Miguel Regueiro:

Hello, everybody. I'm Miguel Regueiro. On behalf of CME Outfitters, I'd like to welcome you and thank you for joining us for today's educational activity entitled The Team, the Team, the Team: Creating a Short Bowel Syndrome Medical Neighborhood. Today's program is supported by an educational grant from Takeda Pharmaceuticals U.S.A., Inc. As mentioned again, I'm Miguel Regueiro, I'm the Chair for Digestive Disease and Surgery and the GI Department at Cleveland Clinic in Cleveland, Ohio. It's my absolute pleasure to introduce two friends, colleagues, experts in the field. And first, let me welcome my colleague, Kishore Iyer. Kishore is the Director of the Intestinal Rehab and Transplant Program, and is also the Program Director of Transplant Surgery Fellowship and the Professor of Surgery and Pediatrics at Mount Sinai Medical Center at the Icahn School of Medicine at Mount Sinai, New York. Kishore, welcome. Thanks for joining us today.

Kishore Iyer:

Thank you so much, Dr. Regueiro. Thank you everybody for joining us this evening. Look forward to the next hour or two of conversation.

Miguel Regueiro:

As Kishore was saying, we have a lot of people logged in from all over the country, I realize it's different time zones, but this topic seems to be very hot. So thank you for your attendance. Now, let me introduce and welcome another one of my colleagues and friends, Donald Kirby. Dr. Kirby is the Director of the Center for Human Nutrition and the Medical Director of the Intestinal Transplant Program, and is the Professor of Medicine at the Cleveland Clinic in Cleveland, Ohio. Don, welcome. I know you're only a few floors down from me right now, but it's always good to see you.

Donald Kirby:

Thank you Dr. Regueiro, and thank you for hosting this evening's wonderful lecture.

Miguel Regueiro:

So let's go ahead and get started, and let's review our learning objectives. Our first learning objective is to integrate the interdisciplinary team to optimize the management of patients with short bowel syndrome. Our second learning objective is to apply the efficacy and safety data to some of our treatment decision-making for patients with SBS. And our third learning objective is to implement the best practices from the state-of-the-art SBS/IR centers to improve access and care for patients with short bowel syndrome. But first I think it's important that we start by telling our audience some of the key definitions that we're going to discuss today, and how our patients might present with short bowel syndrome, and how they may be impacted, especially their lives and their quality of life. So I guess for both Kishore and Don, let's make sure we provide some clarity, some definitions. Don, I'll start with you. Tell us, how do you define, or what is short bowel syndrome?

Donald Kirby:

Short bowel syndrome is a malabsorptive syndrome, and it's related to reduced gut length and surface area resulting in the inability to maintain nutrition, hydration, and micronutrients when you're consuming basically an unrestricted diet. The clinical features vary along a wide continuum and depend with the extent and the anatomy that may be lost. Remember, not every episode of short bowel syndrome meets intestinal failure, and Kishore will talk about that in a second, but the problem is that

the patient cannot compensate for the losses, and they will have significant issues as we will see. And the treatment will vary significantly depending on the severity of the resection.

Miguel Regueiro:

So Kishore, to that point, and Don already brought it up, I think sometimes it's confusing for people out there in terms of short bowel syndrome and intestinal failure. So first of all, is there a distinction? How do you look at one versus the other, especially clinically, when you think about not only diagnosing these patients but treating them?

Kishore Iyer:

Thank you very much, Miguel. That's become in fact increasingly an important question. I used to think we certainly use the terms interchangeably. They are similar. There is some overlap. But it's clear that they're not the same. Intestinal failure, number one, is a functional definition, and it's easy to think of intestinal failure sort of in parallel to say kidney failure or cardiac failure that we are all more used to, perhaps. Short bowel syndrome refers very specifically to anatomical loss of bowel length resulting in a malabsorptive syndrome. Intestinal failure on the other hand requires that the patient needs necessarily are dependent on intravenous fluid support or parenteral nutrition. So it is that need for parenteral nutrition or intravenous support that confers the title, intestinal failure.

To state the obvious, intestinal failure can be caused by short bowel syndrome, as it is in the majority of cases. We think that about 70%, 75% of cases are due to short bowel syndrome but, importantly, the remainder, 30%, 25% of cases, are due to functional disorders of the intestine, the obvious ones, idiopathic pseudo obstruction, either congenital or acquired over time, secondary to often autoimmune diseases or Hirschsprung disease in the child, where the patient may have the entire compliment of bowel length that simply doesn't function. And if that patient requires TPN or intravenous support, that patient has intestinal failure. Subtle but important difference.

Miguel Regueiro:

I think that's well said. I'm going to stay with you for a minute, Kishore, and kind of move to short bowel syndrome in pediatrics and adults, but I think, hearing what you said, basically short bowel syndrome is defined by the length, if you will, but intestinal failure is really defined by the need for that parenteral nutrition. So the bowel is failing and, as you said, in some exceptions it's not necessarily shortening of the bowel from surgery or from some other reason, pseudo obstruction I think is the one. So let's talk about pediatrics versus adults, and maybe look at pediatrics, what that looks like, and adults, and some of the differences between the two.

Kishore Iyer:

It's interesting, if you look at a pie chart of causes for short bowel in pediatrics versus adults, the pie charts look roughly the same except that the predominant causes are slightly different. In pediatrics, predictably, the most common causes of short bowel syndrome are necrotizing enterocolitis, gastroschisis, and midgut baldness, so congenital diseases or perinatal causes for loss of bowel. Whereas in contrast, in adults we are talking of mesenteric ischemia and perhaps Crohn disease in some cases, where I am, a large metropolitan urban area, trauma. But I should let Don perhaps speak to this more.

Miguel Regueiro:

Actually, Don, maybe also we can switch gears in terms of some of the reasons, but also some of the clinical presentations, and I know that Kishore can speak about pediatrics, but maybe some of the

differences between clinical presentation in pediatrics and adults, and how you look at them, especially in adults. What are some of the common symptoms?

Donald Kirby:

Well, one of the things I want to say is, when you're looking at short bowel syndrome in the adult, the definition really is important. We like to think of it as having less than 200 centimeters; Medicare states it's less than 150. So many of the things that we see, probably the most common one that we see over 50% of the time are post-surgical complications, patients who have had multiple operations again and again. In one group of patients we're seeing a lot of bariatric disasters - patients gone for bariatric procedure, several years later, and something happens. They may have had an internal hernia or volvulus within, and they lose a considerable amount of surface area, and they become short for that reason. Inflammatory bowel disease at the Cleveland Clinic is probably the most common reason that we see here. Mesenteric ischemia, episodes of different cancers, and trauma as Kishore alluded to.

But the presentation that we end up seeing is diarrhea, probably the one thing that is common between pediatrics and adults, but one of the keys that you see in the emergency department (ED) is recurrent ED visits for dehydration. Patients will come in; they'll be very dehydrated. They'll have low potassium, low magnesium, and go out again and again, and nobody really is seeing that there's a pattern here. That's a significant issue, and we should be keying in on that. One of the reasons for that is you end up hurting your kidneys with all these episodes of dehydration, and that can lead to chronic kidney disease and later on renal failure. Other symptoms they may have are gas, bloating, abdominal pain, which we'll talk about later, and could be bacterial overgrowth. If you're really dehydrated and you're having a lot of diarrhea, you may have fatigue. You may have fatigue based on other reasons from either malnutrition or vitamin and mineral deficiencies.

Miguel Regueiro:

Right. And I think in kids, Kishore, maybe you can talk about pediatrics. We heard from Don about vitamin deficiencies, obviously the symptoms, the diarrhea, the gas, the bloating, but I imagine in pediatrics that it's obviously a unique challenge to have shortcut in the time when you're growing. So what does that look like in pediatrics?

Kishore Iyer:

You hit the nail on the head. I think it's the critical challenge in children with short bowel syndrome and any related malnutrition, or indeed malabsorption of nutrients is the impact on growth. So linear growth retardation in the longer term is a major concern in pediatrics. But I'll tell you, just to follow on what Don said, when I think of these patients, I think of some general symptoms, general technical features that perhaps all patients with short bowel syndrome have, that risk of diarrhea, the episodes of vomiting, perhaps gut symptoms, abdominal pain, these are general symptoms associated with the diarrhea, episodes of dehydration, episodes of fatigue. But what you can think of is, beyond the general symptoms, if you have a good idea of what is the anatomic area of the bowel that has been affected, you can then start to look for specific clinical features that point to signs and symptoms, and in fact, impact of disease that you might otherwise miss.

So anatomic knowledge which guides understanding of the phenotype is a very, very good clue as to what to look for. And just, if I may, Don made a very good point about the kidney dysfunction, if I may illustrate with an example, even in New York, and this happens unfortunately on quite a regular basis, I have a patient now on our intestine transplant list who had four visits to the ED for dehydration before the penny dropped, and somebody thought, wait a second, we could be dealing with intestinal failure.

Unfortunately, that was just a trifle too late. So not only now did she have intestinal failure, she had early onset of established kidney disease. So I think being attentive to the occurrence of diarrhea in these patients who've had bowel resection and the downstream consequences is important.

Miguel Regueiro:

And I think one of the aspects in short bowel syndrome, by the nature of the disease and the morbidities, is that it really affects many systems. So I know the two of you, first and foremost, are great internal medicine physicians and great general physicians because you really have to look out for the entire system. You mention the impact on the kidney and really so many other organs. For those out there, by the way, if you do have questions, feel free to put them in. We'll certainly leave time at the end and along the way. Don, I want to ask you a question about the anatomy. Kishore kind of started to talk about this, and Kishore, then I'll let you chime in, too. Ultimately I want to hear about your teams. I know the team a little bit at Cleveland, but I don't know about others out there like, Kishore, your team at Mount Sinai. But maybe, Don, you can provide an overview on the anatomy, your thoughts when you see somebody with short bowel, and then, Kishore, I'll get your comments.

Donald Kirby:

Sure. I think one of the important things as a gastroenterologist and someone who deals with these patients, is that it's important to look at the old records and try to get as much information as you can so you know as much about the anatomy as possible. There are three different types, as you can see here. Type one being the most serious. It has the worst prognosis because it has the shortest amount of surface area. And this is really less than 100 centimeters of jejunum to an end-jejunostomy. The fluid losses can be massive, 7-12 liters a day. The gut does not adapt very well in the early phases of this. These patients will have significant hypersecretion. Type two is a little better in that you've got jejunum to colon, and you've lost the ileocecal valve, which I try to explain to patients, which acts sort of like a stoplight.

It lets fluid and nutrients into the colon in a controlled fashion, plus it doesn't allow bacteria to crawl back up the ileocecal valve area into the small bowel. So the incidence of bacterial overgrowth is much, much better. The problem with a jejunum-colonic anastomosis is you get poor adaptation. The jejunum is not smart. It doesn't sense that there's nothing below it, so it keeps on chugging. And the other things that you lose with the ileum is that you won't have those parking spaces for vitamin B12 and bile, absorption. So you're going to get significant malabsorption of those. And then depending on how much surface area you do have left, then you're going to have a variable amount of either calorie and/or fluid absorption. So to really stay off parenteral nutrition in this type, you need more than 65 centimeters of jejunum to at least half or more of colon.

The third type is jejunoileo-colonic anastomosis, which is the most infrequent. There are only about 9% of these. This is the patient who's going to do best. They can do amazingly well with very little small bowel because in this particular type they've got that ileocecal valve. They may not be absorbing the vitamin B12 or bile salts well but the rest of it will adapt, and you will see some slower transit. These patients are the easier ones to rehabilitate and get off parenteral nutrition with time. Adaptation can take 2-3 years to really occur. So hanging in there and working with these patients is paramount.

Miguel Regueiro:

Actually, Kishore, I think Don's given us a couple take-homes. The jejunum is not smart, things want to go through it quickly, and the ileum is a parking lot for B12 and bile. I've actually never heard the intestines described in such a way, but thank you for that picture, Don. So Kishore, one thing I want to

ask is, at your center and then maybe nationwide, I know Don said that type three is the least common, what's the most common type that you see or that people out there should be aware of?

Kishore Iyer:

I really just want to echo Don's comments. I will tell you, I think we will be speaking more about this slide further down. In the current era of GI peptides, this anatomic knowledge has suddenly become critical, not just in trying to understand how the patients present and what their problems might be, but even as guides to management. And if I have the chance, I'd like to speak about that some more down the road but I will say that even if our participants, even if they don't want to get into the weeds and the detail of what's on the slide, I will say that it's useful to think of short bowel and intestinal failure, not the same as I said earlier, but overlapping, to think of short bowel syndrome as a spectrum of severity going from left to right on the slide.

At the left, the patient with the end-jejunostomy, the most severe, the most challenging, and on the right, the patient who has jejunoileo-colonic, easier to manage, because the colon, we know is a very versatile organ, and as physicians looking after intestinal failure, known not just for fluid absorption, the colon with a good diet can be retrained even to absorb energy. I look at this figure as representing a spectrum of severity at the very left. It's not just that the jejunum is not even very smart. It actually adds to trouble. The patients with the end-jejunostomy are in a hypersecretory phase. So you end up with huge outputs that you're combating. These are the most difficult patients.

But with the things that we've talked about, Miguel, if it's not obvious just in the last 20 minutes, these are incredibly, incredibly challenging patients. It clearly takes a village to look after these patients, and the good intestinal rehabilitation programs, as I think of it, have different versions of a model village. So what's the model intestinal rehabilitation team? Well, frankly, I don't know, but I can tell you the types of expertise that a good intestinal rehabilitation team should have. I think what's critical is medical expertise in the form of a gastroenterologist, ideally a hepatologist as well, and there should be a surgeon with an interest in intestinal failure. Our own center and yours are similar in that we also have an intestinal transplant program. Our intestinal transplant program rests squarely within the intestinal rehab program. We view intestinal transplant as just one extreme piece of the intestinal rehabilitation team.

But that's only the physicians. There are others with critical, as we've already said, expertise in nutrition, and Don and I both have an interest and expertise in nutrition. But you need good dieticians and nutritionists who can really pay attention and give these patients dietary counseling. You need expertise in medical management. You need social workers, pharmacists, and often infectious disease doctors. We rely very heavily on our interventional radiologists to provide long-term access. So you can see it's a huge team, not to mention that in pediatrics often you need occupational therapists, behavioral therapists, and people with expertise in speech and swallowing. I could almost go on and on, but the team is important and versions of this team. Not everybody will have all pockets of expertise, but I think there are key versions to this team.

Miguel Regueiro:

Really a tertiary quinary referral. I know for the physicians out there who may not work in these centers, I think you're getting a flavor of, when you refer these patients to a center, the different components of the team that include behavioral health, dietician, nutrition, medicine, surgery, radiology. It's really a huge undertaking. I think before we leave the anatomy slide, Don, I'm starting to see some questions come in, and one of them is: so what type—type one, two, or three—is the most commonly seen?

Donald Kirby:

Type two.

Miguel Regueiro:

Okay. And then, Don, let's move to achieving the early diagnosis and accurate diagnosis. So when you're thinking about the tools that you use to get an accurate diagnosis, and for, again, those physicians or clinicians out there, whether you're in a hospital setting or in the community, what should we focus on for the diagnosis of short bowel? How do you make the diagnosis, what tools do you use, and what tests do you use?

Donald Kirby:

I think the first thing you've really got to do is take a great history. And if they've had multiple surgeries, you need sometimes to even get the op reports out of micro FISH for older patients. We've had to do that for some patients, but getting a really rough idea, and Kishore may have mentioned this a little while ago, but when the surgeons are in there now, in the last 20 years, a lot of the general surgeons are now starting to measure the small bowel and what's left, and put that in their note, which is extraordinarily helpful to someone like me who's trying to figure out whether they're really a type one, two, or three. Type one is really pretty obvious, but between two and three, it ends up being a little tougher. So, history is certainly a key.

Laboratory studies. Well, unfortunately by the time they get to me, we know they're already sick. So when I send them down to the lab, the lab is laughing that I'm sending them down for vampire work, because they're getting a lot of tubes, because there are a lot of different things that we're looking at. We're looking at vitamin levels and certainly we're looking at the standard chemistries but, all in all, those are the basic things we look at. Fecal fat testing, if that's suggested, we generally try to avoid doing the 72-hour exams. If we can, we may give them the quick qualitative one, the Sudan stain as just a rough idea. Sometimes the insurance companies make you jump through the hoops to get pancreatic enzymes approved, so sometimes we have to do that.

Imaging, it's really hard to get an accurate estimate of how much surface area is left, but sometimes you can get a rough idea. It's probably a little easier in anatomy two, rather than three, where there might be more small bowel than you think. Endoscopy and colonoscopy I think are important especially if you're dealing with patients who might have mucosal disease. If you've got someone who has inflammatory bowel disease, you want to know if they have active disease or not. Because if that disease is active, then they're not going to absorb very well from that surface area that is left. Also, if they have strictures that are still present, you may be able to help treat some of those and save them from another operation. So not only diagnosis, but a little bit of treatment can be done with those.

Miguel Regueiro:

That’s really important information as far as how we look at diagnose and then ultimately predict which way we go with treatment, which we're going to come to in a minute. Kishore, I want to ask you one question on the impact of quality of life and the family. Obviously you take care of a lot of the kids with this, and you mentioned the care team. So what's important for the care team to know about the burden of disease and approaching quality of life and issues with the family?

Kishore Iyer:

Miguel, this is something that, if I'm not careful, I can get emotional about, because as some of our patients tell us, think about one thing any one of us does socially that does not involve food and drink.

So for patients living with this disease, it's really quite devastating on many levels. The patient with the high-output stoma is afraid to go out because he or she is always worrying, will the stoma bag leak, will I embarrass myself? If they're going out to dinner, they dare not eat because maybe their abdomen produces abnormal bowel sounds that are audible to everybody in the room, or maybe they have to use the toilet immediately after they eat. So the burden on quality of life cannot actually be emphasized enough.

And just when we think that the disease imposes a huge burden on quality of life, people like Don and I, we are used to looking after large numbers of patients on TPN. I have a fair-sized adult and pediatric home TPN program. We tend to be somewhat dismissive by saying that TPN is life-saving and shouldn't you be grateful because it helps you live a good life and perhaps even go to work or go to school? But the reality is actually quite different. These patients often infuse their parenteral nutrition at night, over 12 hours. The machine is constantly alarming. And we don't do this. We don't hydrate ourselves at night and don't put anything into our body during the day, so these patients can almost never get a full night's sleep between their output and their hydration. They're getting up every hour or so.

So, the burden and quality of life cannot be overstated even if it is sometimes difficult to measure. One interesting thing, kids who are born with short bowel syndrome that they acquire I guess early in life, either communally or in the perinatal period, they don't know any other quality of life. So in studies, their own perceptions of their quality of life is much better than their parents' perception of the quality of life. And of course the impact on the family's quality of life is quite significant. Don, would you agree?

Donald Kirby:

Totally agree. I really think that being on home parenteral nutrition is harder than being on dialysis. You go on dialysis, you go to a dialysis center, you give them an arm, they hook you up, you sit there, you watch TV for 3-4 hours, and you then go home, eat, drink, be merry, come back to the center a couple days later, repeat, repeat, repeat. For TPN, you've got to take the bag out of the refrigerator, you need to let it get to room temperature, you then may have to add a couple additives, and then you put it up on the pole, and then you prime the pump, and then you set it up and let it go, and then the pump beeps in the middle of the night, and then you're infusing things at 200 to 300 mL per hour.

What does that mean you're going to do? Well, everybody's going to get up and start peeing in the middle of the night, so nobody gets a good night's rest. As we'll talk about later, if you can give them a night off, you suddenly have made a best friend. It's really, really important to realize the burden on these patients.

Miguel Regueiro:

That's so important. That sleep disruption and the impact – it's just devastating. Now we're going to switch to treatment and we're going to look at nutrition and some of the medications. Kishore, as we get ready to shift gears, there's a question: how do you handle pushback from parents or other caregivers when you're encouraging adolescents to be more involved in their care? So in the young adult patients or pediatric patients, that's tough, right? I mean, how do you deal with that?

Kishore Iyer:

This is very tough. And if I remember from our earlier discussions in preparing for this, I think we're going to talk some more about it. Do you mind if we hold that question, Miguel?

Miguel Regueiro:

That's fine.

Kishore Iyer:

It's a great question. I want to really give it some attention.

Miguel Regueiro:

So why don't we move on. Don, cover the nutrition and the steps you look at working with the dietician and the other nutritionists. First of all, who's involved? Who are the other key providers? I think Kishore mentioned a little bit of this, and then what are your ingredients, if you will, to nutrition in these patients? And you can go between oral nutrition, enteral, and parenteral.

Donald Kirby:

The first thing that's really important to understand is whether they have a colon or not, because that's going to make things a little bit different. If they have a colon, you're going to have to put them on a lower fat diet than if they go straight to an ileostomy or jejunostomy. We always want to tell them to do five to six smaller meals or snacks because we don't want to overload their surface area. They only have so much surface area, and the more you push toward that, the faster the transit is, the slower you eat, the better it is. So if you're a grazer, you do great. You've got to avoid the simple carbohydrates, the simple sugars, and I'll come back to that, limit lactose, especially if you are lactose intolerant to start with, and artificial sweeteners, certainly the number one here, if you have a colon is sorbitol, because many of you will recall that we use sorbitol and things like lactulose for hepatic encephalopathy in our liver patients. The same sort of thing happens. If you give somebody too much sorbitol they get diarrhea. So if they have a colon and you give them too much sorbitol, boom, more diarrhea; you're trying to limit their diarrhea. And then you always want to see if you can get them to eat a little more than maybe they used to, but they've got to do it more slowly, and then try to be careful of all the dietary restrictions. We do have our dieticians work with patients very, very carefully on diet and fluids, and I think for me, probably the hardest thing to get people to get out of the mindset is this whole concept of oral fluid. From the time they are knee high, they're told by mom, oh, don't get dehydrated, drink water, drink more water, and for a short bowel patient that is the worst thing you can tell someone.

The way I explain it to patients is, you've got water or water-like things, so water, coffee, tea, and then on the other side the very hypertonic things—I won't say the brand names—but all the sugary sodas. So when you're doing those, you end up pushing fluid out and causing more dehydration. The way I explain it to them is, when they're drinking all this stuff, it's like drinking Liquid Plummer, and you're just pushing all this stuff out. The way to fool your gut, if you will, to absorb better and use the physiology is what we call these oral rehydration solutions. Originally developed by the World Health Organization in third-world countries, for things like cholera, when they didn't have IVs, they came up with these. So you've got normal length of bowel, but you've got a colon that's secreting in cholera, these fluids with a little bit of sugar, a little bit of salt, get absorbed very, very well.

And the other thing that we try to impress on people is not to drink quickly like they're in college with the frat party with beer. You can't drink quickly when you've got this low surface area problem. We also have to attend to vitamins and minerals, and that depends on anatomy again, so we have to look at that. For years and years, people thought that doing enteral nutrition, tube feeding, and TPN were mutually exclusive. That's not the case. You may have to supplement the enteral nutrition, what they can eat, with some IV fluids or parenteral nutrition, and that has to be customized to people and their tolerance. And this is part of the adaptation process that we'll talk about a little later. And for these patients, especially with intestinal failure, parenteral nutrition really is their primary treatment. And if we can make it easier for them, that's our goal.

Miguel Regueiro:

So Don, I'm going to stick with you. Maybe briefly tell us the medications for short bowel syndrome. And really, as we start to look at some of the newer therapies, those trophic agents, and then we'll get to audience response question on this. And then, Kishore, you're going to kind of dive in a little bit more to some of the specifics around these newer therapies.

Donald Kirby:

Okay. So we have a number of buckets that we start using. The first one is after diet and fluids, we start talking the antimotility agents. For years and years, things like loperamide, diphenoxylate-atropine, codeine, and tincture of opium have been used. However, *please* realize that these are not approved by the FDA for short bowel, they are for diarrhea. And in fact, codeine and tincture of opium may not be approved by many insurance companies, and I just had this big thing with insurance, and we had to go to the appeal because using codeine wasn't allowed on the Medicare formulary. So, someone who has done well for a decade on a combination of loperamide, diphenoxylate, and codeine is now being denied the codeine because their formulary changed, and they can't get codeine for the diarrhea. You can only give it for pain. So keep that in mind; that may be a problem for you.

We also want to suppress gastric acid, especially in the early phases of this disorder. If they have acute short bowel syndrome from surgery, etcetera, you may have acid hypersecretion. If you have acid hypersecretion that can really make for rapid transit, and it may also denature the pancreatic enzymes, because there won't be adequate time for the bicarbonate to neutralize what's going through the small bowel. So the proton pump inhibitors are very, very useful, that they're stronger than your H2RAs. Antisecretory agents, octreotide—that's a hard one for many patients to use because it requires sub-Q injections three times a day. Your patients are not very happy with those injections. If you can put it into the parenteral nutrition formula, we often do that if possible. Clonidine is generally thought of as a blood pressure medicine, but it does have some antisecretory effects, and they can be useful in some patients. Usually, we use that as a patch, not the pill.

Remember, all medications may have difficulty being absorbed in your patients, and we may have to think about different ways to give them those medications. If the patients don't have that ileocecal valve, they may be at higher risk for intestinal bacterial overgrowth, antibiotics may be required to give them more symptomatic benefit. Probiotics have been used—again, these are off label. Cholestyramine is only good if your patient has a colon and may be useful for excess of bile acids making it to the colon, which can irritate the colon and worsen diarrhea. The trophic agents…somatotropin really is not used these days. It was FDA approved, but we know that it doesn't work as well as the GLP-2 analogs like teduglutide. And I'll let Kishore.

Miguel Regueiro:

Yeah. So we're going to actually get to that now in a second. And actually, I think for the audience out there, the next two slides, Don, you've done a nice job covering. So I'll just say, gastric hypersecretion, you've already talked about the proton pump inhibitors; this can happen about six to 12 months after surgery. The antisecretory agents, you did a really nice job. And you'll notice the asterisks on the slides, because really these aren't approved. We're going to get into some approved therapies. And then the antidiarrhea agents as well, you mentioned the antibiotics, the bile sequestrants. Kishore, I'm going to come to you in one second, but I want to make sure now we get to the audience response, and then I'm going to turn it to you Kishore to add anything to what you said to Don, but also the GLP-2s, I really want to dive into that. So what is a true statement regarding GLP-2s? Kishore, I think you're about to say something. So while the audience is thinking about this, go ahead and make your comment.

Kishore Iyer:

I shouldn't disturb them. I was just going to say, if you are using cholestyramine in these patients, where really on polypharmacy we're using so many medications, we should remember to separate the cholestyramine from the other medications. Otherwise, they become ineffective.

Miguel Regueiro:

Yeah. And I think that's just such an important point. All right, Kishore. So I don't know if Don and you can see the results, but I'll read them out. So 45% of the audience answered the question, *all of the above*, 43% still say *I'm not sure*, so we have some good learning ahead of us, and then some smaller percentages split between the rest. So Kishore, I guess, first of all, how would you answer this question? And then let's go on to the GLP-2s.

Kishore Iyer:

I should tell you, Miguel, it's not a coincidence that I went into surgery, how would I answer the question? Probably badly. But let me just share—I am being factitious here—let me just share that all of the above would be the correct answer. And if I may perhaps walk through very quickly, it is true that naturally occurring GLP-2 has a very short half-life, estimated to be about five to seven minutes before it disappears from the circulation. And GLP-2 is secreted from the intestinal L cells. Most abundantly, these L cells are located in the distal ilium, some in the right colon, and perhaps that's about the only source of the naturally occurring GLP-2, which now explains, to some extent, the importance of the slide with the anatomy that we saw earlier. And finally, we will share some data, I believe, that'll show you that exogenous GLP-2 administration enhances nutrient and fluid absorption.

Miguel Regueiro:

So let's dive into it. So glucagon-like peptide-2, GLP-2. Obviously this has evolved our treatment for short bowel, and I remember, kind of dating myself, but back in the late '90s, 2000s, early 2000s, we didn't have any of this. So what can you tell us about these glucagon analogs? Teach us.

Kishore Iyer:

So this has become a very, very exciting era. Like I tell my patients, intestinal failure is a terrible disease, this is a good time for you to be having the disease. We are in the era of GI peptides that are improving the prognosis for many of these patients. So as we briefly alluded already, native GLP-2, we know it is secreted in response to a meal stimulus and actually appears to help with absorption and digestion. So what it does do, exogenous GLP-2 when it's given, and I'll just point out that teduglutide has been approved by the FDA for adult and pediatric patients aged one or older, who are dependent on PN. And what the pharmaco candid effects of teduglutide…what we see the teduglutide injection is really people focus on the increase in villis height and crypt depth. For those who are interested, this was first characterized by Dan Drucker in Canada.

And there's some beautiful pictures showing its impact on increasing villis height and crypt depth, but there are also some important effects, it slows gastric emptying, which we know is a problem in some of these patients, it increases splanchnic blood flow. So I think we're going to talk a little more about teduglutide, and I will just say perhaps, and emphasize that apraglutide and glepaglutide, I don't know who came up with these naming conventions, but these are pharmacologic conventions. I will emphasize that they're both investigational agents, not yet approved for routine use. They're in phase three clinical trials, but they hold a prospect of longer acting versions of GLP-2 that might need to be given only once a week or twice a week. But teduglutide, that is currently approved by the FDA, needs to

be given by daily subcutaneous injection, which if you remember the short half-life, native GLP-2 is still a very good advance.

Miguel Regueiro:

So why didn't you tell us about some of the efficacy data? What did the studies show?

Kishore Iyer:

So the data is actually very clear, and I should perhaps disclose that I was a scientific advisor to the company during the confirmatory steps trial. In fact, ultimately testified at the FDA on behalf of the company. But the primary endpoint of the steps trial was to look at the percentage of patients who achieved the primary endpoint, which was at least a 20% reduction in parenteral nutrition requirement. And I'll tell you that there was no magic to the 20%; the FDA bought the idea from some of us that for many adult patients, we can manage them on five nights of parenteral nutrition, and 20% reduction could potentially be one night of freedom from parenteral nutrition. Don mentioned earlier, and I agree wholeheartedly, any night off PN for these patients is a good night off.

So as you can see there on that graph, this was a multicenter, multinational, randomized control trial that was in fact, a confirmatory trial confirming prior European data. And the study methods primary endpoint—about 62/63% of patients in the teduglutide—met the primary endpoint of achieving at least a 20% reduction from parenteral nutrition. I just want to point out for a second, we may be getting into the weeds here, and stop me if you need to, but there appeared to be a good response in the placebo arm, but there have been now publications looking at this more closely, and that positive extract seen in the placebo arm was actually a spurious effect because that was achieved at the cost of reduced urine output in the placebo group and an artificial increase in oral intake. Whereas in the teduglutide arm, it was clear that the drug exerted what we call an intestinal trophic effect to increase absorption.

Miguel Regueiro:

And the long-term efficacy. I mean, what is that?

Kishore Iyer:

Yeah, there is actually some data. This is from my former colleague, Lauren Schwartz, who reported on long term efficacy. My eyes are too old perhaps to look at the exact numbers here, but what I can tell you is that she looked at patients who had initially been in the placebo arm and then been in the extension study. Even the patients who had originally received placebo work were allowed in an open label trial to receive teduglutide. But the bottom line is it was clear that with continued treatment, there was accruing advantage, i.e. patients who were treated for longer period with teduglutide achieved continued reductions in parenteral nutrition requirements.

You can see there, as far as 24 months out, there appeared to be a reduction in parenteral nutrition requirement. And in fact, there is now other long-term data. We've published our single-center experience showing patients achieving freedom from PN. There's now been a paper from the French national data showing in a larger cohort, 54 patients, about 25% of patients came off PN. So the long-term data for efficacy, and I should add safety, we'll perhaps see that here in a second, looks really quite good for teduglutide.

Miguel Regueiro:

Yeah. And I think, Don, I'm going to turn to you for the steps too, from baseline and steps to the additional base off of PN. It's just so important for the patients to have this independence. Do you want to share some of that information?

Donald Kirby:

Sure. If you look at this, basically the patients that got placebo or teduglutide in the middle didn't do quite as well as the independence of getting ted plus ted. So the *ted* talk here is basically, if you were in the trial and you got teduglutide for the entire trial, you had a better chance of coming off. Because again, the slide that Kishore showed that over that 24 months. If you really are on it that long, your gut does adapt long term, and you have a chance of reducing your parenteral nutrition. Here, the slide to the right shows 10% gout, one day and two days, three to six for mostly a third, and then PS independent in 33%. That's pretty darn good.

And the way I explain this drug to my patients is it works a little bit like Miracle-Gro—that the wonderful villi or the finger-like projections in their gut get bigger and stronger like those great tomatoes you see with the Miracle-Gro. That they get a little stronger and they work harder, and they will absorb more. So over time, you'll see much more absorption. That being said, sometimes it can increase the risk of intestinal obstruction. That is a potential side effect for this, but all in all, yes, you can get days off. And as Kishore said, any night off from PN, these patients are your best friend. You really want to work very hard to wean them off. And that's what this data shows. You can really give them some time off.

Miguel Regueiro:

And I know that you have some pool data on five adult trials. Maybe briefly talk through this, and then Kishore, I'm going to bounce back to the pediatrics. And then I'm going to want to get to, in a minute, the team-based approach, and people are sending in great questions, so we'll make sure to leave some time at the end. Yeah.

Donald Kirby:

Sure. So this pool data analysis, there are 134 patients included. And remember, when we're looking at studies like this, short bowel syndrome/intestinal failure, we're talking about a small population nationally, or even worldwide, compared to things like inflammatory bowel disease, rheumatoid arthritis, other things where we have lots of different medications for these days. So this is really interesting sort of data. So 16 patients of this pooled group achieved enteral independence. Baseline, these patients all needed parenteral nutrition, and on it for either two to 18 years, days per week ranged three to six.

What's really interesting here, and this is actually Kishore's paper, he should actually talk about this one. But 75% of patients required more than a year to really get the maximum benefit before they were able to be totally weaned off. But again, look at this one patient who was weaned off two and a half years after treatment. So continued treatment really is beneficial. When the initial trials were going on, we wanted to know whether patients would go back to normal or back to the way they were if we stopped treatment and didn't offer continuous treatment. Some patients did okay. Most patients need continued treatment with the medication, just like Miracle-Gro—it helps everything grow.

Miguel Regueiro:

But it doesn't reverse completely. So Kishore, there are a number of questions coming in, and actually this is perfect segue on pediatric experience in terms of GLP-2, and maybe differences in tolerance

between adults and peds. But talk us through some of the efficacy in reducing parental support in pediatrics.

Kishore Iyer:

Yeah. I can make this very easy—that the pediatric trial data looks very, very similar to the adult data. Now, there's one important difference in the construct of the pediatric trial compared to the adult trial. For good reasons, understandable reasons, the children entering the trial were not randomized to placebo. Keep in mind, this is a daily injection for a child, so that the children randomized were randomized either to standard of care treatment (there was no placebo) or they got the drug. And the bottom line was both in terms of efficacy and safety, you can see this was the 24-week report from Kocoshis in Cincinnati at the time, which showed the earlier data. But really, the primary endpoints were again met with a significant reduction in PN requirements for the children who were exposed to PN.

The number of children achieving freedom from PN within the 24-week period of trial was relatively small. From my memory, I think of the 54 children who received drug ultimately by the 24-week period. I think maybe there were only five or so who came off PN during that limited period, but as Don has already alluded to, and we've seen in our single center experience, with continued treatment and care, many of these patients, I guess, who are priority responders have the potential to achieve freedom from PN. And if time permits, we can speak about what types of patients anatomically, because now we are understanding that. What types of patients anatomically, and I will spare the suspense, type three and type two anatomic patients have a greater chance of achieving freedom from parenteral nutrition. Type one, the high jejunostomy patients, struggle to get days off PN. We sometimes cheat a little bit and transfer their reduction in PN volume to a day off, because that's so valuable, but there you can achieve reduction in volume of PN. I hope that helps.

Miguel Regueiro:

Yeah. No, that was perfect, especially in the pediatric group, as you mentioned, that's just such a unique population. And there are a number of questions, and I think you're going to talk about this now, the safety. So tell us a little bit about, I mean, Don kind of touched on this, but how safe is this?

Kishore Iyer:

Yeah. I think it's a very safe drug, but it's a very efficacious drug. But there are some critical, important things to understand. And I will say, even before we talk about safety, it is critical to understand and accept that this is not just one more antidiarrhea. We have loperamide. We have diphenoxylate/atropine for that. We have tincture of opium, if you can get it from insurance, good luck. But this is not an antidiarrhea; this is a GI peptide that has potent effects on the short bowel. What does it do? It increases splanchnic blood flow, it increases villis height and crypt depth. Now, people refer to it as a growth factor, and that's not a term I like, because it's not growing anything artificially. What you're getting is the physiological effect that you would expect from GLP-2.

So that now leads us to what the important safety features are. Number one, and most important perhaps, this drug is contraindicated in anybody with active GI malignancy, and I will emphasize, GI in this context is the gastrointestinal tract with all its embryonic extensions, i.e the pancreas, the liver, et cetera. So it is contraindicated in patients with active GI malignancies, and by extension, it is also contraindicated, not absolute, in patients who have polyps in the colon. If you have a small number of polyps that can be controlled and removed prior to starting GLP-2, that's not a contraindication. But think of the familial adenomatous polyposis patient who's on PN—that is a contraindication. And the other important safety features, Don alluded to obstruction, and that's a feature. It is interesting to me,

when we were in the trial, a couple of our stoma patients who respond to this drug very swiftly called the 24, 48 hours and said, oh, my God, my stoma has gotten very much bigger.

And at the time, we knew nothing better than to reassure them and say, good, good, this is a physiological effect of the drug, and maybe it'll help you. And that's actually exactly it, but it does mean that patients who have had prior extensive surgery, patients who perhaps have a stricture maybe in the setting of IBD, may be at risk for intestinal obstruction. I know of at least eight reports around the world of intestinal obstruction. I don't know of a single report where a patient has required surgery for obstruction. So those are the main things. The last thing I will say perhaps in safety is to keep in mind that some patients respond very quickly and very dramatically to this drug, and you have to be prepared to cut down the TPN volume quite aggressively if you see a response to the drug. Otherwise the fragile patient who's got borderline cardiac function may be tipped into fluid overload and cardiac failure.

Miguel Regueiro:

Great. So these are all important considerations, especially as we monitor the patient. Maybe I'll just briefly touch on the considerations before we use GLP-2, but then, Kishore, I want you to go through then your algorithm and how you approach it. But in terms of considerations, before we use this, the patient has to meet the criteria for short bowel, the IV nutrition and IV fluid requirement has to be at least three times a week for at least a year. You already talked about you and Don optimizing diet, antisecretory, antidiarrheal. So it's not like you're just reaching for GLP-2 as the first treatment. You mentioned very nicely the malignancy contraindication, but now we're going to get into in a minute, after the algorithm, and Don, I'm going to come to you for the team part, the treatment team and the patient, and really bringing that together. But before we get to that and we leave the GLP-2 discussion, what's your overview? What's your kind of algorithm? How do you approach this, Kishore? Talk us through this, and just from a practical standpoint, what does that look like?

Kishore Iyer:

Yeah. This is an exciting time, as I said earlier. I want to make sure we have enough time to talk about the team, but especially given I have two eminent gastroenterologists with me, I have to at least tickle your mind with an interesting idea. Think of intestinal failure as an endocrine disease of GLP-2 deficiency. The patient with type one anatomy. The patient with a high jejunostomy is missing the part of his or her GI tract that has the L cells and secretes GLP-2, quite akin to type one diabetes. That patient has a true GLP-2 deficiency, exogenous GLP-2 acts as a replacement, sort of like the insulin independent diabetic getting insulin. Perhaps I can take this example only so far. The patient who has some colon does secrete some GLP-2, but by giving super [inaudible] levels of GLP-2, sort of like the brittle maturity onset diabetic, you can get some benefit out of GLP-2 even in those patients.

But for the patients I'm thinking of when I'm using GLP-2…I'll tell you, I'm obviously a surgeon in a very aggressive surgical program. We like to make sure that the patient is surgically optimized. If a patient has got a high jejunostomy but has got almost his or her entire bowel distally unused, or has got, let's say the entire colon beyond it, I would not be using GLP-2. The first step for that patient is to optimize nutrition at the right time, go in, operate to restoring Tessalon continuity, and chances are, with a little bit of dietary management and medical management, that patient will come off better to nutrition, never require GLP-2.

But take the surgical patient who's now been optimized, let's say you've got type two anatomy, the patient has 25 centimeters of jejunum, has half the colon, struggling with TPN. Patient's getting three liters of TPN every night, so that makes it, let's say seven liters of TPN a week. You've optimized the diet. You've done the best you can with your nutritionist. You've optimized antidiarrhea. The patient is on a

proton pump inhibitor. You've treated some bacterial overgrow, and you've hit a plateau, perhaps the patients come down to five nights of parenteral nutrition.

And I'm describing, these are typical patients in my practice. And at this point, when you feel like you've hit a plateau about six months after surgery, give or take, not written in stone, the patients optimize nutritionally, medically, in. Now, most importantly, I'm already thinking in my mind of my checklist. There are no contraindications most importantly, no active malignancy, and I will begin the discussion of, should we consider GLP-2? Here are the pros and cons, here's what can happen. Maybe we'll get you down to three nights of PN. If you're so lucky, we might even get you off PN, but you have to go through a colonoscopy to make sure the colon is free of polyps, and you need a daily injection, and we'll have to monitor you closely. And if those things happen, that patient's ready for GLP-2.

Miguel Regueiro:

Right. Wonderful, wonderful overview. I think for the audience, that actually answered a lot of the questions that were coming in. So that's why I wanted to spend a minute. But Don, in the next 10 minutes, I want to end with the team approach, and then leave about 10 minutes at the end for some of the great questions that are coming in. So I know, Don, you work obviously in a large, well renowned intestinal rehab program. What's the intestinal rehab? What are the team members? What does that look like?

Donald Kirby:

Well, it's fascinating that you actually asked me to help you with this program because you are the creator of the IBD medical home. But doctors like Kishore and I really helped invent the HPN, or home parenteral nutrition medical home. We just didn't call it that, we weren't that smart. And you did one really, really key thing that we did not, which was talk to insurance companies and say, hey, we can help your patients if you help us with this medical home. But you see on the slide that it says that one of the team leaders might be a gastroenterologist or a pediatric gastroenterologist. They may be part of the team, but there are actually many home parental nutrition programs in the US, where you have either an endocrinologist, or maybe it's embedded in surgery rather than just gastroenterology. In our department, it is gastroenterology.

I work closely with general surgeons to help put in feeding tubes for many of our patients. I work closely with the transplant surgeons for assessment, possible reconstructive surgery, different things relating to immunosuppression. We may have to work with intensivists when our patients are admitted with sepsis from another catheter infection, and that can be an issue. And we have excellent interventional radiologists that help us get the line in, keep the line in, and maintenance of that line, which is absolutely imperative. We have parenteral nutrition nurses that help us with either line care or ostomy care, and education. We have an entire education series for our new home parenteral patients, and we actually have them sign a patient agreement. Well, you can't do PN without a pharmacist, because they have to prepare the parenteral nutrition in a sterile environment, and they educate us on drug interactions and drug nutrient interactions, which can come up in a moment's notice.

Probably the most important member of my team that I work with every single day that I'm at the hospital is our registered dieticians, and thank goodness for them. They help take my global ideas of what I want for diet and for fluids, and makes it much more personable to the patient, and we try to get into their lives and figure out the best diet we can for them that's going to work. We need the social workers because there are a lot of things that we need at home, and we have to understand the available resources that the patients may need at home. Sometimes we need a psychologist to give either individual treatment…a lot of these patients are very, very depressed about their medical

situation, and it's not just the patient, this affects every member of the family, sometimes the pets. Medical educator, we spend a lot of time teaching these patients various parts of their care, which is very important.

Probably more important for pediatrics is having a speech pathologist. Many of the kids that are very, very small may never have been taught to eat. Maybe they don't have a suck reflex. Maybe they really aren't all that interested in eating. And probably my first foray into taking care of an intestinal transplant patient was someone just like that, who really didn't care whether he ate or not, and he needed a gastrostomy tube to do part of his feeding. We finally got him off parenteral feeding, but we couldn't get him to eat enough, and literally had to tube feed him because he just had no taste for anything. And then child life specialist, again, for the pediatrics. We need the child as well as family support, and then transitioning those patients, Kishore will talk about that a bit.

I get them when they generally hit 18 or up. Sometimes I'll bend that a little bit depending on the child, to 16, it all depends, but many things. This really takes a village. To be successful, you need to have a team of people that are interested, dedicated, and want to work together. Our team really works together, and I think hums. We just know what to do for these people, and we just tick it up and move along and try to give them a quality of life. That's one of the tenets of our practice.

Miguel Regueiro:

Yeah. And I think a lot of the questions coming in, and we'll get to them in a minute is, how do you do this in a rural setting? So I'll come back to you, Don, when we get to the Q&A, and might simply be that you need to refer these patients. But Kishore, let me talk about some of the pediatric IR benefits, and I'm not going to outline them all. But I know NASP, again, has come up with recommendations, and some of the benefits are decreasing the number of septic events, PN dependence, mortality rates, end stage liver failure. But maybe talk us through, just a minute, the IR goals and transition of care. I'd like you to focus maybe on those couple topics, and then maybe what I'll do in the effort of time, because you've done such a nice job touching on some of the other points, I'll take us through a couple more slides and then get to some questions. So go ahead and tell us about the program goals for the IR program, especially in peds.

Kishore Iyer:

Sure. And Don really could have fooled people into thinking he was a pediatrician; he covered that so well. But the goals really, I view the goals as almost hierarchical. For the patient on parenteral nutrition, we want to achieve freedom from parenteral nutrition to the extent that's possible. That should be goal one. And sometimes complete freedom from parenteral nutrition is not possible, but some weaning from parenteral nutrition is possible. You might get a day off, two days off, and that's a good thing. So that's goal one. Goal two, if you can't reduce the PN requirements, let's say you have a patient who has 45 centimeters of bowel ending in a jejunostomy, that patient is not coming off parenteral nutrition however hard we try. For that patient, the second, and if you like, the subsidiary goal then becomes freedom from complications.

There are complications to the disease. There are complications to the parenteral nutrition, to the catheter. You mentioned liver disease. So the second goal of the intestinal rehab program is freedom from complications. The third goal is to focus on quality of life. We have the disease, we have the therapy. The therapy itself is burdensome. The disease is burdensome. We've talked about it. We as a team can understand and try and empathize and help with the patient's quality of life, and really sometimes I tell patients, not for me to comment on a patient's quality of life. I need to listen and hear from the patient and his or her family, what is their quality of life, and is there something that I can help

with? And sometimes it might be as simple as telling the patient, you know what? Your parenteral nutrition infusion at night is posing a terrible burden on your quality of life, why don't we explore that you'll carry your parenteral nutrition bag in a backpack during the day and get a good night's sleep? I've done that. So, that's quality of life.

And finally, look, we're in academy medicine, in a distressing disease field that is now going through almost tumultuous developments for the better. So yes, research is a responsibility, I think. And I'll tell you, John, not to belabor this point in the interest of time, but these benefits have been shown very well by Russell, Morris, and colleagues from the NASP again, for pediatrics. You can improve time to freedom from PN. You can reduce complications. You can improve survival. You can improve quality of life. So enough said, intestinal rehabilitation programs should be involved in the care of these patients.

Miguel Regueiro:

Great. So I think, Kishore and Don, I'm going to take it to the end, because I think you've actually covered a lot of these points for the audience. There are going to be slides on transition of care. We know that there are growing pains that can occur, and there are some guidelines on starting transition as early as age 12, and then taking them to the end. When we look at parenteral nutrition and the patient burden, I think both of you really outlined topics in terms of psychosocial care, risk of complications. You just emphasize that so well, the need for the intensivist in terms of the patient burden. And then you talked about patient support and quality of life, and patient support and quality of life in terms of factors that we look at how to improve. And I think both of you said, yeah, getting a good night's sleep off parenteral nutrition.

I mean, that sounds maybe for those that are not on parenteral nutrition, so simple, but what an impact. The role of home parenteral nutrition, Don, you're right. You actually should have coined the medical home because you were doing this long before I was, and that HPN experience has just been incredible, I know here in Cleveland and New York. And part of the way we connect with our patients now is telehealth. We're using telehealth as a way to digitally communicate. This has really revolutionized the way we treat patients, the pandemic, as it escalated this, but I think especially for these patients that have these chronic diseases, intestinal rehab, intestinal failure, having that check in. I want to remind people of some of the support for this short bowel syndrome for patients and providers. It's listed in the program. It's listed on the slide. I'm not going to go through all of these, but just to make sure you're aware.

And then in terms of patient education, I also want to make sure our audience is aware that we do have a brief video animation for patients describing short bowel syndrome and members of the care team. And these are really unique videos, and the video can be found at the CMEO website in the Patient Education hub. So if you go to the website, go to the patient education hub, and then you'll see the link on the screen. So I'm just going to end with some of the best practices. We want to optimize our remaining intestinal function as both Kishore and Don have mentioned. Decrease symptoms, promote enteral autonomy, the multidisciplinary team, I think you heard that theme throughout the course of tonight. Understanding behavioral and psychosocial aspects of the disease, supporting the whole patient, the total patient, the caregiver, and then Kishore did a nice job of talking about pediatrics and transition to adults.

So I really want to thank Don and Kishore, we've had a wonderful discussion. I also want to summarize our SMART goals, which are action items that we can integrate into our practices to improve the care of patients with short bowel syndrome. So creating that team approach, optimizing nutrition, recognizing some of the barriers when we transfer patients from kids to adults, quality of life, fewer nights on parenteral nutrition, and that regular ongoing education for our patients. Don, I'm going to ask you a

question. What is something you wish more people working with primary care knew about short bowel syndrome?

Donald Kirby:

That there is help available. Maybe Kishore will also address this, but you can learn about this by the LIFT-ECHO program, which helps, which is similar to the Learn About Hepatitis C, which is how it was developed, but that program does invite people, not just singing to the choir, but it invites other people to bring in cases or ask questions or help with management. It's important for the primary care doc to know that they have resources if they look out there. There are other organizations that want to help these people, whether it's the Short Bowel Syndrome Foundation, the Oley Foundation will help patients with enteral and parenteral nutrition. But recognizing and making the diagnosis, I think is one of the key things that primary care needs to start doing. If your patient has had surgery and they're struggling, and they've been in the emergency room a couple of times after their operation, there's something rotten in Denmark. Something's going on. And you've got to ask that question—do they have enough gut to really do the job of what it's meant to do?

Miguel Regueiro:

Yeah. So I think it's recognizing from a medicine standpoint, again, coming back to that cognitive, understanding the patient, looking at the whole patient, making the diagnosis. Kishore, there are a bunch of GLP-2 questions. You've answered most of them, but one that seems to be a couple people asking, and maybe you can answer it again. What's the half life? So what's the half-life of exogenous GLP-2?

Kishore Iyer:

It's interesting, and my disclaimer, I'm neither a biochemist nor a pharmacologist, but the half-life of exogenous GLP-2 teduglutide is of the order of two hours. So not huge but vastly improved from the five to seven minutes of native GLP-2. What is interesting is that two hour half-life, still allows a single daily dose to be given sub-Q, so the speculation is not just that it acts directly on the receptor. For the endocrinologists in our audience, maybe it has some additional paracrine effects that may not simply be related to the half-life. I will say, interestingly, some of the longer GLP-2 analogs. We talked about apraglutide, not approved investigational, center to our half-life being studied now in a phase three trial with once-a-week injection. Miguel, if I may, there was some very interesting question on transition, which will allow us to, I was going to say, kill two birds with one stone, but that's not a good thing to say on a medical meeting.

So the transition question is really interesting and important. I want to emphasize that transition is *not* transfer. Now, I happen to be unique; I look after adult and pediatric patients. But if you are working in a standalone children's hospital, number one, your job in transitioning your patient, after following that patient and that family perhaps for 10 years, is not to say, here's the number, here's the email address of Don Kirby. Go to Cleveland. Transition is a much longer process that prepares the patient and family for the change that's going to come, for facilitating that change, to educate them on what to expect. There may not be child life anymore. Things may not be touchy-feely anymore, but to tell them that you're going to get a safe, competent, very knowledgeable team and doctor, there'll be some things that are different. And ideally what you might like is to have one of your own team members, a social worker, a nurse go along with that patient on the first visit.

So transition is a multifaceted practice, but I will tell you, even though in my team, I see both, other than pediatric patients, I do a form of transition. I saw a question. How do you handle patients who are

pushing back when you're trying to get the adolescent teenager perhaps to become more independent? That's also a conversation that I have with the patient and the parents present. And the method that I like, which I use routinely in my practice, is to encourage the adolescent teenage patient to email me directly if they have questions with an agreement with all parties and the parents, that I will share their questions and information with the parents only with their permission, otherwise they have a one-to-one relationship with me. What it allows us to do is it allows us to get the teenage patient to start taking responsibility for his or her own care. So transition is a complex, long process that we haven't fully figured out.

Miguel Regueiro:

Totally agree, and such a critical part of life too. Two brief questions. So brief answers to these, and then I'm afraid we're going to be out of time. So really the night's flown by. Don, I'm going to ask you about bariatric surgery in short bowel, and then, Kishore, how do you pay for medicine?

Kishore Iyer:

Haha. Credit card.

Miguel Regueiro:

Yeah, that's a whole hour. So bariatric surgery is becoming more common. You already mentioned, Don, at the beginning, the bariatric surgeries and short bowel. Are you seeing a lot more short bowel in these bariatric patients?

Donald Kirby:

I am. There are many forms of bariatric surgery these days. The least invasive of the invasive techniques is sleeve gastrectomy, which leaves the rest of the GI tract intact. But then when you're talking about doing a Roux-en-Y gastric bypass or the biliopancreatic bypass, you're bypassing a lot of gut in those patients. They lose a lot of weight, a lot, because of malabsorption or maldigestion, and then once you've done that, if they get into trouble and they lose more surface area, because they now have had a mesenteric thrombosis, a volvulus, and an internal hernia, and they lose significant more surface area.

We've had several patients, when I first came to the Cleveland Clinic, that were bariatric in nature, and I was working them up for intestinal transplant because they had had these awful surgical disasters. And it's heart rendering, because these people are trying to do something really good for themselves by losing weight and getting healthier. They do so for a while, and then something just happens out of the blue that you cannot predict. But this is a growing group. We know that a lot of people are getting these types of surgeries. Again, you have to ask the question. Recognize patients that have had multiple episodes of GI surgery are at risk.

Miguel Regueiro:

Well, Kishore, I'm going to have to give your home phone number, your email, and your cell phone.

Kishore Iyer:

Just give my credit card number for the payment.

Miguel Regueiro:

Yeah, I was going to say, people are going to call you, and ask you how to pay. And if you want to give out your credit card, then that's great. But I am afraid we're going to probably have to wrap it up there. Both Don and Kishore, wonderful program. Based on the questions we had, the interaction on the Twitter, very nicely done. As I mentioned already, CMEO does have this as a program. You can link to the website as well. And again, with that, Kishore and Don, thank you very much. Thank you very much, CME Outfitters for your program. Everybody have a good night. Stay safe, stay well, and hope to see you soon at a conference.