Transcription for: THE GI CONNECTION

Emma Mertens: Alright. Good evening, everyone, and welcome com. Tonight, I am excited to bring you the next session in the Immune Deficiency Foundation's decoding PI series. Tonight's featured topic is unraveling the GI connection led by Dr. Peter Mannon from University of Nebraska Medical Center.
My name is Emma Mertens, and I'm the Program Manager for Education at the Immune Deficiency Foundation. On behalf of IDF, we thank you for tuning into this virtual event. Throughout this series, guest presenters will provide a deep dive into clinically advanced topics from the world of PI. If time permits, the session will be followed by an audience Q and A with our presenter. We hope through your participation in these programs that we may move forward in our mission to engage and empower the PI community through education.
A brief disclaimer. Please remember that information presented during this meeting is not intended to be a substitute for medical advice, diagnosis, or treatment. We are here today as a trusted source and friend to provide you with information. Always seek the advice of your physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice or delay seeking it based on information presented during an educational event.
This webinar is made possible by our wonderful sponsors. It is due to their partnership and contributions that we can provide programs like this for the PI community. Please join me in thanking today's sponsors. And now I am so pleased to introduce our presenter for this evening, Dr. Peter Manon.
Dr. Manon joins us from the University of Nebraska Medical Center where he serves as a professor in the Division of Gastroenterology and Hepatology and the director of their inflammatory bowel disease center. Welcome Dr. Manon, and thank you for joining us this evening.

Dr. Mannon: Thanks Emma. It's really in honor to be able to speak to the patients and the families behalf of the IDF. I'm just gonna share my screen right now as we get prepared for the formal program. Just a little bit about myself. I'm a gastroenterologist in my area of expertise is inflammatory bowel disease, specifically Crohn's disease, and ulcerative colitis.
And they also have a translational research lab studying the immune response in the gut that has now taken a turn to include study of the gut microbiome and how we can manipulate it in the dietary way or a prebiotic way, and we'll talk about this in a beneficial way, not only for Crohn's and ulcerative colitis patients, but for health in general, and perhaps in some day for primary immuno deficiency patients. I spent eight years at the NIH and the InterMune program at NIH, and it's there where I met a number of very well known

immunologists and where I got involved with this patient population because as a sole gastroenterologist in that institute, I was asked many times to evaluate it. Some of the GI complications primarily of CVID, chronic anti lowness disease, selective IgA deficiency, and then some more unique conditions like soluble CD forty, ligand deficiency, out syndrome and the like. So I wanted to keep the conversation tonight, or the presentation tonight, more of a conversational mode that will be going over a lot of data. And I hope it can be useful to you, and as Emma pointed out, I definitely will make sure we have time for q and a to go over things that you need clarification on or maybe want to have a little more in-depth information.

So in terms of the complications of primary immuno efficiency that affect the GI tract, why do they happen? And how often do they happen? Who is at risk? And what are these GI complications? And how can we manage and treat them?

And then we're going to kind of delve into what's happening to the good bacteria in the gut, particularly after so many antibiotics. So why does primary immunodeficiency affect the gut? Well, one of the biggest reasons is that the gut has the highest concentration of immune cells of any organ, even more than the skin. And the gut is the first line of defense against organisms and antigens and allergens. So it is a very important aspect of the innate immune system.

In fact, even something as simple as gastric acid is very important in handling a lot of the swallowed microbes that can contribute to disease, but also can all it helps regulate the amount and kinds of microbes that eventually get into the lower part of the intestines. The gut is exposed to very large amounts of microbes. And in fact, it contains itself greater than a hundred trillion bacteria. Now when I say microbes, we tend to speak a lot or think a lot about bacteria, but in fact, in the gut, these microbes also include viruses that we carry, yeast that we carry, a type of organism called Arkea, which is kind of a precursor to bacteria. And so there are a lot of different microbes, these organisms that contribute to health and they also can contribute to disease.

So the gut device immune mechanisms to balance these responses like there's a mucus lining throughout the GI tract that is a physical barrier against a lot of exposure to these microbes. The epithelial cells aligning the gut make antibacterial peptides. And they also secrete a type of IgA called secretory IgA that's also important in sort of molding the character of the gut microbiome. So Possible changes of the microbiome can be related to immunodeficiency as well as exposures like diet and especially like antibiotics. And I will say that one of the unique aspects of the primary immunodeficiency is reflected in in, say, animal models, mouse models that we use to try to understand the physiology of some of these deficiencies that there When you specifically block single immune molecule or mechanism, that can change the gut microbiome in that animal.

So we know that the Indian status of an organism or a mammal like us can can modify the

bacteria. And in such a way, there is some mouse immune models that can actually develop what we call a cholidogenic gut and microbiome. You can take stool samples from mice, and you can actually induce colitis and wild type mice because of the changes in the gut microbiome. So with the number of and types of murine immunodeficiency patients I've come across. I what helps me think about the occurrence of GI complications in certain diseases, I've made this little graph for myself So on the bottom of it, the x axis is the frequency of GI complications like how often do GI complications occur in certain diseases?

And then on the y axis, it's what is the severity of these complications? Are they low severity? Are they very high in serious severity? So the first on this list is selective IgA deficiency. And I think it's fair to say that while there can be GI complications, they really don't happen that much.

You know, selective IgA deficiency is the most common. Primary immunodeficiency, but yet it's in general asymptomatic. I'm not saying it can have a risk for certain infections and things. But in general, you don't get a lot of the autoimmune and severe anarthropathies you see in other conditions. So I put this at the very extreme as something called early onset colitis.

So we even have a simple very early onset colitis that occurs sometimes within weeks of a child being born and this is really related to the defect in a very important regulatory mechanism related to interleukin ten and its ability to signal themselves and be active And these babies really sometimes can only be treated with stem cell transplantation. And it's a very severe form of almost like a chromes like inflammation. So something that also is very high severity is an enduropathy in CBID. And we're gonna talk about this more in-depth. And when I say enduropathy, I just mean sort of a specific disease of the gut or specific inflammation of the gut.

But it's high, but it occurs in very low frequency of in terms of the whole CVID population, which is, again, the most numerous primary immuno efficiency that has GI complications. But only a fraction, the small fraction are very severe. Chronic fatty lymphoma disease, which I saw a lot at the NIH, and I don't see as frequently in our university practice. Half of those patients can get severe complications. This is really related to the important immune defense that the macrophages are needed for.

So there are CVID GI symptoms that occur in almost half of patients, but they tend to be much lower severity than the enteropathy. This would be transient diarrhea, maybe some cramp abdominal pain, but nothing like inexorable weight loss, severe, malnutrition, protein loss, and things like that. Another condition that's related to loss of inhibitory, immune functions, a so called iPeX syndrome, has an anneuropathy that interestingly occurs in nearly all patients who have it and it can be particularly severe. But this is a fairly uncommon primary immunodeficiency. And with regard all your syndrome similarly can

have very high complications, severe complications, but only in a small number of patients.
And so this is sort of a construct that I look at because I it's very important to focus on those patients who have you know, severe oftentimes life threatening complications of GI disease and then know how to differentiate them from more frequent complications but that are lower severity. So this is just a little circle diagram of who gets the GI complications? And so if this is a whole population of patients who have different types of primary immunodeficiency diseases, you can see that sort of navy blue and then the tomato red, and then the green and the orange, sorry, the green the orange and then those almost look at fifty percent and this is mostly cheese cell, but also B cell immune deficiency, so that they can be shared among each other despite the fact that we're gonna be talking about maybe antibody dependent immune deficiencies. But as you all know, because I know you have had a lot of experience not only with the disease, with yourselves, or maybe with the family member that even in CVID where we're giving exogenous immunoglobulin to keep levels up that Most people have a demonstrable T cell defect as well that you can you can detect it with special testing.
So what are these complications of primary human efficiency? Then we can break them down to three major topics infections of the gut, inflammation or immunity that affects the gut, and then and then some cancer risk in the gut. I just want to remind everybody that, you know, the gut doesn't just store it in the stomach. The gut starts in the mouth. Where you have an oral cavity and you begin digestion when the salivary glands actually begin to secrete amylase, for instance.
And there's a huge microbiome in the mouth that you swallow along with food all day long. Have an esophagus here that's important obviously for transferring the bolus of food from the mouth to the stomach and also is important for protecting the head and mouth and lungs. From gastric acid reflux. Then we have the stomach. Obviously, it makes acid, so you have protection against certain infection, but it's also important to hydrolyze some of the nutrients that we begin to have.
In the diet with meals and also the stomach churns that food into a liquid that's then put into the small intestine and this is where the real digestion begins where the bile from the gallbladder produced from the liver is able to break down fats together with all the important enzymes from the pancreas that begin to break down your proteins and carbohydrates and fast even further, and then the small intestine is the most important aspect where all these nutrients are absorbed. Finally, once leftover gets delivered to the colon, And the colon's job really is just to extract all the extra fluid back into the body and then hold on to your next bowel movement until it's socially acceptable to find a place to but go of it. So, you know, when I think about the GI tract and you think about transplantation, so we only transplant organs that you absolutely need. Everyone's familiar

with liver transplant because you can't live without that. Everyone's familiar with small intestinal transplant because you can't live without your small intestine.
Even if you have so called short bowel that's less than a hundred centimeters, you're gonna rely on, you know, being fed by being total parenteral nutrition just to keep yourself alive. But you really don't need your esophagus, you don't need your stomach, and you don't need your colon for life. But you do need these other things that we transplant. So what sorts of symptoms come from these areas of the GI tract? Well, the esophagus. Obviously, everyone's familiar with heartburn, but maybe less so with pain on swallowing or foods and liquids getting stuck. In the stomach, you can obviously have pain in your upper abdomen, especially the patient feeling full evil with smaller amounts of food. And then obviously, vomiting, which is a response to some toxic event going on in the stomach and the stomach not being able to empty. And so it's so you just eliminate the food the way it came in. In the small intestine, if you can't digest and absorb all the calories that you're taking in, you're gonna begin to get bloating.
This can give you some crampy abdominal pain. Some vomiting after meals can lead to large volume watery diarrhea, weight loss, excess gas, and diseases that affect the colon can result in diarrhea, seeing blood in your bowel movements, feelings of urgency, incomplete evacuation, and maybe even even stool incontinence. So in a little and and I know that the idea if it's gonna make these slides available to you while I think with the recording of this talk, so you'll be able to go over it again. But I just made a chart for myself and for you listing the primary immunodeficiency features of the primary immuno efficiency, the typical treatment of the primary immuno efficiency, the GI effects, and then management of the GI effects. So we're gonna really focus primarily on CBID tonight. We'll touch on selective IgA deficiency in CGDD. And mostly because these are really would make up the bulk of an outpatient practice for a clinical immunologist and also primarily things that a gastroenterologist would see, particularly in adults, which mostly the patients that I see. So let's focus on CVID. And this slide, so I want to step back for a minute and say, you know, you'd think there'd be a lot of really good data on some of these immune deficiency syndromes, and there are. But when you start looking at subsets, your things like GI disease, you begin you begin to get on shaky your ground in terms of the quantity and the quality of the data.
So in the next two slides, there's just some data. On one from at a time, even one from a Scandinavian group on, like, what do you expect in terms of symptoms? And so from this at a time group, they actually had about eighty seven percent of their hundred and forty one patients had CDID, and about fifty one percent of them answered positively that they're having GI symptoms, a majority having bloating and diarrhea, very few, very few having bleeding. And then a small amount having dyspepsia, which is basically sort of indigestion or discomfort after meals in the upper part of the afternoon. Now, when patients had

colonoscopy done, Really very few had evidence of any chronic inflammation you could actually see through the scope, eleven percent and then about the same amount on biopsy had any evidence of acute or chronic inflammation.
And the reason I mentioned these things is that we're always looking for processes that aren't normal that we can address therapeutically. And so it's important to sort of put together things that you find on an endoscopy exam or biopsies that can help you try to understand what would be a good approach in terms of relieving the symptoms. This is probably among the best studies that was done from the Scandinavian group Again, a hundred and three patients. Now these were all CVID patients. Then the GI questionnaire majority had really a vague symptom of bloating, twenty six percent diarrhea.
Actually, the group had constipation and thirty percent had pain or dyspepsia. Now when they did their endoscopy, they had close to half of them had evidence of chronic inflammation, but on biopsies. And a lot of the types of inflammatory changes we see and you could only maybe see microscopically kind of run the gamut from conditions we might see in celiac disease. We'll talk about that in a minute. Conditions you might see in graft versus host disease, despite the fact that no one is having, you know, transplants.
Think you might see in what we call microscopic colitis, maybe even think you might see in Crohn's or ulcerative colitis. And the take home message is the most common biopsy findings were not associated with any symptoms. And this is one of the challenges for the provider and for the patient is to try to keep an open mind as to what's causing the symptoms and then what we can do about them. So in terms of the three categories of complications that I initially introduced, we always think about infection. There's clearly is a heightened susceptibility to protozone, so called, you know, paraside bacterial pathogens, you know, Jardia, salmonella, Shigella.
I particularly have seen a lot of campylobacter, h pylori, which is a organism that affects the stomach and can be a precursor to get a risk factor for peptidosis disease. It can be seen maybe increased risk for infection and when we find it, we do like to treat it to eradicate it. But it's not a huge, huge problem we look for all the time, but I want to focus on two other things. One is norovirus and one is small bowel over growth. So norovirus has become more recognized as something that you may see particularly in CVID patients who are getting to more of a severe chronic GI complication picture, especially with a lot of persistent watery diarrhea, unexplained weight loss, protein loss, nutritional deficiencies, But one of the challenges is that it's not known whether the norovirus is causing this or it's associated with it because the immunodeficiency is such a state that it's just allowing norovirus stay there in a chronic way.
So the other challenge with norovirus is the fact that we don't have any antivirals for it. People have used Ribavirus, which is something we've used in some hepatitis viruses, To limited success, people have used an antipodazole antibiotic called nizoxenide. I've used it

myself. It's something that sometimes it's just the flip of a coin whether it's going to work or give any improvement or not and reduce the inflammation. I'm sorry, the infection.
You know, one of the things that is really inconsistent as well as that even if you give more and more and more immunoglobulin, it doesn't really treat the infection specifically, otherwise we would be doing it. So in terms of emerging treatments. Most of them that are coming out are for immunocomponent people. There are different types of vaccine strategies. There are some where they're using these antibody fragments that would bind to the virus and maybe you would take it orally, but these haven't been vetted just yet.
A lot of them are in the experimental phase right now. But I think it's important if any of your providers have mentioned, oh, you have norovirus that it may not be causing the diarrhea that you're experiencing. It's necessarily, and it's maybe something you're going to have a lot of trouble getting rid of yourself, and it may be some advocate patient who for the last year and a half every time we do a GI path in Japan, there's always a neurovirus signal there from the PCR that we do. I want to talk about small about overgrowth too, because in thirty percent to forty percent of CVID patients, particularly those who are having diarrhea, they will have an inappropriate amount of in tesicle bacteria that are growing up in the upper part of their small intestine. And this can interfere with normal digestion and absorption. And we can test for this by doing a hydrogen breath test where you would have a small amount of the sugar solution. And even before you drink that, you'd get a sample of your breath. And then we do that every twenty minutes for two hours after the the the sugar is taken in and we see if there's an inappropriately early increase in hydrogen in the breath, which signals the or it indicates that their bacteria very high up in the GI tract because they're the only organisms that can can actually metabolize sugar to hydrogen, your body can't, only they can't, and so we can detect. And if that happens, then we do an antibiotic specific we do antibiotics targeted to the small well over growth for, say, ten to fourteen days and see if that can help reverse some of the weight loss and diarrhea. So, other things that can affect the gut include autoimmune activity that can lead to inflammation of the provided lens, the salivate lens, you can lose some of the lining of the stomach that's responsible for making acid.
People can get a product inflammation of the liver and more over can also get we're not going to talk about this as a length today, but can also get nodular regenerative hyperplasia in the liver, which can lead to portal hypertension and a backup of the blood trying to get through the liver and has its own sort of sets of potential complications, including, you know, spleen and enlargement and other things. But one of the things that happens in the gut is this nodule lymphoid hyperplasia, which is people feel is just sort of a heart and parcel of the inability of B cells in particular to class switch and so normal germinal centers which are all over the gut, in the lining of the gut, begin to get enlarged as they, you know, try to overcome this blockage in their maturation. So if someone's it can lead definitely to

things you see under the microscope. But sometimes you can actually see little nodules under the lining of the gut. And then one of the things we're going to focus on now is the small number of patients with CIVID who develop a chronic diarrhea weight loss, malabsorption syndrome unrelated to gi pathogens, and it is not treated whatsoever by immunoglobulin therapy.

So this is the so called CVID enteropathy. It really just has a insidious onset. Usually with unexplained weight loss is what I've seen primarily. Chronic diarrhea, there's no inflammatory component to the diarrhea in terms of no blood cells in there. And evaluations can show evidence of poor digestion absorption with increased fat in the stool. We actually can do an absorption test called a desirous absorption test to see how well your small intestine can can absorb small molecules without any particular requirements for special transporters and things, and then less often approaching losing enteropathy through the gut. And the malnutrition effects, particularly if you're not able to absorb fat soluble vitamins, you'd be to have low calcium, you can have prolonged bleeding times, megal blastic anemia, which is related to B12 and folate low serum proteins, and this can affect other condition like even like the skin and dermatitis where you can get particular rashes when you have micronutrient deficiencies. So and I don't know if this has happened to anybody, but typically patients who have this are seen by other gastroenterologists and the patients told, well, you have celiac disease. And this is because on the biopsies, the changes can look like celiac disease and the symptoms can certainly seem like celiac disease but it's not celiac disease. You know, when you have a good GI pathologist who understands the differences I want to look for, there clearly are microscopic pieces of evidence that can help you understand, no, this is in celiac disease.

In addition, because we often screen for celiac disease using an antibody based screening test, that can't be used in So I'll do genetic testing, looking at HLA background for the risk for celiac disease. And the only utility of this is, if it's completely negative, you cannot have celiac disease. So at least it helps us say, the celiac disease is off the table. So, you know, how do we approach the treatment of this condition? Well, You know, we eliminate any treatable causes that could be contributing, bacterial overgrowth we just talked about any gut infection.

Very often, this condition will respond initially to corticosteroids, whether it's of budesonide or prednisone taper. But, you know, steroids while they're useful in the short term is not something you can rely upon. And often over time, people become less responsive to the steroids. People have used other sorts of anti inflammatories that like hydroxychloroquine, which is used a lot in rheumatology for certain types of inflammatory states, cyclosporin, in your anazithyarpine, and life use azithyarpine in CVID patients who either become dependent on steroids and you want to spare them from the steroid's effect long term. But again, it's always kind of a balance where you have an immuno

compromised person and you're putting them on immunosuppressants despite the fact that you are supplying them with adequate amounts of antibodies, but you may be altering the function of their t cells and you could potentially have other complications with infections, particularly viral infections.

If we need to, we definitely use parenteral nutrition being fed by vein just to support people through periods of time where we're trying to get their gut to heal. And then you'll hear about a read about biologics. Many of the ones that we use, I use inflammatory bowel disease, REMICADE and HUMIRA, which target antigen alpha. Antibio, which is a drug that blocks white blood cells from getting from the blood into the gut and STELARA, which is another type of anti cytokine against twelve and twenty three. So I just want to say a couple of things.

The experience with these medications in CBID in this condition is very limited. I would probably only use it in particular instances where I felt that the evidence of the type of inflammation that was going on seemed to be either more Crohn's or UC like, and in fact, I was at the NIH, we did a study on CVID and neuropathy and found that the cells in the affected lining of the gut were making excessive amounts of a cytokine feron gamma, but not a lot of IL-twenty three. So this is a very specific sort of signature. And we didn't at the time have any available antibodies. But STELARA now would be one of those antibodies that would be just upstream by blocking IL-twelve that induces endocrine gamma, could be useful.

And in fact, this one report I found of a CVD patient who actually sounded like he had more like Crohn's disease because it was they had fistulas and a lot of other things that don't happen in routine, severe gyneuropathy, but anyway had a good response to it. So that I will say something about ENTYVIO as well, very, very mixed reaction, probably about maybe less than fifteen patients worldwide being reported. A small number seeming to do well, a larger number. Sometimes seeming to to get worse with the ENTYVIO. So it's it was it's it's this is still a work in progress, but we understand the need in the gap and our understanding.

I put this on the bottom. I would look today to see if we had actually had a STELARA trial going on from the NIH. And I think it's over because it's not registered anymore. But I, for particular patients, I have actually tried to get STELARA. Just to see if in the short term we can make any any impact on the inflammation.

And in the future, it may be that we do use something like a JAK inhibitor. Which has a very broad activity like steroids to see if that would help. But again, I don't have to emphasize enough that using these immunosuppressive drugs in immunodeficiency state carries a certain amount of risk. So let me just shift gears temporarily to chronic retinal disease, and the reason I'm using this is because it's one of the diseases that has such a high penetrance of GI complications. And if you haven't heard of this before, it's a condition

where mostly a different not lymphocytes, but a different type of cell that's important for engulfing bacteria and destroying them inside.
Don't have that capacity anymore. So people develop a lot of abscesses in the liver, in the skin, in the mouth, and some of these abscesses that occur a lot along the intestine can actually grow so large that you get difficulty swallowing, you get difficulty for the stomach, emptying, small balance direction. And again, in this condition as well, while there have been applications of conventional therapists who are using Crohn's ulcerative colitis, they don't offer a great benefit. But other things like G CSF or GM CSF, and these are These are growth factors for the same types of cells that are deficient in the activity to so the idea was that if you can induce maybe more of them you can help control some inflammation and there's some data just that in fact that is true. HLA identical cord blood stem cell transplants have been applied to this because it is it's You're fixing the germ cell tumor, germ cell defect can be beneficial.
People have used infliximab, this is Ramakade, but there really had been caution because, again, there are some cases of exacerbating infections and abscesses, especially after fistulas closed. But one interesting aspect is another drug that we use in certain inflammatory conditions, especially periodic fever conditions like familial, mediterranean fever. Anakinra, these anti IL-one beta drugs that attack new inflammasome have had some success in chronic rhinosinusitis. And I just mentioned surgery because if you have, you know, you you often require surgeons to drain perianal or perorectal abscesses. But if you have abscesses in the liver, you really need a skilled surgeon who's can even has dealt with them before because it's gonna be a very technically a challenging procedure to to train and fix those abscesses.
So let's just talk about risk for gastrointestinal cancers? Well, to be honest, though the rates seem to be increased compared to the normal population, the rates are generally low, less than five percent I have to say with all the patients I've ever seen, only one person had a lymphoma, which was a mucosa associated lymphoma. And so it's not even that treatment that we actually have an accelerated screening program for them so that typical colorectal cancer screening is no different than for immunocompetent people. So it's not a big big risk, GI cancer risk. So the and next few slides through the end of the talk.
I just want to introduce again the concept of the microbiome. And Emma told me that Gimi Deficiency Foundation had a whole webinar on the gut micro or on the microbiome, I'm hoping is the gut microbiome. But just as I said before, there's an enormous number of bacteria in the gut, and it typically is the highest numbers are in the in the colon. And it decreases as you go up towards up towards the the stomach. And that there's a lot of bacteria that flow from the throat into the stomach every day.
Typically, gastric acid is well, if you're not on a on a acid suppressor like a proton pump inhibitor, the acid is very good about neutralizing a lot of those bacteria. But the good

microbiome is very very sensitive to environmental factors. And diet composition is one big thing, and antibiotics are the other big factor. Also, there seem to be some genetic factors, and I already mentioned how the gene knockout mouse models can definitely alter the gut microbiome in a very specific way. But also, we know it from human studies where early on when people were saying, well, if you live in the same household, how similar is your gut microbiome?

So the idea is that everybody really has their own gut microbiome. But if you have siblings, if you're particularly around the same age of the household, their gut micro Biota will be more similar to each other than they would be to their parent, and it would be definitely much more similar between their parent than it would be say to a neighbor in another house. So if there's something about the genetic fact that helps control the gut microbiome composition. So in really the landmark study that I also happen to be fortunate to be part of analysis at the NIH was the the human microbiome project part one. And so they looked at they were just really observing what like, they asked, what is a healthy gut microbiome?

So if you look at this picture on the left. You see all these colored spikes. Well, if you go from top to bottom, each spike represents an individual, and you can see the green is are all the organisms that belong to this filing from machete's the blue bactore d d's, the yellow proteobacteria. But if you look from one spike to the other, you can see that they're not the same. Right?

You look at both extremes. So this again was sort of surprising. There doesn't seem to be a core a normal core microbiome. However, when you look at each individual's gut microbiome and you look at all the genes that each individual's organisms contain, and then the metabolic pathways that they predict you're going to be functioning in those gut microbiome, that they're very similar. They're very stable.

They look it's almost linear across. So The idea is that the composition, the actual identity of the organisms, may be different, but what they do is very similar, what their capacity do is very similar in healthy people. And the thing is, this changes. This changes in disease, and it's not just changing in primary immune deficiency, it changes in inflammatory bowel disease, Crohn's disease, it changes in renal failure, it changes in liver failure. It changes in metabolic syndrome.

It changes in obesity. And so we are now in this revolution of trying to understand what is it about the character that gut microbiome and the interaction with us that predisposes us to some of these conditions. So we know that the big influences on the gut that we wanna consider are diet drug exposure, antibiotics, your disease state and your genetic background, all things we already talked about. And these were some of the aspects of the diseases that I also had mentioned, but I want to point out that One of the aspects of the gut microbiome that we think contributes to the risk for these diseases is the way it metabolizes things in your diet. And how these things interact with the gut barrier?

Because the gut is supposed to really keep things separate. It can let obviously, it can let nutrients across. It can let certain metabolites across, but it's not supposed to let bacteria across. And in some of these conditions inflammatory and otherwise, you can actually measure in the blood components of bacteria like bacterial DNA, components of the bacterial cell wall like lipopolysaccharoid, they're not supposed to be there. And that's where you get this kind of leaky gut.

And the one of the consequences of leaky gut is the fact that these compounds can actually stimulate your immune system to be active. And we know that chronic inflammatory states are not good. For certain diseases, heart disease, diabetes, obesity, certain neurologic conditions. Clearly, not for inflammatory bowel disease. So that's why there's a big focus on how can we restore the microbiome from what they call a dysbiosis? How it gets away from what is otherwise looks like a normal composition in terms of the genes and gene pathways and certain types of organisms that should be there? But also powered functions. So this is just a little drawing of on top here you see which has been really touted as probably the most beneficial way to eat in terms of the composition of the diet, this Mediterranean diet, rich in very produced. And then the key about this is it's very low sugar, and it is zero processed food. A diet rich and highly processed food.

And what might mean is, we're talking about food additives, we're talking about food coloring, the titanic white that's used in icings, bakery icings. Emulsifier stabilizes preservatives, and sometimes even just processing a whole change its character when it gets fermented by bacteria from something that's good to something that's not good. And we do know that there are certain metabolites that are associated with disease, most famously the trimester mean that is implicated in, say, the progression of atherosclerotic heart disease. So, and, you know, you'll hear the term dysbiosis. And one of the things that has been done in an early fashion in terms of studying the gut microbiome in, say, CVID or primary immunoficiency is that the the gut microbiome is dysbiotic.

It's not like a healthy gut microbiome in a couple of respects. The primary respect is that it's not as rich in different types of organisms. It has lost diversity. And loss of diversity is one of the most consistent findings about gut microbiomes that are associated with disease states. And also, they don't metabolize dietary components in a beneficial way.

So that and I'll talk about some of at least my advice for how to sort of restore your gut microbiome. We have let me see what time it is. Okay. So I'm gonna try to finish up in the next two or three minutes. So the gut microbiome ensures approaches to maintain and restore it.

There are a number of different ways that are possible. One is probiotics, and I'll just say off the bat, I don't describe probiotics, and the reason I don't is we don't know who's going to respond better to which probiotics, number one. You don't know what you're buying when they get them off the shelf. Nothing's regulated. So you don't know if they're dead or alive.

And if you do, if they're alive, you don't even know what they do. Once you stop taking them, they go away. So they don't become part of your gut microfluorine. Prebiotics in the are they're not organisms, but these are things Prebiotics are things that stimulate bacterial growth in the gut microbiome. So the primary ones are fibers, resistant starches, ructance, and even some polyphenols.

And these are all found in unprocessed seeds and nuts and root vegetables and whole grains and beans. And so the thing about what what I prescribed from my patients, my IVD patients, that's well known as when these compounds are in a diet and we aim for about twenty five grams a day of a varied amount of fiber from different sources that you you begin to stimulate the growth of your own good bacteria. And they are sustained by the fibrin diet and they ferment fiber to the short chain fatty acids that help maintain the gut barrier They have anti inflammatory effects themselves, and they seem to be have important effects when they're absorbed into the bloodstream and and distant parts of of the body. So that's in a symbiotic is when you have a combination of a pre and a probiotic, presumably a probiotic, a fiber that the probiotic and organism is gonna metabolize, and so you can maybe juice up the effect. They're not a lot of the symbiotics on the market, but people are interested in developing them.

You may hear about fecal transplant, fecal microbial transplant, and this is not a way to restore your gut microbiome right now. It's The the materials we have access to right now are not suitable for that. There may be other living biological products in the near future that may be a grouping of six, eight, twenty different organisms that have been chosen for their biological effects. And that you could take orally. But fetal transplants are really just used.

And even in in primary medicine, I really reserve them for chroniccy difficile, recurrency difficile infection. And in fact, the probiotics, they're not regulated by the FDA. They have been some cautionary tales, particularly in pediatric patients where they had been contaminated, and they actually had resulted in a death due to a a a a yeast infection, and then they can also be contaminated with other pathological bacteria. And the organisms you'll see on a lot of these probiotics, these lactobacyls, diffittal bacteria, saccharomycin, biliary arteries, these are probably, you know, I I I can't recommend them robustly because I don't have the data to do that. But what I do in the future when it's available and seems to be robust.

Absolutely. Yeah. Absolutely. I'm just gonna just very briefly, one of the challenges with being exposed to antibiotics time and again and maybe being in and out of hospitals getting colonized with cholestrating difficile and having recurrent infections that can really be quite morbid. In terms of the watery diarrhea, getting an actual inflammatory colitis.

I've had patients who required a collect any immunocompetent people who required a collect any because the disease has been so severe. And what I believe is that if you can

increase the resiliency of your own gut microbiome to this infection that you could get colonized with from ever overtaking things, that's probably one of the best preventive strategies if you can't avoid antibiotics. And in the future, we may have we do have an antibody to one of the toxins that we sometimes use in patients vaccines are probably not going to be helpful in primary immuno deficiency, and then potentially oral antibodies that can absorb, maybe not absorb a toxin, primarily may be available. So I just wanted to sort of give an overview to maintain awareness of the risks and possible primary immuno efficiency specific complications. And also just emphasize that not all GI symptoms are due to primary immuno deficiency itself.
You can have routine GI things that happen, irritable bowel syndrome, heartburn, ulcer disease, all things that would require a thorough workup as usual. And I think that there's a lot of opportunities that exist to study the effect of the gut microbiome and primary immunodeficiency and its relation to GI and non GI symptoms. So thank you for your attention. I'm happy to be here for your questions.

Emma Mertens: Thank you so much, Dr. Mannon. Alright. So as Dr. Mannon mentioned, we now have time for a brief audience Q and A.
If you would like to ask a question, we request that you put it in the Q and A box in the control panel of your screen, and we're going to be sharing a few ground rules for q and a. Now in the chat, if you don't mind, taking a look at those. Alright. Give me just a moment, everyone. Alright.
We have our questions ready to go. Alright. First question for Dr. Mannon, at what age should someone with PI get their first colonoscopy and how often after that. Are there different guidelines for different PI diagnoses?

Dr. Mannon: Howard Bauchner: Yeah, good question. So, no, there's no strict recommendations for when you should begin colonoscopy. I think I had mentioned before that even for like colorectal cancer, it's no different than an immunocompetent in populations. So that would be age forty five. Obviously, for any sort of alarm symptoms like refractory diarrhea or GI bleeding, seeing bloodiness tool, then that would require a a a colonoscopy to see if there's any active inflammation as well as get biopsies for the pathologist.

Emma Mertens: Thank you. All right. Next question. This is more of a comment, so just wanted to share this. This individual said thank you for the great talk.
I had never actually had GI problems related to my PI until after they started receiving IG therapy. This person says, sorry if I missed this earlier, but can treatment itself bring on GI issues as a side effect?

Dr. Mannon: Yeah, interesting question. So the short answer is no. It wouldn't be expected to be honest. You know, one of the things is that you're getting IGG, immunoglobulin G. So that's not even a a sub class of antibody that secreted into the gut.
So I wouldn't anticipate that that treatment itself would cause GI symptoms And I would maybe look for another ideology.

Emma Mertens: Thank you, Dr. Manon. We have had a lot of interest in the comment section about the fecal microbiota transplants. I know in recent conferences we've had talks on this topic for a fecal microbiota transplant for CGD, for example, So just to kind of capture a few of these people's questions. To clarify for the audience, do you mind sort of broadly restating who in the PI community would be eligible to potentially benefit from having a fecal microbiota transplant?

Dr. Mannon: Right. So the only people who would be eligible without question would be those patients who have recurrent clostridium difficile infections. There had been a lot of interest in fecal microbial transplant in inflammatory bowel disease, for instance. But there's no robust data showing that it's very beneficial. And people have done fairly rigorous studies using it.
You can't project who's going to respond to it, and there's always a potential of having an increase in the colitis or an infection. And that's one of the things that had plagued the commercial source of the fecal transplant material from open biome because they had a couple of fairly severe e coli outbreaks for pathogenic e coli. And I think the future a fecal transplant is gonna be these biological living biological products. And these are gonna be They may be organisms that at one time were isolated from somebody's stool, but they're grown up now. In their own, you know, in their own way.
And so there's a lot more quality control about what goes into these products. So I had mentioned, like, maybe a consortium of up to twenty different organisms that are chosen maybe for different reasons, like, There's a group at Mount Sinai in New York who's very expert at research into this area for not just concentrating difficile but maybe applying them to inflammatory bowel disease as well. Where they they could follow donor organisms, right, the donor of the skin transplant, in the and they chose recipients to have very good responses in terms of resolving their posterior difficile infection and were able to actually follow because of the molecular signature of organisms, ones that had actually engrafted into recipients for years. And so they chose specific organisms for their ability to not just transfer it from one patient to another, but stay there. Okay?
It didn't say what, you know, it didn't say that these particular organisms were the ones that conferred the healing of infectious colitis, but they clearly were there for a long time. And one of the challenges of choosing organisms is what we call engraftment Like, if you give an organism to a person, how long is it gonna stay there? And that may be the challenge of

keeping it standing there. And that's why it may be a better strategy to foster a person's own gut microbiota, even those that may be at very low levels when you start, but you can increase your numbers if you feed yourself the right resistance starch, the right fiber, the right front hand. So and that's and I think a lot of research is focused on on that.
Can we find out who's going to respond to what fiber and what's responsible for that response. And this may become more about precision medicine rather than say one size fits all. But I don't think there's really anybody right now in inflammatory bowel disease or on human efficiency who's really eligible for these fecal microbial transplant. Just to see if you can change the Gov Micro Plan. Howard Bauchner:

Emma Mertens: Thank you, Dr. Manon. All right. So we've also had a few people ask questions in the realm of food and diet. I know you talked about the Mediterranean diet in your talk.
And they're really wondering the extent of the impact, how helpful it's going to be to them to make these, what can sometimes be drastic changes to their diet. So for example, we had one person in the comments say, They are living with CVID and they likely have mesenteric myelitis. They've been spoken to by, I'm guessing, their GI about the high and low FODMAP foods. Which I know that's something that actually came up in our last talk about the microbiome. But they're feeling a little skeptical and they're not sure if it's worth their time and worth this drastic change to their diet to adapt to the lower high fodmap diet.

Dr. Mannon: Right, right. So I just want to reiterate that the fodmap diet is only developed for chronic diarrhea and maybe irritable bowel syndrome related to the inability to digest certain naturally occurring carbohydrates and carbohydrate alcohols and different types of sugars that occur in particular classes of fruit and vegetables. So the FODMAP diet, the FOD MAP actually stands for the dominant carbohydrate in each one of those food categories. Okay? And it's because we know that there are people people who have an inability genetically to metabolize that type of sugar, sugar alcohol, carbohydrate in their diet that's contained in high amounts in those particular fruits and vegetables.
So so it really doesn't have anything to it wasn't developed to shift the microbiome in any way. It was developed to eliminate basically an elimination diet. You're eliminating a complete class of carbohydrates that you may or may not have difficulty digesting. So that's what the Fodmap diet is. So it shouldn't be confused with an approach to the gut microbiome.
So having said that, I understand about drastic diet changes. And I also appreciate the fact that people sometimes spend a lot of time trying to figure out what they can and cannot eat because it affects them in certain ways. I understand. Appreciate that. What I how I come at this is trying to educate people about their nutrition.
I think that we have in this country a dis nutrition, meaning that you can get the amount of

calories you need for the day, but they are not coming from good places. Okay? And and I think that our highly processed food sources have really done a tremendous amount of damage to us in an unintended way. Okay? In an unintended way.
But now we can't quit it. So, you know, the mediterranean diet is one response to that. It's just actually pointing out that this diet, you know, rich in these types of fats, low in sugar, high in fiber, unprocessed food has you know, does it does it cure disease know? Okay? But it can improve quality of life, but it also can can shift the gut microbiome.
What I'm working on with colleagues down in the Lincoln campus here in Nebraska who are experts at plant genetics and food science is using some of these heirloom maze and sorghum and bean stocks that they have because there are particular types of carbohydrates in them that we're actually looking at now, not and in fact, we don't even change somebody's diet. We just add twenty five grams of this fiber to them each day. And we've successfully seen a shift in the gut microbiome to beneficial, you know, organisms and a loss that we call, pathobions. And also an increase in production of the short chain fatty acids that we associate now with anti inflammatory effects. So we can actually measure in their blood and in the stool decreases in inflammatory markers.
Okay? So what I'm so you're improving barrier function. So I don't tell my patients, oh, you must go on them better training diet. I we talk a lot about very simple things. No or low sugar.
That's a that's a real important thing. Low, highly processed foods or just processed foods. Well, I should say highly. I mean, you know, if you take an egg and scramble it, that's the process food, but that's not what we're talking about. And also fiber.
We talk a lot about fiber. And I tell people and I don't tell people to do this overnight. I tell people to do this over four to six weeks, gradually increase the amount of this a fiber in your diet, sibilant and sibilant to about a minimum of twenty five grams a day. And I think that that can help you to support your own probiotic gut microbiome. You can enhance short chain fatty acid metabolism.
And we're studying right now whether that will change a trajectory of the natural history of inflammatory bowel disease. So I hope that answers your question.

Emma Mertens: Thank you. That was very thorough. Alright, next question. I know in your talk you touched a little bit on antibiotics. Can we just revisit that quickly?
We had someone who was wondering What is the effect of prophylactic antibiotics on overall health in a person with PID?

Dr. Mannon: Well, I am not anti antibiotics, but I have an anti casual use of antibiotics. I understand that if people have bronchiectasis and they need to be on a suppressive antibiotic, that's just the way it is and we have to deal with it. But I do think that especially broad spectrum antibiotics can knock down the gut microbiome in an amount of organism

and then change its composition. And in fact, we know that is a study that had been done with healthy volunteers. They gave them, like, three days of superfluxis in on three separate occasions.
And at some point, the gut microbiome had a lot of difficulty coming back to what it used to be. And my concern is that

Emma Mertens: –

Dr. Mannon: and we don't even really know, say in a condition like CVID or cystic fibrosis, where people require antibiotics chronically or even something like liver disease where you require rifaximin for treatment of hepatoencephalopathy chronically that there's no doubt that infection got microbiome. But the the challenges you need it. Okay? And so I my approach would be, let's support the gut microbiome as much as we can with, say, the dietary change I sent to make it as resilient as possible, even in the face of of antibiotic use.

Emma Mertens: Thank you, Dr. Manon. And I want to be respectful of your time, so this is going to be our last question. I definitely do want to touch on this, though, because we have a lot of differing opinions and a little bit of controversy as you said in your talk. This last question is going to be about probiotics and probiotics.
We've had some people in the comments shared that they're using them, that they've been advised to use them by their primary care provider, can it be helpful for some individuals?
Howard Bauchner:

Dr. Mannon: So if I have my patients decide to take probiotics, I don't make them stop it, okay? I think everybody's different than I think if people feel like they got a benefit, and I'll give you for instance. I had a patient I saw two weeks ago, and he was just he was just been a tough customer to to help improve his life. But he was a little proactive and he got this fermented milk product to Kaffir. And he said that changes life.
And you know what? I'm like, that's great. But did I begin to prescribe to all my patients? No. And the reason is that I know a little bit about the effects of fermented foods and drinks on things.
But it's I mean, if I was at the end of my recommendation, I would say, I said, you know, I had a patient here two weeks ago, and we were trying all these things, and he tried this. And I can't explain why it worked, but it's not gonna hurt you. Why don't you try it? So I don't like to be dogmatic about these things. I understand people are proactive.
I know people want to try to find natural solutions to things like this. I appreciate that. So I try not to be dogmatic and bad. Unless I feel it's gonna hurt you. Okay?
But so I didn't mean to be well, I didn't mean to stir controversy or to discourage people about things. But I just I always like to have a data driven life, especially when I'm making

recommendations to patients. And and, you know, that that's all where that's where I come from.

Emma Mertens: Sure. Well, thank you so much, Dr. Mandon, for answering all these questions and for putting together this wonderful talk. I know you have another commitment to get to you. So we will thank you for your time and let you get on about your evening, but thank you so much we got great feedback in the comments.
Our our community really appreciates this talk and all the great information you shared. So thank you so much.

Dr. Mannon: My pleasure. Have a great evening.

Emma Mertens: Thank you. You too. Alright. And to the rest of our audience, that's going to wrap up our Q and A. We thank you so much for these great questions and for your engagement.
And before we close out, we are just going to go over a few of IDF's resources and upcoming events. So if you haven't already, we hope that you'll check out our website for additional resources, upcoming events, and more. All materials are free to print, access, or have mailed directly to you. And if your question was not addressed tonight during the program, you can contact our board certified patient navigator through AskIDF. She will personally connect with you to tackle your question and direct you to appropriate resource courses, and we're sharing the link for accessing Ask IDF in the chat now.
You can even take IDF on the road with our engaging podcast series. You can find programs like bold conversations and undiagnosed by searching for the IDF podcast. We also have a brand new young adult podcast that we launched recently called chronic twenties. And finally, we have a YouTube channel where you can find all the recordings from every IDF educational event. And tonight's program will be uploaded to the IDF YouTube page and website and will be available in just a couple of weeks.
We're also including the link for the YouTube page and the chat. One of our newest resources that I know our team is particularly excited about is the immune system self assessment. This ten minute questionnaire can be used to help identify potential signs of PI and start a conversation with your doctor. Again, we will be sharing the link for the survey in the chat. And applications are now being accepted for IDF's twenty twenty five research Grant program.
This program supports research initiatives, focus on improving patient outcomes and expediting the time to diagnosis for individuals affected by PI. To submit your project for consideration, download the application, which we are also linking in the chat. Are you looking for ways to connect with others who are navigating life with the PI? You might be interested in joining one of our many get connected groups. These groups are free, virtual

volunteer led opportunities to connect with others with PI all over the US.
And it's not just for folks with PI. We also have groups for partners and spouses, parents of children, siblings, etcetera. We offer location based groups or nationwide groups and because the groups aren't virtual, they are on Zoom. You can join any group time or leader that works for you. IDF's new documentary, compromised life without immunity, offers an intimate look into the world of those living with primary immune deficiencies.
Screenings and private watch parties are available now by testing the film at primaryimmune dot orgcompromised. And one of our biggest events of the year is open for applications now and that is our twenty twenty five IDF Advocacy Day and Young Advocates Academy. Apply today to make your voice heard, impact policy, and influence meaningful change for those impacted by PI. And if you don't know, IDF offers webinars each month and different programs and events throughout the year. A few of our upcoming programs include our Volunteers foray on December tenth and our walk for PI coast to coast celebration on December fourteenth, and anyone and everyone are welcome to join those events.
And we hope you'll come back for our final webinar of the year on December nineteenth, where we will tackle mental health at the holidays. And on that note, if you have a great idea for a topic or a presenter for a future event, we want to hear from you. Visit the link in the chat to submit your idea for consideration. And before we close, we want to once more thank our incredible sponsors for supporting our education initiatives here at the Aimmune Deficiency Foundation. To our audience.
We so appreciate your participation this evening, and I want to give a huge thank you again to Dr. Manon for sharing his time and expertise with us with us all. I'm going to leave the webinar up for just a few minutes. I know we shared a lot of links in the chat, and I wanna give folks time to copy and paste those or save them or check them out. So we'll leave that up just for a few minutes.
But in the meantime, we hope you'll take care and on behalf of the foundation, We wish everyone a happy and healthy thanksgiving, and we thank you for joining us this evening. Thank you so much.