children.

But there are other diseases that are of later onset. They are acquired diseases that we begin to see after birth and the development of the pancreas. We've begun to understand that there are a variety of complex disorders in which 2 or 3 genetic factors and environmental factors will come together, in different combinations that put the pancreas at risk.

Sometimes this is signaled by an attack of acute pancreatitis, and other times it's much more insidious, so that the pancreas slowly is destroyed by inflammation, without the patient even recognizing it, or having vague and poorly defined symptoms such as abdominal pain, cramping, indigestion of certain types of food, those types of things.

And lastly, there are diseases in which the pancreas does not function properly, without inflammation though. Shwachman–Diamond Syndrome, or problems with processing of RNA so that the digestive enzymes are not made by the pancreas, is an example. And these patients have sort of waxing and waning pancreatic insufficiency. They also tend to have short stature and recurrent infections. But this is a relatively rare disease. There are diseases that are also important, such as cancer-related diseases, IPMN especially, in which the pancreatic duct is blocked by mucus, and they have a pancreatic insufficiency from that. Certainly, any cancer that blocks the pancreas will cause insufficiency.

And then surgery that removes a substantial portion of the pancreas, or where there is a surgery to sort of rewire the GI tracts, such as a gastric bypass, so that the coordination between emptying of food from the stomach and signaling of the pancreas to secrete enzymes and mixing of the enzymes with the meal at the wrong part of the digestive system, so that it misses the area such as the jejunum, that is critically important for absorption of fats.

And so these are a variety of things that can sometimes be difficult to identify and manage, especially since there's not a uniform disorder among patients. It seems to vary a little bit, from patient to patient. Finally, Steve mentioned diabetes, and that's a tough one because the diagnosis of type 1 diabetes is obviously an autoimmune disease. The diagnosis of type 2 diabetes is a fasting blood sugar greater than 125. And what the heck does that mean? Well, it can mean that the pancreas beta cells or islet cells aren't working. But it can also mean that there is undiagnosed chronic pancreatitis that's destroying the pancreas. And this also becomes a huge problem. Since the diagnosis is so ambiguous and symptomatic, it makes it very difficult to diagnose.

Dr. Freedman: So if we think about the signs and symptoms in our evaluation of someone with suspected EPI, as Dave was mentioning, it can mimic a number of other conditions. The classic features that we think about are, "Does a patient have steatorrhea, this kind of oily, greasy stool that's thick and difficult to flush?" There may be associated weight loss with this. There may be abdominal cramping and distension, as well as flatulence. Malnutrition can be present, especially if it's an infant. We're thinking about is there underlying cystic fibrosis? It's not unusual, if not brought out of newborn screening that, within the first few months of life that, as a result of failure to thrive and perhaps loose stools, that that will bring out the work-up for CF in the setting of underlying pancreatic insufficiency.

There can be other symptoms. If it's more advanced pancreatic insufficiency, patients may be presenting with a coagulopathy or bleeding disorders. Perhaps edema, if there's enough protein losses. But typically, EPI tends to be somewhat more subtle in its kind of earlier presentation.

If the patient has known exocrine pancreatic disease, then you should always be on the lookout for the development of the 2 main complications, being exocrine pancreatic insufficiency and diabetes. I would say another complication would be the development of pancreatic cancer. So basically, if you have imaging that confirms chronic pancreatitis, if a patient has symptoms that are potentially reflective of pancreatic insufficiency, then either a further work-up should be done or, perhaps, empiric testing.

Ashley, do you want to maybe comment about the history that might be helpful otherwise?

Ms. Salamone: Yeah. So the history is really an important piece of beginning the investigation of EPI. Sometimes, as you mentioned, it can be pretty straightforward or associated with common disease processes such as cystic fibrosis. But other times, it's not as straightforward. So taking a thorough history, first very broadly, and then narrowing it down with more specific questions, is really important. I think it's also very important to set the platform that anything that's said is not going to be embarrassing to the patient or to the provider, and that this is a judgment-free zone. A lot of patients are uncomfortable with speaking about GI issues, especially with their bowel movements. They're perceiving diarrhea or what we perceive as steatorrhea. This is something that they're often uncomfortable talking about.

So paying careful attention to your line of questioning. The type of answers you're receiving, to try to read between the lines a little bit, and extrapolate more. I feel like doing this can provide a more welcoming environment for patients, and allows them to be a little bit more forthcoming with information. It's also a good platform to discern whether or not they've already tried common tricks of the trade, like eliminating dairy from the diet, trying gluten-free trials, yet they're still suffering with symptoms of malabsorption. It's also a good area to question whether or not they've already begin to understand fat correlation with symptom onset.

And again, with the specific questions about diarrhea versus steatorrhea, to help discern between something like IBS and EPI. Really specific questions such as, "Are you seeing fat droplets in the stool or floating on the toilet? Are these very malodorous? What's the frequency of the correlation?" Things of that nature.

Dr. Freedman, do you see anything on your physical exam that correlates well with history taking?

Dr. Freedman: Unfortunately, there's not that much in the physical exam that'll help you in sorting out if someone has exocrine pancreatic insufficiency. So usually, it's left to testing or an empiric trial of pancreatic enzymes. Unfortunately, the cross-sectional imaging studies may not be so helpful. We're not good at visualizing fibrosis to the pancreas in a reliable

fashion, whether it's MRCP or a CT scan. There has been a number of different tests over the years that have been utilized to help diagnose exocrine pancreatic insufficiency. The gold standard has been the 72-hour fecal fat test, where a patient is given 100 grams of fat per day as a diet, and then there's a 72-hour collection of stool. And then you look at the fecal fat content. Anything over 7 grams per 24 hours being abnormal. This is obviously a cumbersome test, it's difficult for patients to be on such a high-fat diet typically, and over the years, other tests have been looked at.

One of the more common ones that we tend to use nowadays is the fecal elastase test because it's a relatively simple test. It's based on just a random stool sample. You're looking at whether the fecal elastase is less than 200 micrograms per gram of stool. And definitely, less than 100 micrograms per gram of stool is probably a more specific indicator of exocrine pancreatic insufficiency. It's a relatively easy test to do. The issue is that if you have a loose stool, or a diarrheal stool, that that fecal elastase value will be low, even if you don't have exocrine pancreatic insufficiency.

A number of published studies do show that's the case, and therefore a relatively solid stool is required in order to actively diagnose a lower or subnormal fecal elastase value. Yeah, some of the other tests that are out there have been serum trypsinogen, though typically not used so much based on its sensitivity. And it's not unreasonable in a patient with suspected exocrine pancreatic insufficiency, so in the right clinical context, to simply give a trial of pancreatic enzymes and see whether or not a patient's symptoms, such as their steatorrhea, completely resolve with an empiric trial. If they do, then that generally, in the right clinical context, would be sufficient to diagnose exocrine pancreatic insufficiency.

Dr. Whitcomb: Steve, one thing that I think is worth pointing out here is, we really do not have a good diagnostic test for pancreatic exocrine insufficiency. This is an important need. A part of the confusion is many of the tests have been used in the past to make a diagnosis of chronic pancreatitis, and that's not really what they're used for. For example, we are revisiting the use of the serum trypsinogen level, which is useful, perhaps, in looking at early evidence of pancreatic exocrine dysfunction. One of the important concepts that is beginning to emerge more and more is the idea of compensated pancreatic insufficiency where your pancreas is struggling, but it has enough ability to produce enzymes, with the adaptation of the small intestine, that you see more in children, in order to appear that you're pancreatic sufficient, when you're not.

Though the idea of being able to know a little bit in advance and treat the patients before there is complete failure, I think is very important. You don't want to wait until a patient needs to be rescued from a nutritional disaster before we start treating.

Another thing that we've been paying attention to is a problem with vitamin B12 deficiency because that is not a fat soluble vitamin but requires pancreatic digestive enzymes to be absorbed, as the Schilling test demonstrates. So patients may take large enough doses of fat soluble vitamins that do not require digestion to be absorbed and eat a small, low-fat diet and be okay. But over time, they can develop a number of neurologic symptoms of vitamin B12 deficiency, if that's not been addressed.

So making the diagnosis is often challenging. Patients self-regulate their meals. They take fat out of their diet or are recommended to have a low-fat diet, which is not necessarily the best option. The best option is obviously that they treat the pancreatic insufficiency with some replacement therapy. And the other area that's important is protein malnutrition and sarcopenia; that has not been studied very carefully in pancreatic disease. But in liver disease, it's clear that patients that have poor muscle mass and sarcopenia do extremely poorly during surgery and recovery. Usually, the patients get stuck in the intensive care unit for weeks, because of these underlying problems of protein malnutrition, that aren't so bad when the person is in a controlled environment, but under stress, they do very poorly.

So those are some of the other things that we're becoming more aware of, and I guess, rediscovering things that were known in the past. Every generation has to learn the same lessons. So these are things that we think are important as well.

Dr. Freedman: David, these are all great points. Do you want to talk a little bit more about the management of EPI in someone once you have confirmed or suspect that diagnosis?

Dr. Whitcomb: Yeah, so there are a variety of approaches to it. I think the first question is, how much pancreatic enzymes does your pancreas actually make, in a typical meal and typical day? And there's been a lot of confusion because of the units that have been used in research testing, and the ones that are on the label of the pancreatic digestive enzymes. The famous paper by DiMagno, that was in the New England Journal of Medicine, that showed that you had the ability to digest fat through compensation of the intestines until 90% of the pancreatic function was lost, measured the amount of lipase that was required in a suggested 30,000 units a meal. But those were 30,000 international units that do not correlate with UPS units. And therefore, it's probably 3 to 4 times as much that's needed.

If you look at a normal human adult, they produce about a million units of lipase per day. And so I think we have a tendency to grossly undertreat patients that have no pancreatic function at all. In the past, it was also assumed that in an adult, the pancreatitis was caused by alcoholism, and the fact that they were malnourished suggested that they were probably alcoholic. It was probably our fault because we're learning that only a minority of patients with chronic pancreatitis have alcohol as their primary etiology. They also tend to smoke and have more stones, which was one of the features that was used to make the diagnosis of chronic pancreatitis years ago, before high quality imaging studies.

And so the amount of pancreatic enzymes needed is much higher than we thought. Into that, we have to back into how much pancreatic function remains in the pancreas. And this becomes a little bit of a trick because often we don't know how much pancreatic enzymes are produced. This is where either direct or indirect pancreatic function testing can come in. We tend to use the fecal elastase as a measure because of convenience. The formal secretin-stimulated pancreatic function test, where the person is intubated is cumbersome and expensive, and many times, hard to get reimbursed. That is probably a better measure.

We're concerned, however, about the use of the fecal elastase, especially when other tests are compared, head-to-head with this test. There's a test that's used in Europe, which is a test of digesting a compound that releases a labeled carbon atom, and you can measure the amount of carbon dioxide in the breath and see how fast the pancreatic lipases are digesting the food. And the problem is that a person has to sit on a chair for 8 hours for this test. I've tried to explain to my European colleagues that Americans are impatient with microwave ovens, let alone sitting for 8 hours to do this test, even though they've improved it to 6 hours.

But when this test is compared to the fecal elastase test, there is no correlation. So I don't know what they're measuring. I mean, you would expect there would be a fairly tight correlation if they were both accurately measuring pancreatic function. But in fact, the lack of correlation really ties the point that these tests are sometimes helpful, but not completely reliable, and we really have to pay attention to the patient's weight, their energy, laboratory values, quality of life, those other types of things as well.

Ashley, what are your thoughts on this, because I know you spend a lot of time with patients and deal with these issues?

Ms. Salamone: Yeah. So I think one of the biggest questions we all ultimately are asking ourselves, in the setting of EPI and management is, "What are we doing for our patients to optimize their nutrition?" And part of the way I broach this question is making sure the patient really has at least a basic understanding of what EPI is, how the pancreas responds to food, responds to fat. They understand the role of lipase, and how it's important to aid in digestion. And that they can also appreciate that there are both short-term and long-term side effects that can develop in the setting of EPI that lead to serious complications of malabsorption. So that leads into the importance of nutrition and that patients should be educated on the importance of eating small, frequent, low-fat meals spread throughout the day, in order to evenly distribute their fat intake.

As previously mentioned, really limiting their alcohol intake and advocating for a complete tobacco cessation is important, to just preserve what pancreatic functionality is currently there.

In addition to that, enforcing the need for a well-balanced diet. Not only are patients, maybe unfamiliar with how they should be eating, but they might not be eating the right sources of vitamins, such as with vitamins A, D, E and K, which they can often be deficient in. And sometimes, despite patients' best efforts with this and compliance, they still might require individual vitamin supplementation. Pain might be a limiting factor in this setting as well, when we're trying to optimize patient's nutrition. And if they're not eating as a result of pain, this is a platform to discuss whether a pain-modulating agent should be initiated or some sort of other discussion regarding pain management should be taking place.

Overall, a main component to the management of EPI is with pancreatic enzyme replacement therapy, as previously mentioned. Dr. Whitcomb, are there any other thoughts you have with specific pancreatic enzyme replacement dosing?

Dr. Whitcomb: I think that the idea that we want to shoot for 72,000 to over 100,000 lipase units for a normal adult meal is important. Secondly, is that we recognize that the meal is not sent into the gastrointestinal tract as a bolus. It trickles in continuously over about 18 hours. So the mixing of the enzymes and then delivering it with the meal so that it's activated in a perfect time, it's important. Those are some of the things that I think that we want to pay attention to.

One of the questions I'd like to ask Steve is that you've had a lot of experience with patients with cystic fibrosis and CFTR mutations, as well as adult patients with pancreatitis from a variety of different etiologies. Are there differences that genetic testing, showing CFTR versus other types of etiologies ... How do they affect your thought process on how to treat the patients in terms of diet and therapies? Do you treat them all the same?

Dr. Freedman: So, Dave, that's a great question. I think it's important to make the diagnosis of cystic fibrosis. And in cystic fibrosis, as I mentioned earlier, we know that pancreatic enzyme replacement therapy is lifesaving. In a patient who's diagnosed as having cystic fibrosis, generally it's 100 grams of fat per day, is the recommended diet in conjunction with pancreatic enzymes. It's been shown in a number of studies that, in fact, it is this combination that improves morbidity and mortality, versus a number of years ago, in the United States where patients were put on a low-fat diet and put on less pancreatic enzyme capsules.

So a patient would see, it's important to make that distinction, and they should be on a high-fat diet and on a high dose of enzymes. As far as the dosing ... You brought up a great point where we don't know exactly what's the ideal dose. These are porcine-based pancreatic enzymes. They don't completely recapitulate what our own native enzymes would do as far as effectiveness. Because of a rare complication called fibrosing colonopathy, the FDA has set a limit on the amount of enzymes that should be given to a patient, and that's 10,000 lipase units per kilogram per day or 2,500 lipase units per kilogram per meal.

And that's based just on the case reports, as well as experience at the University of Toronto Hospital for Sick Children, for this complication of fibrosing colonopathy. I think we're all aware that, in fact, using weight-based calculations to define how much enzyme someone should take probably doesn't make that much sense. In part because we know that the pancreas normally would grade its response of how much it would normally put out in response to the amount of food an individual takes in, especially the amount of fat, for example, that someone takes in, in a meal.

I think one of the things you alluded to is we don't just have an instant bolus of food that comes in. And so although there's not a lot of hardcore science on this, we have patients that'll take their enzymes with the first bite of a meal, frequently in the middle of the meal. For me, I ask patients how long does it take them to eat a meal. If they eat a meal in 10 minutes, I'm probably going to give them their enzyme doses at the beginning and middle per meal. If someone tends to drag a meal out over a half hour or longer, then perhaps it helps to split up their dosing so it's at the beginning, middle and end of a meal. Again, I think there's not a lot of hardcore science on this.

One of the things that we're trying to do is to try to figure out how to maximize compliance. Especially in kids and adolescents who have cystic fibrosis that are taking 9 to 12 pancreatic enzyme capsules with a meal, it's in front of their friends. It's not so easy and it's not something that's going to obviously ... where we're going to see perfect compliance, by any stretch.

Ashley, do you want to comment on this? In your practice, how do you deal with the education, the compliance in exocrine pancreatic insufficiency?

Ms. Salamone: So compliance is a well-known issue I think all of us see, and yet despite our awareness, it's very difficult to challenge. I find most of the common barriers to compliance include cost, include lack of education. Include not only lack of education as to why the patient is using it, how they should be dosed, but also lack of education as to how they should be eating, amongst others that I'll touch on.

In terms of cost, pretty much all pharmaceutical companies, in current time, have some sort of financial assistance program established. All of this information is accessible online, so that you can sit down in the office with a patient at the time of the visit, help them fill out the form if they need that type of assistance. There are also monthly vouchers that can be provided while the patient is trying to establish themselves with this pharmaceutical company. I think it also behooves providers to establish a relationship with their local drug representative, as often times they can be very instrumental in trying to help a patient get really what they need.

In terms of understanding or lack of understanding, being very aware to compliance, this is really, where the nursing piece comes into play. I think a lot of times patients are seen in the office, and a lot of information gets thrown at them, often in terms they can't really understand or relate to. So taking some time to come back in, and from a layman's maintenance perspective, explain broadly what the issue is that the patient is facing, and what the recommended treatment or work-up includes. So they can have an understanding of why they're being told to do what they're being asked of. And they can have some sense of control over their own feelings.

It can also includes a lack of understanding with how to eat properly. Whether it is a cystic fibrosis patient who needs to try to attain 100 grams of fat per day or someone with pancreatitis. Working with a dietitian who has some knowledge base in pancreatic disease can be often educational. And a lot of times, insurance companies will provide this free, with entire cost coverage.

Another thing to think about in terms of compliance, kind of on a sidebar, is whether or not—if we're seeing ongoing signs and symptoms in EPI—whether or not it's because the patient is truly failing to respond to therapy or if they're taking the liberty to dose themselves the way they see fit. And particularly, cost is a barrier. A lot of times, patients will underdose themselves or avoid eating because they can't afford their enzymes. So this is something to always consider when we're questioning compliance.

I think another really important piece of this is that when we're concerned that a patient is not following our prescribed regimen and recommendations, that we're not approaching them in a judgmental or accusatory fashion. That we're coming into this conversation concerned, but presenting ourselves with open-ended questions so we can figure out what some of the underlying issues are. And I like to begin with broadly asking, "How are things going over the past month or few months since you've been seen? Has this been perceived as a good time for you, or have things been going on in your personal life or financial life that have presented themselves as barriers? Does your insurance cover the cost of your pancreatic enzymes? Are you able to afford the copay? If you pay for this, can you pay for other medications that have been prescribed by other providers? Are you able to pay your electric bill, your grocery bill?"

Try to get a sense of if there's something external going on. And if it ends up really not being fruitful, then you can always end up investigating whether or not the patients have been refilling your prescriptions. This is easily tracked now with electronic medical record systems and prescribing systems. We can always do a full count as well. And before we even get to that, I think sometimes asking the patient, "How many days will 300 capsules last you?" to get a sense of how many they're using on a day-to-day basis. With a quick question like that, they're not often going to sit there and do the math and calculate, based on what the prescription is, how many they should be using in a month.

Other things, in terms of compliance, aside from cost and education, will just be lack of motivation. Based on the number of times a day we have to dose, or patients have to dose rather, this can be something they just find cumbersome, unsightly and just annoying. I think, for the pediatric population, helping the parents and the child come up with some sort of incentivized program to reward themselves, whether that's extra computer time, a sleepover, or going to the movies. Something they find rewarding.

And likewise with adults. Although this is more individually driven, establishing some sort of reminder or reinforcement or awarding system to help motivate them follow through with our recommendations.

Dr. Whitcomb: I just wanted to reinforce what you're saying. We did a survey on patients to find out the types of things that were important to them. Of course, it didn't match what was important to the doctors—we have a different perspective—but they really emphasized issues, wanting to have dietary counseling, and to help them with a lot of the social issues, some of the guilt of being a burden to their family, financial cost. All those things really ranked very high in the perspective from the patient. And having somebody who has the time and expertise to sit down and counsel the patients and to help direct them to available resources is really a critical part of managing these patients.

Ms. Salamone: I agree, and I see that in my practice very much. Other things, I think that are common barriers are lack of access to these medications that are required 6 times a day. In a pediatric population, you want to make sure this is as easy and as convenient as possible. So packing their backpacks with these enzymes, putting them in their lunchboxes, having them accessible in their lockers, having the school nurse have an emergency supply. Using the school nurse as a source of a reminder that the patients are taking these medications with their meals, with their snacks. And then likewise, for

adults; that these are in their purses, briefcases, office desks, at home on the kitchen counter. Something as a visual reminder and accessible reminder as well.

There are support groups that are also available that I think can help with the patients who are struggling with overall perception of EPI, and how to live with this on a day-to-day basis. I know the Cystic Fibrosis Foundation has a very strong support system, both for patients and for family members, and this has been a very rewarding avenue for people.

Other things that we can provide in the office are common tricks of the trade as to how to administer some of these medications, if that's perceived as a barrier. For a lot of our younger pediatric or baby population, who have to take these with--or can't swallow a capsule, I should say--extracting the microspheres and dissolving that in some puree or breast milk and then being spoon-fed, is one easy way to administer this. However, it's important to educate the mother that, if the baby will be breastfed shortly thereafter, that she's protecting her skin, her breast tissue, her nipple tissue from any plastic degradation of these enzymes produced on the skin. And likewise, if the baby is having some sort of dribble come out of the mouth after having those enzymes that the baby's surrounding skin is protected. It's a little bit easier for someone older, a child and upwards, to swallow a capsule. And usually, it's not that much of an issue as we get older.

I think an often overlooked portion of compliance is the fact that this requires long-term therapy. This isn't a quick 1-month or 3-month fix. That similar to other major medical diseases, enzyme replacement therapy is long term, even if a patient perceives themselves to be corrected or fixed or treated. That this suggests that the medication is working, but it doesn't mean that the medication is no longer required.

So keeping this open line of communication, even though the patient's feeling better, but knowing that our door's always open, that we do want to see them back for a follow-up, whether that's in 3 months, 6 months, yearly, down the line. And that if anything does develop in the interim, while they're not seen in the office, that we're always here for them. When their insurance change and cost coverage become an issue, we're here, we have resources, we have dietitians. That we're here to support them, and ultimately, the success that they will have with managing EPI, is going to lie in their hands, with their compliance.

Dr. Freedman: Yeah, I would just add that I always kind of start off the conversation that, "This is tough. It's tough to take this many capsules with everything you eat, whether it's a meal, whether it's a snack." So I agree with all of your points that both of you have made in this regard. One of the things I also tell people is that if you become constipated, that's not a reason to back off on the enzyme. Some people will do that, trying to normalize the bowel movement. As a result, they're having partial malabsorption or maldigestion. And that's not really the right approach to take. And also, especially in adolescent young women, they do it so they can keep a certain body image and keep their weight down. Again, not a great reason to let pancreatic insufficiency be left partially or untreated here.

Dr. Whitcomb: I think the other things we want to keep in mind here are there are a number of conditions with pancreatic ... with the delivery of adequate nutrients to the meal, adequate enzymes to the meal, from the pancreas is affected. Gastric bypass surgery: very important to recognize that the normal mechanisms for stimulating pancreatic secretion is disrupted. There is no release of CCK from the duodenum, which is bypassed. And the absorption of really the nutrients from the jejunum are bypassed. The intestine does have the ability to adapt, to upregulate some of the transporters for certain nutrients in other parts of the GI tract in some people, but not others, such as iron, for example.

By being able to add digestive enzymes in pancreatic enzyme replacement therapy for patients with gastric bypass may be an important step. Another area that we're seeing more and more is patients with severe pain that have total pancreatectomy with islet auto transplant. They obviously need to have a full dose of enzymes. In some patients that appear to have motility disorder and pain, cranking enzymes up to much larger doses, in our experience, seems to help some of them fight it dramatically.

Another problem we have is patients that have a Whipple from pancreatic cancer or other surgeries. Many times, they are not given the necessary pancreatic enzyme replacement therapy, and they're malnourished and losing weight and nobody knows exactly why. It's assumed to be the cancer—but it may just be failure of the physicians to treat their patients effectively.

The last one one would talk about early is patients with poorly controlled diabetes mellitus. Patients with subclinical chronic pancreatitis can destroy not only the exocrine pancreas but also the endocrine pancreas, and they end up with something called type 3c diabetes. If you look at the American Medical—excuse me—American Diabetes Association classification of diabetes, there are 3 types. Type 1, which is diagnosed with auto antibodies to the beta cells. Type 2, which is a wastebasket of just abnormal glucose tolerance in patients that do not have auto antibodies.

Then type 3 is all the other things that are known to cause diabetes and they're seldom looked for. Among those, a third category, type C, are pancreatic diseases. And these are very important because when a pancreatic disease causes diabetes, you lose not only the beta cells, but also the alpha cells. So the patients do not have the counter regulatory hormones that are necessary to keep them from becoming hypoglycemic.

Glucose control in these patients is even worse because if they're not making adequate digestive enzymes, then the timing of the insulin and the anti-diabetic agents with the meal is not correlated or synchronized with the actual absorption. If you eat the meal—but if the digestion is delayed because of inadequate pancreatic enzymes—and you treat them with insulin, then you end up with very brittle diabetes, with the blood sugar dropping very low because you think that there's going to be absorption of the sugar, but it's not digested.

The blood sugar drops down because there's no counter regulatory hormones. You'll finally be able to get the sugar back up again, then the meal is digested and the levels of glucose go way up because of late flow digestion. These patients are very difficult to

manage. There's asynchrony between eating the meal and delivering the enzyme and adding pancreatic enzyme therapy to these individuals and recognizing that they're also missing the glucagon and other counter regulatory hormones. It is important to manage these patients.

Everybody that manages diabetes has these patients that are extremely difficult to treat. And the reason is they both are missing the alpha cells, the glucagon. And so these are the kinds of things that are really underdiagnosed, under-recognized and undermanaged problems that, are in addition to the obvious chronic pancreatitis.

Dr. Freedman: Great. Why don't we in our wrap up here ... As you've heard, as clinicians we know that EPI presents a number of challenges. In this conversation, we've looked at ways to approach the differential diagnosis and work-up, to distinguish this difficult disease from others in both children and adults, as well as how we can approach our patients. I think what's important is that this needs to be very individualized, each individual, as to the optimum management strategy, and potentially what the work-up has been.

And given the multifaceted nature of EPI, we know that we must supply overarching strategies, within each patient's treatment plan, not just enzyme replacement therapy, but also importantly, nutrition and diet, and any concomitant conditions that can impact exocrine pancreatic insufficiency. I think we all realize that even the best laid out plans require that someone carry them out to be successful. And that means we have to be ever vigilant in terms of compliance, and especially ongoing education of our patients.

Ashley, would you like to give us maybe 2 or 3 take-home messages that our colleagues need to know about compliance and in interacting with our patients?

Ms. Salamone: My top 3 compliance issues would include that patients have an understanding, not only what their underlying disease process is, but why they're being required or asked to commence enzymes or undergo whatever type of testing that's required for diagnosis. And ensure that they understand this, presenting it in simplistic terms. This would ensure more, long-term guarantee that then you'll have better success.

Also, educating patients that enzyme replacement therapy is a long-term therapy. It's not just a quick couple weeks here or there. This is long-term commitment, and the success that they will experience as a patient who are suffering from symptoms of this really lies within their hands to follow these directions. And lastly, if there is anything they need, any kind of support from us, assistance with finances, assistance with diet, we are here for them, and we have access. We have resources to provide them with what they need to overcome these challenges.

Dr. Freedman: David, do you want to comment on kind of what your clinical pearls are regarding EPI management?

Dr. Whitcomb: I think the things that we pay attention to is, first of all, we want to have a high level of suspicion and a holistic approach. A patient that are not seeming to be doing well for unknown reasons. One of the things we look at is, for pancreatic insufficiency, and the

signs are vitamin deficiencies including vitamin B12, and to be able to measure those things carefully. And also, using prealbumin to help us get an assessment of their protein mal… the protein digestion.

A second thing is that what we try to do is to look at the patient symptoms very carefully and then start with a larger dose of enzymes, perhaps even a full dose. And then seeing whether or not the patients respond with a change in the symptoms or biomarkers that we can follow, and then back off from there until you get a sense of what's most effective for them as well.

And the third thing is to really have the support structures, such as Ashley talked about, in order to help educate the patient and encourage them. I know there's patient advocacy groups and other resources that are very useful because it is a lifelong management issue. And we want our patients really to avoid serious complications from maldigestion, especially when we have effective therapy.

Dr. Freedman: I agree. And one of the most common reasons for "refractory steatorrhea" is that patients are way underdosed. I think clinicians—and not surprisingly—are confused with all these different doses, depending on which pancreatic enzyme you're looking at. People get concerned when they see numbers of 20,000, 25,000 lipase units and will sometimes end up choosing a much lower dose. I also ... My craft is, I started the full treating dose. I want to see is there clear effect, and then I will back off and see what's the dose that still controls their symptoms. That's the least amount of capsules so that you're still able to maximize compliance with a regimen.

I really like to thank both you, Ashley and David, for a lively conversation. I know you join me in thanking the learners who have tuned in for participating in this program as well. The fact that the audience has taken the time to really want to understand what exocrine pancreatic insufficiency means for our patients, and have the best opportunity for successful management of the disease is really important. And we hope our conversation has provided you, the audience, with some new perspectives to achieve that goal more effectively. Thank you.

Ms. Salamone: Thank you.