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Research Update: Evolving understanding of SIBO / IMO and IBS

with Dr. Mark Pimentel

Your hosts Shivan Sarna & Dr. Allison Siebecker

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Shivan Sarna: Hello and welcome. I'm Shivan Sarna, your host today, founder of SIBO SOS®, and I'm honored to have you join us and these two incredible people. Dr. Allison Siebecker, my co-host and founder of SIBOinfo.com, world advocate for SIBO patients and practitioners, the creator of the SIBO Pro Course, the co-creator with me of the SIBO Recovery Roadmap® course for patients.

And the incredible, Dr. Mark Pimentel who is our featured speaker and he is going to be talking to us about the developments revealed from the American College of gastroenterology 2022 research updates with us today. He is the person who I think is going to cure SIBO in our lifetime. No pressure, Dr. Pimentel like you don't already feel that anyway. He's the one who told us about Rifaximin for SIBO. He's the one who eats an elemental diet for SIBO. He's the one that's driving forward this differentiation of IMO versus SIBO. As well as his new book that we'll be telling you about and sharing a

link with as well as working tirelessly with his team at the master's program at Cedars Sinai. I think you get the idea. Let's get started. Hi, Dr. Pimentel.

Dr. Mark Pimentel: Hi. Great to see you both.

Shivan Sarna: Welcome. I know you've got a fantastic presentation for us and a lot of hope for us as well. Thank you so much for being here.

Dr. Mark Pimentel: It's what I tried to do, inspire hope because I think we're close. I've titled this evolving understanding of SIBO and IBS. Because it continues to evolve.

One thing that I start my lectures with, especially on this kind of platform is that I get feedback, whether it's on social media, or from folks out in the community, patients and so forth, that you keep saying things are coming. And I know that sometimes I say that a lot, that the next thing is going to be even more interesting, and it always is.

As we develop things for SIBO / IMO, it's critical that we understand everything in fine detail because by understanding the fine detail, and as you'll see in the lecture, understanding some new things in there, will refine the treatments to be correct not just better. And so I hope that sort of perspective makes you realize it, I mean, we're doing a ton of work, and it just has to be done correctly, scientifically, in order to do it right when it comes to treatments. That is the preface of the MAST program here at Cedars Sinai, which is actually in front of me, I'm looking at it and behind me is sort of the window out to the lobby of this building.

We have 22 people here, seven PhD scientists, three MDs all working to try to help the patients who have this condition to find and unlock their small bowel microbiome signals that are giving us the problems in human health and disease. And we have some very interesting stuff that we published this year, not related to SIBO, but also amazing stuff in SIBO that I'll share with you in this presentation. For those of you who have heard me talk before, this is the template that I use. Now, it's not changed much over the last two years, what's changed is our understanding of every single step here.

And so we now know that IBS, SIBO and food poisoning are linked, and they're linked in that food poisoning is the trick the tripwire is the trigger for the development of these problems, in most cases of SIBO. And the CDTV toxin, which is the second plaque here, is the culprit from the food poisoning that leads to an auto antibody or auto immunity to a protein called vinculin. And that these two then set up a nerve damage of the gut. And that nerve damage leads to a reduction in migrating motor complex which leads to bacterial overgrowth that I'm going to show you is now proven by multiple means and techniques. And then IBS being a part of SIBO and that the SIBO and IBS are in some sense synonymous.

At least 60% of the time. So I'm going to use the term 60%. Because you're going to see that over and over and over again through the presentation, that it's about 60%. So, go back to H. Pylori and ulcer disease. H. Pylori causes ulcers about 60% of the time, the other 40% Is your NSAID or your aspirin or Advil or other causes of ulcers. But that's 60% of explaining 60% of IBS is huge, considering this as a 40 million in the US patient disease or condition. So I'm going to break it down a little bit differently this time, as I've done, as I have not done previously, and I want to break down what the evidence is. How did we get to this roadmap that I showed you? And the first step is, does food poisoning cause IBS? What's the evidence? Well, there's one paper to lean on.

It's the Clem paper. And it's not one paper of evidence as you can see down here, 45 studies of evidence, all saying the same thing in a meta analysis that was published in this one paper. And a meta analysis means you put all the papers together and say, Is this true or not? And the answer is, it's absolutely true. And then if nine people got food poisoning, one would develop irritable bowel syndrome. That's how likely you are to develop IBS after a case of food poisoning. We now know for a fact that food poisoning trips you into developing IBS. The question is how and that's what will continue to take that journey. But here's that 60% number at the bottom, you can see in the right lower corner. Don't fret on the details of this slide. What we did though, is we said, let's pretend 307 million adults are present in the United States today, zero have IBS or SIBO, zero. And then we take the center for disease control rates of food

poisoning in the United States, and say, Well, now let's pretend food poisoning is happening on an ongoing basis where it didn't before.

And we know how IBS develops from food poisoning. And we use all the data that was available from the research literature. And then at about 10 years or nine years, we reached steady state, which is it flattened up. At that point, 9.1% of every human in the United States would have IBS slash SIBO, if you want to call it that, which is abou 60% of IBS, which was at the time 15% of the population. So 60% of IBS could be explained mathematically from food poisoning.

Okay, so it's very clear from the clinical data that food poisoning triggers IBS because I showed you a paper to summarize 45 studies. But how does this fit into bacterial overgrowth? Does food poisoning cause the bacterial overgrowth we now know overlaps with IBS. So we can't poison humans because that's unethical. So we had to use animal studies. And so in this study use was way back in 2008. We gave Campylobacter which is the most common bacterial food poisoning agent in the United States. 233 Rats, the other 33 got nothing, they just got placebo. And then we waited for them to clear the Campylobacter and then three months after they recovered from Campylobacter, we were looking to see if they develop weird bowel movements.

We didn't know if they had SIBO or not, we just wanted to check if they had weird bowel movements and quantify that. And then we were able to see if they had bacterial overgrowth. And it turns out the rats that got Campylobacter, in contrast to the control rats, 27% of these rats got SIBO. So a model of post infectious IBS, the rats developed bacterial overgrowth. Not only that, if they got C+, which is Campylobacter, and they developed SIBO. Those rats 84% of them had basically IBS, like stools altered stool consistency pattern. And this bottom one is the only thing ever found in humans with post infectious IBS, which is a little bit of increase in a special type of white cell in the rectum. And so these rats, why is this important? It basically proves food poisoning causes SIBO and causes IBS.

But what's more important is for the first time we have an animal model where we can study the whole link and all the links in the chain of how this happens. And we have and I'm going to skip some of the papers because there's so much to go over now, but sort of touch on the highlights.

Now I want to fast forward to 2022 before I kind of get back into the more nitty gritty. In 2022, this is a paper we published with Taka Cora, our fellow and Mark Riddle, who's an infectious disease expert, and this is called the Bradford Hill criteria. The Bradford Hill criteria is cause and effect with regards to bacteria, so if you had a tuberculosis bug, and you gave it to somebody, what is the likelihood that that's a pathogen? And how do you prove it? This is a very complex approach, you have to have all these things for you to say, cause and effect, and we have varying degrees of certainty. And so the point of this paper is full stop 2022 Campylobacter causes IBS at least one of the pathogens that cause obvious.

Now we get into the nuts and bolts and this gets into some deep, heavy, basic science, but I don't dumb things down. It's not about dumbing things down. It's about explaining it in a way that you'll understand what we did. I'm going to show you the actual science and explain it so that it's very clear to you how we got to this point. This took 10 years and in some parts of it five years. It's a lot of work and steady work. But what we started to realize early on, is that okay, food poisoning causes IBS but Shigella can do it. Salmonella can do it. Campylobacter can do it. E. coli can do it.

You can see they're not the same. They're different organisms. But what do they have in common? What toxin do they have in common, and they all had this only this one toxin in common called CDTV Seidel, lethal distending toxin B. So we did a study where we knocked that toxin out of the Campylobacter and gave the rats Campylobacter, and they didn't develop IVs. So we knew this toxin was important. But what is the toxin doing? And so here in this study, it's a lot of colors here, but I'm going to just describe this, what I'm, what we're seeing here, forget about the top row for a second. These round circles of green are the interstitial cells of the hall. These are the pacemaker cells for your gut.

These pacemaker cells make you have cleaning waves of the gut, that sound you hear when you're hungry, that's your gut cleaning itself, your small bowel cleaning itself, you need those, because if you don't have those, you get overgrowth. So I want you to focus on these round cells. This big glob of cells is the ganglia or the nerve hub within the wall of the small intestine. And so that ganglia is also in this case screen. But it's green because we use antibodies to the CDTV toxin and put it on the tissue from the rats who had got Campylobacter or didn't get Campylobacter. So what we see here is, in fact, weirdly, the rats who never got Campylobacter, so they don't have the toxin. So the antibody to the toxin is binding to ARATS nerves who never saw the toxin don't have the toxin. So what that means is that the antibody to the toxin is by for some reason tricked into binding something that's you in these nerves. So what is it that's you in these nerves, that is getting confused after recognizing the toxin. And so this took a lot of work over many years, and we've isolated the protein vinculin vinculin. 117, is in these nerves and in these ganglia, and the antibodies to CDTV are tricked into binding to your nerves of your gut, causing changes in those nerves.

So what is vinculin? So vinculin is this, if you look at the green lines, these are cells in our lab. And the green lines are acting. This is the skeleton almost like a scaffolding on a building to hold the building a structure in place. And the little red things at the end, really at the tips of all of this are like a little motor that's on the end of this chain of action that makes the cell stretch out grab onto the cell next to it. So think of it like this. When you talk about nerves you've got you've got the nerve nerve cell which is controlling electricity, and you got the wires going out to the next cell. So the electricity can go from cell to cell to cell to cell coordinating the muscle function of the gut. So you need these things to be connected.

And vinculin is the process that stretches the wire to connect to the electrical outlet so the electrical outlet works and can conduct it to your computer or to whatever you're using. Okay, so what we did see is that if you gave rats Campylobacter and they developed SIBO, the number of these special cells that conduct the electricity for the cleaning wave area are markedly reduced. So here are all the cells here

beautiful, this is normal, they're all lined up, one after another one after another all interconnected. And down here is if they had Campylobacter but Have and Have SIBO.

So they're very few in number as you can see here compared to the control group, and you can see they're hard to see and they're very far apart. And you just, they're just not connected. So you're not getting the cleaning leaves. So is that what's happening in humans? So now we go back to 2002. I know it's backwards. But we already knew that in 2002, the cleaning waves weren't working.

Why were they not working? I just showed you because the nerves are reduced. But here's the study from 2000. To look at the Healthy People. This is the number of cleaning waves they get in a four to six hour window of fasting measurement where we put a catheter in the small bowel, look at it in the IBS patients with SIBO. In fact, 50% of IBS patients with SIBO detected zero cleaning waves. This is the average, but we detected zero and half of the patients. And even when they occurred, they were these weird, weak, inefficient cleaning waves. So we've known that cleaning waves are important in the IBS SIBO connection for a while. And then going further back 1977. I'm not going back there to say this is the proof.

But I'm going back to say that we've known this for a long, long time, that if you don't have cleaning waves, you get overgrowth, because you're not cleaning your small bowel properly. And so all the debris builds up in the bacteria. So this is a well known phenomenon and is occurring in IBS and is causing the SIBO we believe. Okay, so now let's integrate all of this to try to understand what's happening. So if you want to prove we proved its Campylobacter, I showed you the Bradford Hill criteria Campylobacter causes IBS. Now we want to prove it's not Campylobacter, it's the toxin CDTV in Campylobacter, that's all you need to cause IBS. And so that's what we're going to show here. We took the toxin out, purified it, and injected it into the arm of the rat, like a vaccine like a COVID vaccine, it's not going in the gut, it's going in the arm. If CDTV is causing the gut to be a problem, it doesn't matter where it goes. If it's an antibody issue, it doesn't matter where you put it. If you develop antibodies

to CDTV, it's causing the problem. Well, sure enough, after the immunization with cddb, you get a ton of CDTV antibodies their way up. Look what happens to vinculin antibodies, you didn't get vinculin, you got CDTV, and the rats develop anti vinculin antibodies.

So CDTV exposure created auto immunity in the rats to vinculin, a protein that the rats have in the nerves of their gut. So this is an autoimmune disease.

Not to mention, if you focus on the on the graphs on the right, the rats who got the antibody, developed SIBO and got the CDTV inoculation they developed SIBO as compared to the control rats. So the CDTV toxin all by itself causes IBS.

So it works like this, you have CDTV you form antibodies to it after you've gotten an infection. And you form antibodies to a lot of it because you don't like any of it. It's not a foreign substance. But one of these areas looks a little bit like vinculin on purpose to cause this autoimmunity and mess you up. And then this antibody starts to affect the nerves of the gut because it's attacking the vinculum. Okay, so now this was a DW abstract. This is in the publication process now, but it's public information because it was presented at DW. This is the next step in this whole CDTV process.

We did the study again, we gave CDTV to rats, just like a vaccine. And of course again, as we saw on the first experiment, this antibody goes up. Now we had a larger number of rats and we were able to see the stool wet weight of these rats went up and while it looks like it's only 3% Believe me 3% of eight litters that are in your gut during digestion is a whole heck of a lot of water coming out of diarrhea. So this is a lot of increase in stool wet weight. And the higher the anti CDTV antibody was in response to that toxin, the worse the rat was in terms of diarrhea. So we're proving cause and effect again Gotta get really deep in the weeds, I'm sorry, I forgive me, if you if you, if this is just too much for you just cover your ears and go, Oh, la la la la la and you don't have to hear it. But here's the part that's interesting from a scientific perspective.

So we took the blood of these rats, and they have all sorts of cytokine changes, in particular, these for il two, il five, aisle 18, TNF alpha, you don't need to know what they do, you just need to know that these are signs of particular types of inflammation. But if there's a computer software that if you just didn't know anything, you just put these changes into the software, the software says, I can predict what this rat would look like if they had these four like this. And so it's a way of double checking your math. So we plug these four cytokines into that software, and it gives you what's called an upstream and downstream analysis of what these cytokines are doing. If they were to be seen, let's say in a human. Okay, so here we are, this is 123, and four.

And if the direction of change of these four happened in a human, it would be because the human was seeing too much lipopolysaccharide, which is a toxin, or a chemical from E. coli and Klebsiella, and coliforms, which are the organisms of SIBO. Number two, if you had these four in the direction they are, it would predict you have an autoimmune disease.

Number three, if you had these four, it would predict you have diarrhea, most likely. And that's exactly what we saw on the animals. So backwards and forwards looking at the data. The CDTV toxin is predicting the development of SIBO, the development of diarrhea, the development of autoimmunity, and the cytokines affirm that we also did sequencing of the microbiome. And people say, Well, how do you know the breath test is not in the colon problem versus small bowel? Well, in the animal models, nothing's changing in the coal in the cecum, nothing's changing in the stool with CDTV. All the changes are in the duodenal, and the alium, which are the small bowel. So the small bowel is changing because of this toxin and all of these effects, it is not changing the colon bacteria.

But here's what we learned. And this is really important, as we get into the breath testing part of this presentation, the rats that God's CDTV drifted after they got CDTV into three directions. Direction one is the green. So after three months after the CDTV vaccine, green dots lined up with orange dots with our healthy rats. So a group of rats who got CDTV, no change, a group of rats that got CTB went into a cluster here,

the blue dots, and those turned out to be elevated E Coli in the small bowel, which is the hydrogen producer of the small bowel. And then a group of dots, purple dots was another cluster. So cluster three. And they are linked to the elevation of the soulful Vibrio in rats, which is the hydrogen sulfide cluster.

So even with this, we're seeing that the diarrhea development in IBS, D rats is either a hydrogen cluster or a hydrogen sulfide cluster. And as you'll see, we need a three gas breath test to be able to sort this out in humans. And finally, how do these antibodies stack up with humans? So we developed a sort of a first generation test, and then improved that this is the second generation blood test now. It's called IBS smart. This is the one that's validated with what we call epitope optimization to give you a better separation between IBS, D and red, and other people with diarrhea. So this is really important when you develop a blood test for IBS. And people have some of these blood tests well, it's up in IBS, but not up and healthy.

Well, if you have a normal bowel movement, you're not seeing me. If you have diarrhea, I need to figure out what's causing your diarrhea. So it's more important than the tests so just to be clear, the test separates from healthy, but a more important result is that it separates two people with diarrhea, you have IBS and you don't because the test is negative or you might need further testing because your antibodies are negative. So that's a really important separation and that's what we get here. The IBS verb says other conditions.

This is for anti vinculin. And this is for anti CDTV. So we measure both of these antibodies. But here's what's really important is that if these antibodies are positive, you're over 80%. For either marker, if both are positive, it's 98%. certainty, you have IBS for those of you who don't know, anything over 80% is considered medical certainty in post test probability testing. So we reach medical certainty if these markers are positive. And so this test is very valuable. But I'm going to show you this part. So if you look at either, either one, it's 43 and 42%. If you do either, or, which is the way the test works, it's 56% 56% of IBS patients will test positive on this test. What did I tell you at the beginning 60% of IBS is post infectious IBS, we believe.

So 56% is right there. The point is, your sensitivity will never be greater than 56%. Because there's another 40% of IBS, we still need to figure out, but 60% That's the important. Okay. And then finally, this is sort of my last slide on this whole CDTV vinculin story, but I think it puts it in a sort of a summary slide that's a little bit more colorful and interesting. This is your microbiome in the small bowel, beautiful colors, all sorts of different bacteria are present here. Look at the nerves. These are the interstitial cells of the hall that we were talking about, those round circle cells that were in green, this is the nerve Plexus, the ganglia here, and then you've got these green guys who come in with just Campylobacter.

And they produce a toxin called CDTV. And then you start to develop antibodies to see TB. And we have a case report that we published, I'm not showing it here that shows exactly how this works, you first start to form antibodies to CDTV after food poisoning. And then about three months later, you start to form an anti vinculum. So a comes later as the cells open in the vinculin.

As exposed, you start to increasingly form antibodies until you reach a plateau. And as you get the vinculin antibodies, the nerves start to diminish, we believe. And then you also get some inflammation around the nerves as well. Because of that, and the poor motility, we think that's why you get SIBO. And the SIBO is these lots of blue and not a lot of those nice colors we saw before everything started to take a turn.

Okay, so the last part of this, which is, you know, a little past the halfway point of this presentation is breath testing, SIBO and IBS. So it's pretty clear now this meta analysis kind of settles it. Look, if you did a breath test and an IBS patient and a healthy control. It's way more likely the IBS patient has a positive breakfast. And this sham meta analysis from Australia really kind of settles it. It's 25 studies, we can put this to rest. Now, the breath test findings we described 25 years ago are correct that IBS has more SIBO by breath testing. But SIBO was complicated in 1996. When we first started doing research on this, all we had was data on hydrogen.

Some of the tests had methane on the breath test. But nobody ever told us what to do with methane. We didn't know why they were there or why there was nothing even

on the breath test, we don't know. But what we learned very quickly was that when methane was present patients were constipated, as you can see here. But the problem is methane bacteria are not bacteria. These are archaea, they use four hydrogens to make one method. So if you have nothing antigens in your gut, they're sucking up all the hydrogen. So if you only measured hydrogen on your breath test, you can't rely on the number because you don't know if there's methane, because the hydrogen could be zero, because the methane bugs are eating all the hydrogen. So hydrogen is a fuel for other bacteria. And we never found a good correlation between the level of hydrogen and symptoms. All we know is if hydrogen is elevated, you have SIBO and you have symptoms.

But if the hydrogens are 100 or 50, both are abnormal. Those two patients don't really have different symptoms, they just have symptoms. So the and it's because the things that are producing the symptoms are mostly the hydrogen sulfide and the methane with now we know hydrogen sulfide produces diarrhea, now five hydrogens to make one hydrogen sulfide. So hydrogen sulfide is even worse. But we are learning that E. coli and Klebsiella do produce symptoms by themself. And it's more complicated than even the story that's shown here. But I'll show you that later. But now so breath testing is one thing but let's culture the bow because there are pure Are US scientists out there that say well breath testing? You know, it's an indirect measure, show us the meat and potatoes like what's going on literally in the gut.

And so this study in 2007 said, Yep, absolutely IBS patients, if you use this cut off five times 10 to the 340 3% of IBS has SIBO. Now, that's five times the standard of three. But the new North American consensus says no, no, that's still too, too high a cut off, use one times 10 to the three. And if you use one time, standard three, there's that magic number again, 60% of IBS D meet SIBO by culture, as compared to non de IBS patients who are sick, undergoing endoscopy. These are not healthy controls. But again, 60% We keep getting 60%.

Okay, now, we then started to unravel. Okay, who are the bad characters? Now, in those days back in the early part of the last decade, we were, you know, taking a

stab at it. We know E. coli and Klebsiella. Were the hydrogen producers. And we measured them by qPCR, which is just a single organism PCR. Is it there? How much is it, and e coli was 10 times higher this is every number is 10 times higher than the previous number. Is there a login earthquake scale?

So this is a huge difference 10 times and 10 times versus healthy for these two bugs. But we had to go further. And this is where the reimagined study is so important to reimagine study we started about four years ago now. And we wanted to collect juice from the small bowel with biopsies with the blood of the patient with all their information, and to be able to put it all together to understand how the patient's the test and responding to the bacteria. We need to know all of this because there could be many ways to develop drugs to treat SIBO, and IBS, not just antibiotics. And we needed to unravel this. And we're of course using this data to look at obesity and other diseases conditions. But I will focus on SIBO.

One of the early papers seems early for me now, because we have so much more data, but this was in 2020. And we published this paper showing greater than 10 to the three in the small bowel less than 10 to three meaning non SIBO. But look at what is one, one category of bacteria is taking up 45% of everything in the gut. But it's even more interesting than that. Because when you go down to this last spring's This is the genus, and this is the species back then we did 16 s sequencing, which can only get to roughly maybe some species.

We're now doing shotgun sequencing, we see everything to the strain level. And I'll just say DW 2023, I'm going to tell you exactly what strains of these bacteria we're talking about. And I think you'll be even more shocked when I tell you what's going on there. But I'll leave that for now. But look, Klebsiella and Escherichia or E. coli are the majority of that orange ring at the beginning, literally 40% of every you have 500 to 1000 species in the small bowel and 40% are just a couple. They're literally taken over, it's almost like an infection. This is an important part of the study. It is really

complicated to understand every single column here, but the point of this is we did breath tests on some of these reimagined study patients and 20 parts per million by 90 minutes on a lactulose breath test is your best test for SIBO as an indirect measure when you compare it to culture, when you compare it to sequencing. And when you have that cut off positive. It is associated with upregulation of hydrogen producing pathways in the juice of the small bowel. So for people who say the hydrogen is coming from the colon, that's not lining up, this hydrogen is coming from the small bowel. And then finally, with our sequencing, we're able to show that really the 10 to the three cut off the 1000 If your bacteria on a McConkey agar plate suck juice from the small bowel grows more than 1000 colonies per milliliter. That's the tipping point because as soon as you go over 1000. This is over 1000 the microbiome you can see by the colors, they suddenly change.

That's the tipping point. Okay, I'm not going to spend as much time on intestinal advantage and overgrowth because that's a whole shebang that takes a long time to talk about because we have so much data now but you know, hydrogen is in the gut from other organisms and then M smithy i That's the myth antigen We now know that's the main character that's producing methane. And now we know methane is associated with constipation. Not only that more methane, more constipated, more methane than that even more constipated. So it's proportional. So this is what we call a gesso transmitter, the more you have, the worse it is for you. And again, DW 2023, we're going to present the entire RKO home, which is this category of organisms from duodenal, jejunum, ileum, and colon. For the first time in human history, we will know the full RKO home of the human intestinal tract. And that's all I can say. That's my teaser again.

We thought for a long time that E. Coli Klebsiella, those two hydrogen producers, were the ones producing the hydrogen for them with antigens, but that is not the case. And I'll show you why with our new study, hydrogen sulfide is really the new kid on the block fuse of bacteria and is one of the key hydrogen sulfide producers of the gut. We do believe E. coli lines up with this and that these two are working in partnership and the sulfur Vibrio is the other one, but the important thing is this is hydrogen sulfide

producing bugs. And they cause diarrhea, urgency and pain. So how do we measure hydrogen sulfide, this took years to perfect because the problem is hydrogen sulfide is a reactive gas.

You have to have the right system to carry the gas, you have to be able to keep it in that system, whether it's a bag or whatever, for up to seven to 10 days to get it to a lab so that it can be measured. And that you can then you have to develop sensors that are aligned absolutely perfectly in an instrument to optimize that you measure those three gasses correctly, and they're not interacting with the other sensors and data, etc. And then you need to do some research studies to prove that, hey, this works, this is the cut off and so forth. And so that took years of course, and now it's available.

But just to put it in perspective of previous instruments, the new instrument that's measuring the three gasses is more precise is the right word. So if it's 20 parts per million, it only deviates plus or minus 0.2. So it could be 19 Play can mean 20.2 previous instruments are plus or minus two. So if it's 20, it could be a team as the real number, or it could be 22 is a real number. But that can be really important. That difference if you're right on the cusp of either SIBO and on SIBO. So having more precision is really important around that 20 ppm, so new instruments are more precise, but overall, they line up for hydrogen and methane pretty well as you can see here. But in the first study, we set the cut off at five because we all all we had was really sort of diarrhea patients, not IBS D which are milder diarrhea, but diarrhea and surely over five, you have over five for hydrogen sulfide, it lines up with those bad diarrhea patients, we now know that IBS D. It's three, but it could even be lower.

You know, it's better to be conservative when you're launching a test, then to make everybody hydrogen sulfide positive and then say, Oh, oops, you know, we got that wrong. Because the data shows we have severe diarrhea. First, we do the IBS D next, and then we look at the milder patients to see where the cutoff could be even more precise, but higher hydrogen sulfide, higher symptoms, so that's real. So the more

hydrogen sulfide you have on your breath test, the more severe your diarrhea appears to be. Okay.

How do we treat SIBO IBS in this contact context? Well, we know Rifaximin is FDA approved for IBS, and it is approved for IBS on the basis that IBS is a microbiome condition. In part that's a mechanism of action. And so you know, it's not called out as approved for SIBO but as an understanding that the microbiome is abnormal in IBS and that Rifaximin corrects that abnormality. But if you look at breath testing in the target three study, if you just flat out gave Rifaximin and didn't think to put a blindfold on your IBS D you're getting Rifaximin. 44% of people respond without any testing at all. But if your breath test was negative to begin with, almost half of those patients responded.

It suggested that breath testing was important. And certainly if the breath test was positive, you're more likely to respond if the breath test was positive and the Rifaximin really got rid of that overgrowth. 76% met that really difficult FDA endpoint which is amazing because there's no drug that I know of that can get you 76.5% of FDA endpoint improvement, but it really dependent on knowing they had a positive breath test. Okay, for methane, it's different. Meth antigens are archaea, we developed antibiotics for bacteria, not archaea. Now, archaea are single cell organisms. And so some of the antibiotics do have some effect on those organisms. But I can tell you Neomycin by itself, not much Rifaximin, by itself on that bug, not much we happen to find out in the lab, that when we combined Rifaximin with Neomycin, wow had an effect. So we actually did a human study, double blind study where we gave real drug Neomycin. And then real drugs, Neomycin plus Rifaximin. And as we saw in the lab, if you combine these two, you get a better improvement and constipation. And if you can get the methane less than three, those patients did the best.

Now, we're a little bit stuck with hydrogen sulfide. And when I say stuck, I mean we have something coming. It is looking very promising for hydrogen sulfide. But it is not FDA approved and won't be FDA approved for a couple of years, probably, if it continues along the path of success. But we do have business and Bismuth has been

known for a few decades to be or have an effect on hydrogen sulfide. And there was a paper earlier this year. Interestingly, I don't have it in my deck even quickly where they use bacteria. That's a hydro gentle trophic bacteria. And this bacteria I brought the paper because it's relatively new.

But basically it's eating hydrogen, the bacteria eats hydrogen, but it doesn't produce it. It's in a seat engine. So it doesn't produce metal, it doesn't produce hydrogen sulfide, and it gets rid of hydrogen. And it shows promising results. Well, not quite statistically significant. But it shows you that the field is paying attention to hydrogen, hydrogen sulfide and methane. And it's all declared in this paper. So more things are coming that are going to be able to treat hydrogen sulfide. And so stay tuned. But we use Bismuth right now, and I'll show you how you do that later.

But the final piece of science I really wanted to highlight here is because this really puts sort of everything collectively that I've shown you today together. And that is that this was a study where we took really amazing patients with IBS D who are part of a randomized control trial. When I say amazing, that means they had to meet the FDA sort of guidelines for being enrolled in a clinical study, they had to have really, really IBS D. And we took another group that were ibsc from another trial. And in both trials, breath tests were done. And in both trials stool was taken for those who are enrolled in the study. So this paper just got published in the American Journal of gastroenterology and was presented at btw, but it really kind of brings the breath test to the forefront in terms of understanding IBS.

Looking at methane, this is nothing first, if you do a methane breath test, if your IBS D, there is no methane, you can see it's down here, if your IBS see 56% of IBS, C patients had methane, and that methane was up here. So these patients went on to have stool and the IBS D patients went on to have stool. But before we go to the stool stuff, look at hydrogen, IBS D as hydrogen. That's the blue line. Of course, you know that with lactose, it goes up, whereas methane, it doesn't matter. You're either methane or not. So it's even at the beginning of the breath test, it can be positive or over 10. But here's what I want to point out to the diarrhea patients in 90 minutes.

This is 20. And this is 90. On average, the diarrhea patients were more than 20 by 90 minutes. But here's what I want to share. That's really interesting. Look at the IBS see with methane versus the ibsc with no methane. No methane is here didn't meet the 20. Methane is here. It's lower than even non SIBO patients, because the methane is eating the hydrogen. So the hydrogen levels in these patients are even lower than everybody else, because the methane is eating it. And that's why you have to measure three gasses because you can't tell what the hydrogen is when you have these other gasses eating. Okay. And then finally, hydrogen sulfide. So it's very clear here. If your D, your hydrogen sulfide is elevated, the diversity of the microbiome is much lower in D. But here's here's the important thing and I know I've said this already, but it's so good to see it in the best trial yet that in that vein, with constipation, it's this bug the bento brava back your smithy and I we can stop I mean, we really know what's this bug and the higher this bug is the Higher your methane is on your breath test. The higher this bug is, the lower your hydrogen is in your breakfast.

Again, it's more bugs, eating more hydrogen means less hydrogen on your breath test. And all of that just continues to live. But this is something new, and maybe a little bit too much for the audience, but I'm gonna say it. It's not E. coli and Klebsiella. When it comes to that thing, these are the two hydrogen producers that are partnering with Emma Smith ei to make methane. These are the two hydrogen producers, we need to think about attacking if we want to treat nothing, or to just go after the M Smith UI. But we know the cast of characters for the first time. This is the cast of characters, we either attack these two as the source of hydrogen, or we attack this character one way or another, we're going to get them down.

So now that we know, on the D side, it's about hydrogen. Yes, but it's about hydrogen sulfide. More importantly, because these are the two bugs that correlated with the breath test hydrogen sulfide. So these SOT This is the character M Smith, Ei is the character for methane on a breath test. These two are the characters for hydrogen sulfide on breakfast. Again, we know the cast of characters, we didn't know that a year

ago. Okay, I'm gonna skip this. And so idsd It's all about hydrogen, hydrogen and hydrogen sulfide production ibsc. It's all about methane production.

And we're able to show that these pathways for producing these gasses were also elevated in the stool. And this is sort of a summary of all about, so my last two or three slides, is really just kind of saying, Look, you know, things have changed. We now have the North American consensus, which was 2018 Ali Rezai, who some of you may know, my partner here at Cedars, who does breath testing and is head of motility now at Cedars. So we set the standard for how you should think of SIBO and breath testing so that the field would be standardized.

Well, guess what the Europeans came up with their guideline, this was in 2021. And they line up very closely with the European North American guidelines. And a few weeks ago, the Asia Pacific consensus occurred and when I say Asia Pacific that included experts from Australia. So the entire world now understands that SIBO is important, that SIBO needs to be evaluated and diagnosed accurately, and that they've set the standards for how to do so across the globe. As you can see, most of those experts around the world now agree on the importance of SIBO and how to diagnose if most of them agree how to dose the substrate. And most of them agree that SIBO and IBS are interlinked and interrelated, which is a really super important sort of development in the whole SIBO phenomenon.

I'll come back to this slide. It's not as simple as hydrogen. I know I'm, you know, the more you know, the more complicated it gets. But the more you know, the more you know how to treat it properly. And so hydrogen is the starting point. But you got these two characters eating hydrogen, this is driving diarrhea, this is driving methane. These guys do produce symptoms, but it's a little bit difficult to quantitate how that works with just a breath test. I've shown you evidence for every step. I've cut corners, because I can't show you everything. 300 papers will be impossible to show you all the details of how we got from here to here. But I tried to give you the sort of the key nuggets of how this has been proven that food poisoning leads to IBS. But what I'm going to show you today is this is how I do it.

This really kind of just settles in on how I treat my patients. And so if I have a patient with chronic diarrhea or mixed mixed diarrhea, constipation, my first step is I measure the anti CDTV and the anti vinculin. Because we now know that tells me and the patient, you got this from food poison, and the higher the antibody, the harder they are to be treated.

It's harder to keep the seagull away and we know that now because we've been doing this for a little while. I do the three gas breath tests now basically routinely because of the importance of hydrogen sulfide if it's hydrogen, I give Rifaximin if it's hydrogen sulfide to give Rifaximin and this myth, I had a patient who took three courses of Rifaximin from their doctor we did a breath test it turned out it was hydrogen sulfide. Give her facts on the best myth. One of the first patients and the reason I'm quoting the first patients, is because treat her with Rifaximin investment. A year later, she's still normal. I saw her in the clinic recently. So normal in terms of her symptoms, not not just her hydrogen sulfide. So knowing is important because Rifaximin alone doesn't seem to work.

The other thing is if the antibodies are positive, back here, I give travel prophylaxis because I am they have to be very careful, because the more food poisoning they get, the higher the antibodies go. And for some people, I follow these antibodies over time because the CCTV will go down, the vinculin will either stay the same, or go down extremely slowly over five or 10 years. So sad to say that this guy is really important as a therapeutic if we can get rid of it as we move forward here in terms of our research. But when this goes up, as I had a patient yesterday, it went up from 1.8, which is abnormal now to 2.99. And she is beside herself more unwell and difficult to treat. We now know why she had some form of food poisoning between a year and a half ago. And now. So I use that as a sort of a thermometer.

If they're constipated. I don't measure routinely those antibodies because they're only about 25% of the president. Only if a patient says oh, you know this all started after food poisoning would I measure it, but I don't find that it's all that useful at the cost of the patient. But I do the three gas breath tests because occasionally I see

people with methane and hydrogen sulfide. When you have methane or hydrogen sulfide together, methane wins so you can be constipated. But you have to treat all three, but for the methane positive I give Rifaximin plus Neomycin. Based on that randomized control trial, nothing negative. You need to figure out why they're constipated, something else is going on. And again, knowing that they are not tells you who to investigate and spend more money on and spend more time on to figure it out. One caveat here Neomycin, the generic company that was making Neomycin stopped making it so it's almost impossible to get now in the US.

We know from our clinical experience and metronome and from our basic science experience in metronidazole seems to work as well as Neomycin with Rifaximin. So I give Rifaximin with metronidazole. Unfortunately, we don't have a double blind study of new Rifaximin plus metronidazole. But my lab and clinical experience tells us that this works just as well as noodles. So in conclusion, IBS is commonly a small bowel microbiome disease, full stop, even though even the global consensus suggests that SIBO is an important contributor to that process.

The most important organisms of SIBO are E coli and Klebsiella. You're going to hear a lot more about that at DW methane. And the fan engines are the culprit and constipation. For the most part, hydrogen sulfide is becoming the big culprit in diarrhea. Getting these things down improves constipation or diarrhea, depending on which gas you have, you know, knowing if you have these antibodies is really important in my view, because it really tells the patient they have an organic disease, you have a real disease, not it's not in your head, this is where what happened. And they need to be more careful, because if these antibodies go up, they get worse.

And so we're, if I were to say one thing, sort of to conclude, which is number nine, we now know the actors, we didn't know them even a year ago, not as completely as we do now. We now have already started developing the treatments, and they are already in clinical trials. So some of those clinical trials are done. I just can't speak about it yet. So we're a lot further down the road than I can reveal today. And I want

you to have some optimism that we have a lot of things coming. And it's not just us, which is really the most important thing. I highlighted this paper about this hydrogenic tropic bacteria, we didn't have time to put a slide in because relatively new people besides us are thinking about ways to manipulate hydrogen and methane in hydrogen sulfide, which is even better.

I mean, it doesn't have to, you know, we have it should be everybody working on this because then there's going to be something for you all or people with these conditions faster. So I'm really excited about the future because now that the roadmap and the cornerstones are now very well laid. I think we're going to see some really interesting things in the coming years. So thank you. Sorry, maybe I went a little too long, but hopefully that was helpful.

Shivan Sarna: It was extraordinarily helpful and absolutely not too long. Thank you so much. Dr. Pimentel.

Dr. Siebecker, I know you have a lot of questions. I do too, but I need to ask the one question that I know is on everyone's mind. When is Digestive Disease Week 2023? a gastroenterology conference.

Dr. Mark Pimentel: It's in the first part of May. I don't have the exact date.

Shivan Sarna: The countdown is on.

Dr. Allison Siebecker: The W stands for digestive disease week, people who don't know. And it is a gastroenterology conference. It's International. And it's typically held. Isn't it always held in the US even though it's a worldwide conference?

Dr. Mark Pimentel: Yeah. It's held in the US and it's gonna be in Chicago.

Shivan Sarna: Thank you. I'm sure we'll be keeping people posted about what happens there. I want to hand things over to you Dr. Dr. Siebecker, because I know you have some questions already prepared.

Dr. Allison Siebecker: Thank you so much, Mark. That was fantastic. As always, some of that information that you gave us is so brand new, that the official publication of it just came out on October 27, I think was when the paper was published.

On that paper, I just had a couple of questions I wanted to ask, it was great that you clarify that now that you know these bacteria that are making the hydrogen that then goes to feed the methanogens, for example, that is a place we could target our treatment. And I'm sure you're working on that but I just wondered since we always give Rifaximin and Neomycin or Rifaximin and metronomic together. Do they target the central?

Dr. Mark Pimentel: The answer is yes. Rifaximin should work on those. The question is does it work on those and why am I saying it that way. E. Coli Klebsiella, Rifaximin is amazing for it, but some of the problems we have with Rifaximin is that it's not water soluble. It can't penetrate some of the deeper parts of the small bowel fluid. That is where these bugs are sort of hiding, including the mucus. And so then if you go to Christensen, all ACA and Ruminococcus. ACA

In the small bowel, the Rifaximin has more effect in the colon, it doesn't have as much of an effect. And so it may not as thoroughly diminish those organisms in the colon as if they were in the small bowel. But in the clinic, we see it works about 70% of the time, if you combine it with Rifaximin, and metronidazole. Maybe that's why it works because metronidazole has a better solubility and maybe they're working in tandem, you're sort of, you know, slugging them in different ways. And you get the same effect.

Dr. Allison Siebecker: And can you tell us if that is one of the things you've been working on is finding treatments that target those. Okay, so we have that to look forward to.

I was wondering if you could talk, I don't know if it was in your presentation. But it was in the paper about the Cofactor F420. That's involved in Santo Genesis. And you

could just describe its role. And also if that is what has been targeted by the status that it can turn it on.

Dr. Mark Pimentel: A sort of a traditional approach to medicine is that you find an enzyme or sort of a protein that makes something happen is part of the machinery of cells and bacterial cells in this case, and one of the last steps in making methane is the f 420 protein. And the F 420 protein is. The reason that one's important is because there's a lot of ways of making methane. But in almost all bugs that make methane they use F 420 As the final step. So if you want to get rid of methane and make sure that it's not you know, just happens to be you don't have Smith Ei, you have one of the other ones, F or 20 still there, so it's a good target. And so Lova starts and you show it in a paper a number of years ago that sticks in the socket of that protein and blocks the protein doing what it's supposed to do.

We did one study with Lovastatin and tried to create a Lovastatin that doesn't get absorbed, but it wasn't that successful mostly because what the statin did was reduce cholesterol and didn't really stay in the gut as it's supposed to. So in the lab, we put Lovastatin in a dish with antigens. They don't produce much methane. So it works in the lab and it works in the stool. have humans but it has to stay in the stool and not get in the bloodstream. And so those are some of the things we're looking at in the future.

Dr. Allison Siebecker: Thank you, really interesting. Do you have any new thoughts on why we see constipation so often clinically, when someone's positive for hydrogen sulfide, and they're not positive for methane. It's not like both methane and hydrogen sulfide are positive. Clinically, I know many of us have seen constipation, it's surprising to us. And also, my group did a community study. And we saw that results as well, many people seeing it positive any new thoughts on why that would be when the study so clearly shows diarrhea is linked with hydrogen sulfide.

Dr. Mark Pimentel: Studies are one thing, but the real world is different. For a lot of reasons, I mean, in our practice, for example, we see hydrogen sulfide, we see it once every couple of weeks, and we treat it. But our practices, maybe more of the extreme

cases, maybe not as mild diarrhea, so it can vary across the country, depending upon pocket. I don't do breath tests necessarily in somebody with one out of 10 symptoms, but eight out of 10 symptoms, I might. Maybe diet works and offers one out of 10 patients rather than antibiotics. It just depends on who you're testing, the severity of their condition, and so forth.

If a patient has diarrhea, once every two weeks, they may not have much hydrogen sulfide, or the threshold for positive for that patient is a little bit lower. And we just haven't got to the granularity of that research. But if nothing is present with hydrogen sulfide, and methane wins, these patients are often constipated. But we had one patient like that, where we treated the methane and all of a sudden, the hydrogen sulfide came up because the methane was gone. And now they have diarrhea, so you have to be that's why it's sometimes an important matter, all three gasses.

Dr. Allison Siebecker: I've definitely seen the switching back and forth between nothing and hydrogen sulfide and the clinical correlation going back and forth. Thanks. Okay.

This paper made such an excellent clear correlation between the IBS types and the SIBO types, really linking them together. And I just wanted to know, what are your thoughts now on whether or not SIBO should just be considered IBS? Should these two, SIBO and IBS, be separate? Should they be joined? What are your thoughts?

Dr. Mark Pimentel: You know? It's a tough question for a lot of reasons. First of all, if you go back to H. pylori and peptic ulcer disease, H. pylori causes ulcers 60% of the time. So, peptic ulcer disease means you have an ulcer in your stomach, hey, we don't know why. But they never changed the term peptic ulcer disease to h pylori disease. And so they just basically said, you know, you have peptic ulcer, 60% of people can have
H. Pylori as a cause and look for it and treat it when it's there. I think the challenge with IBS, and this is the historical part of IBS, has always been a clinical diagnosis, you must meet the Rome criteria. If we take SIBO, there's two ways to handle what your

question is. Anybody with any diarrhea should have a breath test. If it's positive, then don't apply the Rome criteria.

That's going to be hard to convince people because, you know, that basically pulls the carpet out from Rome, nobody's left, maybe 30 or 40% of people are left, which cuts IVs true IVs down instead of 40 million people in the country, maybe five, or six, because the rest of Arecibo, you know what I'm saying? So it's, I don't know what the answer is. And some of the, you know, the people who do the criteria, and all of that will have to wrestle with that. To me, those things don't matter as much. As you know, if you have a breath test, you're determining the micro type and you're treating it. And I think people are starting to well, people have gotten it, they understand what they need to do. For the most part, most gastroenterologists are starting to understand this whole story, how it's playing out. And so maybe the Rome criteria becoming less important, more important for clinical trials still, but less important going forward. But you know, time will tell.

Dr. Allison Siebecker: I'm the same, I don't care what you call it. I know what it is. I'm looking for and treating and I know how it behaves, right. You can name it whatever you want. The last time you were chatting with us, five months ago. You told us about some of these and I was wondering if you could give us an update. It was a prevention, basically a vaccine for preventing food poisoning, that would then prevent the development of IDs. Can you give us an update on that?

Dr. Mark Pimentel: That's a lot but yes.

Dr. Allison Siebecker: Is there anything to add to what I just described?

Dr. Mark Pimentel: Mostly no, but because I can't talk about it. I mean, the whole point is, if we could prevent this from ever happening, you know, I gotta tell you, people are vaccine fatigued. I'm not sure everybody wants an IBS vaccine, but the point is, if you're somebody who, for example, is missionary work, and you're working in underserved populations in the world, and you're going there, and you're getting food poisoning, and you're gonna get IVs, or the military, or people who travel a lot.

This is where the vaccine may be extremely important, because they're gonna get IBS, for sure. And then people at home if they love to eat street food, or catch squirrels in their backyard and roasted on the barbecue. I'm joking. Okay, that doesn't happen. Well, not in Los Angeles.

Dr. Allison Siebecker: I understand people are very vaccine fatigued, but you know, what we see in the clinic is people who've just gone on a vacation to some place. I don't want to say one country or another because it's just so common. You go on vacation, you're having a fun vacation in the sun and then this is what happens. So common. And also, I saw tons of people who just like you said, eat out all the time. And that's how they got food poisoning..

Dr. Mark Pimentel: If you think about it, I mean, it's a little different than COVID killing people. Let's be clear, if and when COVID is a milder illness then maybe vaccines are less important. But for IBS, if you get one bout of food poisoning, and you have lifelong IBS, I think, people might think, Hey, I don't want that. And people with IBS need to be a little bit more vocal, it shouldn't be sort of a humorous disease. It's a real condition that's that people suffer with immense

Dr. Allison Siebecker: Okay, another thing that was fascinating about what's what's been brought out in this research is that difference between the small intestine, microbiome diversity that changes between the hydrogen type of E. coli and the hydrogen sulfide type, the hydrogen type of E. coli, you saw of decreased diversity. And that is what I hear all of my colleagues always talking about is, the diversity in the microbiome, whether they're talking small or large, is too, is too diminished, and we need to build it back up.

What is fascinating is that you found this second type, the hydrogen sulfide has increased diversity. As you've explained previously, in the paper, it's with bugs that are typically found in stool. And I was just wondering if you can comment on that, and particularly, any thoughts on treatment for correcting that isn't just a matter of getting the bacterial overgrowth down? Any thoughts?

Dr. Mark Pimentel: It's a challenging question from two angles, if you slow the gut down, you have more time for diversity, more time for bacteria to grow. So maybe that's the explanation for methane, why the diversity is higher there and lower in diarrhea. If I took a laxative every day, my diversity would be diminished, just because you're taking a laxative, and you're just washing out the bugs constantly. Diarrhea in and of itself might lead to lower diversity, but we're going to show a teeny amount in the small bowel, exactly how diversity is truly destroyed by the polis and the club Clos. I will give you more information on that. Basically, we now know how that's occurring, and who the species and strains are that are doing it. We're gonna get down to that level. That's going to be really exciting. But yeah, diversity is important, but the problem is, you know, when we treat Well, let me say it another way when we treat with Rifaximin, and we get rid of the SIBO we have data on this. You look at the small bowel again.

All the diversity came back. It's sort of like a gang moving into your neighborhood and all the neighbors just say I'm out, they move out. To the neighborhood. And then when the police get rid of the gang, everybody moves back in. And everything's back to normal. And that's exactly what it's like with SIBO. So once they're gone, the healthy microbiome just recovers. It's pretty amazing.

Dr. Allison Siebecker: What is so amazing about that, what you just explained is that Rifaximin is an antibiotic. An antibiotic, you can actually restore diversity.

Dr. Mark Pimentel: That's the brilliance of it is that you know, people say, Oh, you're taking the antibiotic, you want to destroy the diversity, it's exactly not what's happening. You're getting rid of the bullies. And the bullies are gone, and now the kids are playing in the yard again.

Dr. Allison Siebecker: Okay, now, what's interesting is you were just talking about how with methane, there's increased diversity. But what I was pointing out here is how, in this paper, it said, in hydrogen sulfide type, there's increased diversity. So is that the part you can't talk anything about?

Dr. Mark Pimentel: Well, so yes. Okay. Got it. I'll say one thing that is published, E. coli or hydrogen producers, when they produce a lot of hydrogen. That hydrogen can intoxicate other organisms, so anything that eats hydrogen or reduces hydrogen in the environment will allow other organisms to be more successful. Hydrogen is sort of like your pickling the environment for other organisms. So if you can get rid of the hydrogen, whether it's through methane, or through hydrogen sulfide pathways, you might give some organisms a chance to stay. And that's sort of how we see it.

Shivan Sarna: Okay, these are just different than what we've been talking about, but I was wondering what your opinion was when you talk to a patient who's going to go have a colonoscopy. And they are constipated patients. Do you have any tips for them for the prep? Any tips? Because I know I'm not alone. Right? I know. I'm not alone.

Dr. Mark Pimentel: Yeah. You have to pinch your nose when you're drinking it. Now, do you gotta drink at all? Otherwise, it isn't, you know, the worst. I can say the worst day of a patient. They come in. They did the prep last night. They kind of cut corners. The doctor goes in, it's full of you know what, they can't see anything. And they tell you, we're going to reschedule it, and two weeks from now and you start over. Don't make that you, because you don't want to do that twice. That's the most important thing. Just take the whole amount prescribed.

Shivan Sarna: Okay. And we were talking to somebody else who said like, the day before you do the prep a lot of people sort of gorge, because they're thinking yeah...

Dr. Mark Pimentel: go like meals that they or just clear fluids just so that there's not a lot of things to come out. And yeah, so easy. I´m excited for you!

Shivan Sarna: It's my third, right, because before I knew you and Dr. Siebecker. And then I went to SIBO . I was convinced I was dying and I had cancer. So as so many people can relate, like, I see it all the time in the Facebook group. Well, I, you know, my colonoscopy showed nothing. Right? That was a big discovery for me. SIBO doesn't

show up on typical colonoscopies unless you're doing the aspirate, like you do, or, you know.

Dr. Mark Pimentel: Amazing point because we see this all the time. I had a patient in my practice. She's 25 years old, and when she came in I said, have you ever had a colonoscopy? She said, Yes, I've had three. And I just blew my mind. Why would a 25 year old young woman after the first one's negative? Why would anybody want another one? And then another one after that? I mean, so yes, abusive colonoscopy.

Shivan Sarna: It's a desperation that so many patients experience and bless the GI doctor who's like, my Dr. Michael Shulman in Florida. I begged him for the second one because I was having a flare up, but I was his last colonoscopy on the last day before their Christmas break. They just really moved heaven and earth for me to bless them and he's like, you got nothing, sister.

Dr. Mark Pimentel: The severity of the symptoms are such that patients like, look, something's gotta be wrong. Exactly.

Dr. Allison Siebecker: And gastroenterologists and primary care professionals around the world, not just the US, really understand that you run the colonoscopy, but understand about the idea of smart test, and the SIBO breath test.

Shivan Sarna: There's your great trifecta. And then any thoughts on a diet for mythology and overgrowth?

Dr. Mark Pimentel: I've been so busy with so many other things. I keep saying there's going to be a diet for all three types. And I think there will be we're trying to sort out that, but we haven't made a lot of progress there. I have to say, no teaser on that one.

Shivan Sarna: Okay. And then last, but not least, is the correlation, I guess, might be the word connection, relationship between diabetes and SIBO. Do you see? Do you see that happening?

Dr. Mark Pimentel: We do. We don't have any teasers there either, except that we're investigating a lot of areas there because there's something connecting the microbiome to diabetes and high blood sugar. And we have some lead bugs and things but we need to, we need to spend a little bit more time in that direction and try to sort through that. But what we do know is that IBS patients do have weird inflections of blood sugar that are difficult to explain. So yeah, more need more work needs to be done there

Dr. Allison Siebecker: Do you see a pattern as more hypoglycemia or hyper.

Dr. Mark Pimentel: It depends on the beginning and younger people, we see a more hypo. Especially if we do a sugar to glucose tolerance test, partway through the test, they usually go down to like 30, or 50. We published that about 15 years ago. But if they're older people, then they tend to go high. So whether it's something the bugs are doing or something you're doing and adapting to the bugs over time. So the challenge with diabetes is because it changes in time. And so some conditions, you know, if you have staph aureus in your skin and effect equates an infection, it's like there and now, what we're starting to see is that if you have a bug, it does one thing now, and you continue to react to it, and it does something a little bit different as you age. And so when you start to add age as a factor increases the complexity of our associations, we're not talking about SIBO. But I'm talking about all these different diseases for which a microbiome might be important.

Shivan Sarna: What do you think about since we're talking about other conditions, psoriasis and SIBO email?

Dr. Mark Pimentel: There's definitely a connection between what we saw psoriasis ankylosing spondylitis, writer syndrome, scleroderma all have microbiome connections. For example, Campylobacter can precipitate, psoriatic arthritis and writers and ankylosing spondylitis. And so you can see that there's a connection with Campylobacter causing IBS Campylobacter causing another autoimmune disease. Campylobacter is just a nasty figure that can also cause GI and flare. A nasty

organism that can lead to some of these autoimmune conditions including psoriatic arthritis. So how that works is not clear. I do have some patients where some of their skin manifestations go away when SIBO is gone. Like rosacea patients tend to get better when they get their SIBO treated. I have two psoriatic psoriasis patients with psoriatic arthritis who claim that when the SIBO is gone, there's psoriasis and psoriatic arthritis is better. But it's small numbers

Shivan Sarna: It's interesting. They've been also doing some figuring out about how staff and psoriasis work together. So it's another thought on that but obviously, more to come. And this really is my last one that is fatty liver and SIBO.

Dr. Mark Pimentel: Oh, you gotta wait for that on

Shivan Sarna: Yeah. Well, I've always appreciated the fact that Rifaximin does such a nice job for fatty liver. And you know, it's very efficient. Yeah, you gotta wait.

Dr. Allison Siebecker: You're always asking about that. So it sounds like we're gonna get answers. Okay. I think I just have like three questions. I thought Neomycin was really interesting. I didn't realize I've been hearing people say that it was hard to get. And I didn't understand why, but it's that the generic manufacturer isn't yeah, there's, there's no it's all it was only generic. There's no brand in the US.

Dr. Mark Pimentel: No, it's been generic for a long, long time. The problem with generics, they disappear for a while, and then the company brings it back or another company buys it and brings it back and gives it an explosively high price. And says, well, it's no good for this. And we're bringing it back, we're starting a whole new manufacturing line. And so insulin cane is like, generic, it's been around for 100 years, not 100. You know what I'm saying? 60 years and why is it so expensive? So, shenanigans?

Dr. Allison Siebecker: On that front, I just wanted to ask a political question about it, and then, you know, maybe not as relevant now that it's not so accessible. But I was wondering how often you might have seen tinnitus or tinnitus, however, people like to

pronounce it and like how, how common is that for you to see? And when and if you've seen it, was it temporary or not?

Dr. Mark Pimentel: You can imagine how many people I've given Rifaximin, Neomycin to, it's a lot. It's over 1000. Let's put it that way. And I have never seen a human in my clinic with tinnitus. I have seen tinnitus in one patient in a clinical trial. The clinical trial was a whole section on tinnitus because the FDA wanted us to meet and wanted us to be very careful about tinnitus. They required for that trial, this was the lowest and predilection that all the patients get ear testing before they start the drug for two weeks. And then if and when they describe anything, we repeat the test. So sure enough, the first patient in the trial says, Oh, I think I got a ringing in my ears. So he said, Oh my god, so we stopped the drug. And you know, and we stopped the drug. And then one day later, they have sniffles that runny nose, they have a sore throat, they basically have a cold coming on. And then two weeks later, still, they're out of the trial, we repeat the ear testing, and it was better than the first one.

Dr. Allison Siebecker: I had heard this story before, you know, I felt that was in the context of whatever when getting so afraid about Neomycin is deafness. I didn't realize it was tinnitus.

Dr. Mark Pimentel: Well, it's both but yeah, obviously if you bring it long enough it becomes deafness. But you have to be on your mind to do my studies that suggested that that happened. We're back in the day when we used to treat cirrhosis with encephalopathy with Neomycin. And for that you take it every day for years. And for about a year you start to get these things. And we know from Neomycin that gentamicin is an aminoglycoside antibiotic. If you take gentamicin intravenously directly in your blood for three, four weeks for example endocarditis, then you can have tinnitus and ear changes. So it's a category assignment of tinnitus. It's not that Neomycin doesn't get them to work, for the most part. So you have to take a long, long time to see anything. But the FDA wants us to be careful, and just monitor. So have you can't get Neomycin anymore

Dr. Allison Siebecker: right? It doesn't now. Okay, and then this is a question that comes up so often we just had it recently, again from those who listen to us. Can you help explain why someone could bloat from drinking water?

Dr. Mark Pimentel: There are generally two types of receptors in the gut that turn on digestion, mechanical receptors. If you stretch the stomach, you drink like half a liter of water, you'll stretch the stomach and inhibit the cleaning. You got to stretch the stomach, it's got to be a good amount of water. You have a couple of sips, it's not going to do it. So that's why you can have you know, when we're doing our little fermentation meeting, if you just drink a little water, sip a little coffee, it's not going to get you out of the cleaning. But if you really like God guzzle like people do when they're drinking, you see these athletic young people who have these cylinders beside them full of water and they're just drinking that stuff. There you go right there. You're the athletic young person that I'm talking about. I'm a sipper. And, and so you know, you drink that you'll activate McConnell receptors, and then the gut will start moving. And we know patients with SIBO have air in their deck because they're fermenting even at night. You'll get a consolidation of that air and it will feel like a pressure point in the gut. So it's more that the air is moving around and suddenly becoming in these pockets. instead of being just sort of spread out over 15 feet. So that's how I see it. Some people say, Well, what happens is you empty your ilium into the colon and the residual stuff might cause a little bit of gas fermentation. I sort of believe the first one more than the lab. And the other receptor is chemo reception. So it's detecting food and turning on your system. You don't get that with water. You just get that with food.

Dr. Mark Pimentel: It's detecting food and so on as it starts to detect real food coming.

Dr. Allison Siebecker: Okay. And then my, this is my last question I saw you had an article that you just published, just recently came out on via glasses and IBS, with Dr. reside and and you know, there was a comment, comment in there about rumen o copy sia and bile acids and IBS diarrhea, and just anything you would want to comment on? Just so you know, the nature of this article is very interesting.

Dr. Mark Pimentel: I think the thing about bile acids has been much, much ado about something in bile acids. But there was no randomized control trial. None of treating bile acids in diarrhea, IBS, there are open label 2030 patients studies that say, Hey, this might do something. But overall, the bile acid story is a bit complicated. I was at dw and I went to a bile acid lecture. And this is from the group in San Diego. And they do mass spec of bile acids and stool. They detected 2000 Different bile acids and stool, like I'm done, I can't deal with 2000 bile acids, I, you know, it's violences are so complicated, that to unravel, the mystery of bile acids is going to take a decade, and maybe I'll retire by then. So it's going to take too long to really understand the mystery of bile acids. But yes, bacteria degrade bile acids into these toxic bile acids, which can lead to diarrhea that we know. So, but in my view, it's the bacteria that are the problem, not the bile acids that are the problem in most instances. So that's really what the paper was trying to say is that, you know, you have bile acids, now you have a whole bunch of bacteria in the gut. And they're converting the bile acids prematurely, to things that are more harmful to your colon into your gut, and then you get this diarrhea effect. So the diarrhea effect of SIBO might be multifaceted. It's not just the gas or the hydrogen sulfide into the bile acid changes and other things.

Dr. Allison Siebecker: Thank you. Okay, I'm gonna do Shivan. And one last one, measuring stool. That's a question we get a lot from clinicians, they want to know how useful stool analysis is for SIBO. And I feel like there might be a changing landscape because now we know that managing overgrowth can be in the large intestine, so can hydrogen sulfide. And we do have in functional medicine, many of our labs offer Smith EI and desulfovibrio. Sampling, they you know, they'll measure. Do you use it? What do you think of it?

Dr. Mark Pimentel: You must have a sneak peek at our data for the RKM for DW because the republishing presents what I'm saying is, I don't even know that information yet of what almost everybody has with antigens in their small in their colon almost every

day. What's normal, what's abnormal? What's causing IBS? See, I mean, we're still trying to figure that out. So I guess what I'm trying to say is, I'm gonna say something really controversial. It's sort of like the story. Okay. Everybody has a little bit of yeast in there still, but what really is true yeast overgrowth, because I believe there's a clinical true yeast thing.

We want to treat those who have the true story rather than those because the colonizing is happening all the time. I just want to make sure that when companies say you have an advantage means that it is really truly a pathogenic level. Not just that it's above their, whatever so called normal range. Because so what if I had the, you know, six burritos yesterday, maybe my meth antigens would be a little higher today, but it's not high tomorrow, what is the pathogenic range? So, you know, publish among guys, publish some papers. Show me I'd be happy to use these tests. And it frustrates me when you People are making money on things, but they're not publishing the data.

We can see how they got to this point, how they know this is abnormal, how they know that we should be doing X, Y, and Z because of what they're finding. You know, it's the same with the probiotic companies, a lot of them are selling probiotics that are never dense, published science, some of them have. You know, maybe they don't want to take a chance, take a risk.

Shivan Sarna: These are just some hot topics in the SIBO SOS® community Facebook group and so even a couple of sentences COVID and SIBO.

Dr. Mark Pimentel: There are a couple of papers. I can tell you up to 1000s of SIBO patients, I can't find one that got worse because they had COVID. I really can't find one that can truly choose her or he says, Look, the COVID really wiped me out. My SIBO is not going away. Now. I'm having a tougher time. I haven't seen it.

Shivan Sarna: Okay, and then SIBO and iron levels, serum iron levels and ferritin.

Dr. Mark Pimentel: There can be some changes depending on the organisms. We're trying to look at that. Well, the other thing we're trying to look at is folate. More importantly, because folate is a really strong marker for SIBO. And what organisms are responsible for making that poll, they go higher in SIBO. And then B12. can go down. There's a few things that can be markers of SIBO.

Shivan Sarna: And it was weird for me, I had very high B12 levels, like 8000 or something ridiculous, and they're like, Oh, you must have been supplementing, but I don't take B12 supplements.

Dr. Mark Pimentel: There's weird things with bugs that can produce stuff fully people. Some use iron, some use B12. You know, so it's all sorts of things that we're learning just as we continue to look.

Shivan Sarna: It's the wild west in there. And then last, this really is the last one gallstones, any relationship do you ever see any?

Dr. Mark Pimentel: Interesting question, but we haven't haven't looked.

Shivan Sarna: And we thank you so much for it. Well, as usual, you forget it. So well.

Dr. Mark Pimentel: I'm glad to be with you. And hope this was helpful to you and your audience.

Shivan Sarna: Incredibly helpful and so we will look forward to talking to you after DDW.

Dr. Mark Pimentel: I'm sure you will have been delighted to do what you're doing to get the information out there.

Shivan Sarna: So important. Not worth it to do anything less than that for sure disservice. Anyway, we are in our thoughts and prayers to continue with your beautiful work. And Dr. Dr. Siebecker, thank you so much for all of your insights and questions as always, and we will see you next time. I think that was a really hopeful session full of a lot of science. I want to encourage everyone to go back and watch it

over again. because it's obviously dense in a good way with, you know, material for us to ponder and figure out and to start smart conversations with our practitioners. And to not give up, he's not giving up. We're not giving up. We're gonna keep getting the information out to you. And I think we've got some really good news on the horizon coming sooner rather than later.