Digestive Disease Week 2023 Research Update

with Dr. Ali Rezaie

Your host Shivan Sarna and Dr. Allison Siebecker

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Shivan Sarna: Hello and welcome. I'm your co-host, Shvian Sarna, founder of SIBO SOS®, and I'm here with my fellow co host, Dr. Allison Siebecker, my friend who is the founder of SIBOInfo and lifelong student and fortunately an advocate for all of us. We are (SIBO) Small Intestinal Bacterial Overgrowth patients ourselves. And I started collaborating with Allison, around 2016. As a result, we have been working to educate the world about these conditions. Small Intestine Bacterial Overgrowth, Intestinal Methanogenic Overgrowth, Irritable Bowel Syndrome and what to do about it.

We have a very special guest, his name is Dr. Ali Rezaie And we use the excuse that the Digestive Disease Week 2023 has completed and we use that to get him to come on and talk to us. We would love to talk to him every day but we have made this an annual tradition. If you haven't heard of Dr. Ali Resaie, you will hear more about him in the world of gastroenterology. He is a specialist in irritable bowel syndrome, gut microbiome, and internal UV therapy. Fascinating. He's published well over 100 research articles in peer reviewed journals including Gastroenterology, American Journal of Gastroenterology, Digestive Diseases and Science, and Canadian Science and Canadian Journal of Gastroenterology. His work has been cited more than 8000 times by other scientific journals. He serves as the associate editor of the Journal of Digestive Disease and Sciences. He is out of Cedar Sinai and Medical Director of the Gastroenterology Motility program at Cedar Sinai Medical Center. He's director of bioinformatics at the Medically Associated Science and Technology Program also known as MAST at Cedars Sinai. He and his colleague Dr. Mark Pimentel are changing the world in terms of the microbiome, mapping the small intestine microbiome, and helping us all come up with ways to live with SIBO - Small Intestinal Bacterial Overgrowth and IMO - intestinal methanogen overgrowth - until they come up with a cure. No pressure. Hi, Dr. Rezaie.

Dr. Rezaie: Hello, and thank you so much for that kind introduction. And it's a pleasure to be here again.

Shivan Sarna: We love having you. Digestive Disease Week, the largest gastroenterology conference, just wrapped. And I know you were presenting some phenomenal information. Tell us what your highlights were? What are you excited about? What do you want the world to know about?

Dr. Rezaie: I'm very optimistic. The world is moving very fast, especially in the field of microbiome. And we have been playing around with the microbiome and trying to modify it. And now we're seeing that the treatments and the diagnostic tests are getting to a point that patients can be helped. And that's the eventual goal and very exciting to see. And every time that we see new technologies and new developments, all of those will help delineate exactly what we need to do and what bacteria need to be targeted, what fungi need to be targeted, what viruses need to be targeted, and what is the interaction between these three, right?

It's exciting times and happy to share some of that data and talk about them, whichever route you want to take us.

Shivan Sarna: Can we talk about IMO, Intestinal Methanogen Overgrowth? Because a lot of times I get feedback on our YouTube channel and in the Facebook group (now closing in on about 30,000 people) who comment that they don't hear enough about Intestinal Methanogen Overgrowth. We hear a lot about Small Intestine Bacterial Overgrowth. Could you explain the nuance between those two conditions, There's no confusion. And then let's start there.

Dr. Rezaie: Absolutely. Let's just maybe step back. All of these fall into microbial overgrowth syndromes, right. These are diseases where certain groups of microbes overgrow. And obviously, when that balance goes away, they cause trouble. The most known condition under that category is obviously Small Intestine Bacterial Overgrowth. But then we have small intestinal fungal regrowth when the fungi is overgrowing. And that becomes a problem. We can talk about that as well, because there was a lot of data to deal with as well.

And then when the metabolic regions increase, and remember, eventually, we will figure out what happens when the viral components of the microbiome will be imbalanced. So, that will come. But obviously, the research in that field is much tougher and harder, considering the bacteria phages, and also viruses.

If you think about domains of life … so we have life, and then it breaks down into three categories; it breaks into Archaea, it breaks down into Bacteria, and then breaks down into Eukarya. What Eukarya is is essentially all the fungi, all of everything with like big cells, but then on the other side, or the Archaea, and Bacteria, and they're completely different to different domains of life, they are as different as they are to Bacteria, they're that different, they’re completely different things.

And they were the original microorganisms that showed up. And that's why they can produce different gasses such as methane, that we're now understanding what's the role of these gasses as

well. Traditionally, we considered Archaea, which produce methane to be harmless guys, they're just hanging out, and they don't have much of a role. They're just there. But obviously, that's not true.

Whenever you ignore part of nature, you just get burned at the end. And now we are understanding that most of the time, actually, they are there to help us. But sometimes they can just behave abnormally, and they can cause a problem. So one of the gasses that they produce is methane, they do produce other gasses as well. And what's interesting is that, by itself, methane is active in our body.

There are some gasses in our body that don't have much of a physiologic effect. For example, hydrogen, oxygen is just the gas that goes around, doesn't attach to any receptor, they just cause a little bit of trouble and distension. And then eventually we breathe it out, while methane is different, because it does have physiologic effects.

And if the best example of gasses having physiologic effects, what we call gas, Transmitters, or the ether, right, and all the gasses that we use in anesthesia. Those are just gasses. If you think about it, they just go in and Halothane goes in, and then 20 seconds later, you're unconscious, right?

These are gasses that can have physiological effects, and methane is one of them. And what we have shown is that they can affect the function of smooth muscles. Smooth muscles are the muscles that we don't have control over. We have two types of muscles; we have skeletal muscles in our body that have control over the way that I'm moving my hands, but we have smooth muscles that are in our heart that are in our gut, bladder, uterus, and these we do not have control over, that our body controls. Methane can affect the function of these smooth muscles and the primary site that it affects is the gut.

It leads to spastic contractions of the smooth muscles. The movement of the gut is not as good and that leads obviously to abdominal cramps. And when the bowel is not moving, with it comes dysbiosis. Obviously, the balance of bacteria and also fungi and that becomes a problem and because the bowels are spastic, these spasm are not propagating, they don't let the gut move forward. They are essentially useless contractions as opposed to being coordinated.

This leads to slowing of the bowel transit that leads to constipation very commonly in these patients or the IBS mix, meaning that some days they're constipated. Some days they're on the looser side. They alternate depending on how much gas there is.

Very commonly, they have Irritable Bowel Syndrome (mixed type) or Irritable Bowel Syndrome (constipation) because there's one study actually done by Magnus Simran in Sweden that was presented at Digestive Disease Week that is a very interesting study.

Because previously, Dr. Mark Pimentel did show that if you infuse gut methane gas into the small intestine, it slows down. What they showed is that in over 150 patients and also over 30, healthy controls, those who have elevated methane, they give them the smart pill, which goes in and measures the transit of the gut.

And what they showed is that doesn't matter if you are a healthy control, or even even our IBS patients, if you have excessive amount of methane, your colonic transit is double the time of somebody who doesn't have methane, which is actually very fascinating the data that they're showing, and hopefully they will publish this very soon.

But that was one of the fascinating studies that I saw. I hope that at least differentiates what is Intestinal Methanogen Overgrowth versus Small Intestinal Bacterial Overgrowth.

Another point that I want to make is that this overgrowth can happen in the small bowel and can happen to the colon. It's not necessarily just in the small bowel. And that's a very important point to notice. Sorry, I talked a little bit too long on that one. But there was good data that I can go over as well, but I'll stop there and see what you guys think.

Shivan Sarna: I want to know more, but I also want to ask you about what we were talking about before we hit the record button, which is it's in the small intestine, and it's overgrown also in the large intestine.

You know, when we think about people testing the microbiome, prior to your work with MAST, there were just stool tests. What can we look forward to in the future? And what are you all doing now about mapping the different microbiomes of the intestines?

[12:08]

Dr. Rezaie: Right. Because remember all the tests that we used to do and then not more than 90% of the microbiome tests that are being done still focus on bacteria, right? And just focusing on bacteria, you're not going to pick up the archaea. You need a different technique of deep sequencing to catch them.

Now, obviously, shotgun sequencing is now becoming more prevalent and a little bit cheaper, but it's still extremely expensive. That's fine. A lot of research and research teams, including us, struggle to find funding to do shotgun sequencing, because it's very expensive. I do pick up RKO as well. Maybe I will just open up that one, because it's kind of interesting.

16s sequencing, when we say 16s, that's just a segment of the gene of the bacteria that is very stable throughout the evolution. No matter what bacteria are out there, they have that segment, and it looks like a barcode, and we can look at it and say that, hey, this is in this family, this one is in the E. coli family because you're just looking at a small segment of these bacteria, it's much cheaper to look at and you can quickly do it. The problem is that it's similar to looking at the last names while ignoring the first names, right? If you're looking at all the Smith's out there then it

was like, okay, this person is Smith, but you can't go deep enough, because outside of that 16s. You have to look to say that, Oh, is this John Smith, or Kevin Smith or Martha? Right? You can't go that deep.

When you have this 16s shotgun it's a different shotgun that looks at the whole genome and looks at it like, 'oh, yeah, whatever I get, I look at it.' That's why it's much more expensive, and much more time consuming. And in terms of gathering the data, and also analyzing the data, the supercomputers that we use to break down and analyze these data, we just got them, essentially, in the last few years that are now commercially viable. That's the advantage but when you have the shotgun, you can go all the way not only to the genus, but even to the strain of the bacteria.

That's the difference, but it comes with one issue though. It picks up the genome of everything, including food that you eat, including yourself That there is a lot of noise. It has introduced a new bioinformatics challenge that you have to deal with that data and take that out. But that's just the evolution of medicine that we have to go through.

That's why we are trying to move from 16s to shotgun. But obviously, that's expensive but it's a transition that is occurring. That's the point that I wanted to make about 16 s and deep sequencing, so what's the good news here?

The good news is that when you are doing 16s you mostly pick up the bacteria, you can pick up the fungi, you can pick up viruses, you can pick up some of the archaea, but not all of them. But now that you're doing shotgun there's going to be a host of new data that are focusing on not just bacteria, but also on different parts like fungi and archaea, and more importantly, interaction of these three, along with the viruses. And that will become more complex, but definitely, that's a bigger picture to look at. And that's pretty much the future.

Shivan Sarna: Well, that's exciting. Let's talk about fungus because he brought it up a couple of times. And I know a lot of people in our communities, you know, toy with the idea, maybe they have a candida overgrowth?

You know, I've tried all the usual treatments for Small Intestine Bacterial Overgrowth and Intestinal Methanogenic Overgrowth and I even have a negative Small Intestine Bacterial Overgrowth breath test, and I'm just not getting better. How often do you feel like a fungus plays a role in that? And if someone's like fungus among us, I've never even thought about that. You guys are like 'what is it?'

Dr. Rezaie: Right. The whole concept of fungal growth in the small bowel is not a new one, it goes back more than half a century, in the New England Journal of Medicine, they quantified how much fungi exists in the small bowel and the large bowel.

And amazingly, that kind of still holds. What we showed actually, on this technology is that we went to the small bowel. Now we can pick up the fungi with the new technology, and we did a

deep sequencing on them. And lo and behold, patients who have more than ten of the three fungal elements in this small bowel do have more abdominal pain.

And interesting enough, the more fungi that you have, the more Small Intestine Bacterial Overgrowth you have, it was interesting to see that they do actually interact with each other. Not all Small Intestine Bacterial Overgrowth patients had an excess amount of fungi. But almost all patients with excessive amounts of fungi did have Small Intestine Bacterial Overgrowth on top as well, which is fascinating, which shows what we call microbiome, bacteria interacting at home, which is essentially the interaction of these two, which is definitely interesting.

Now in concordance with the previous data, the dominant fungi in the guts belongs to the Candida family. And I'm talking about plus 90% now Candida albicans, Candida glabrata, those are the two common ones that are in there.

Yes, there is definitely a concept of small intestinal fungal overgrowth existing. There appears not to be much of a correlation with small intestinal fungal overgrowth and the amount of Candida in the stool, which is not surprising considering how much bacteria is in there. And how much interaction is in there; they suppress the fungal growth there. That's the newest sort of approach. That definitely puts SIBO on the map for future research and target for treatments for sure.

Shivan Sarna: Speaking of target for treatment, do you ever see patients where you're like - even if you didn't scope them - “I think you probably have fungal overgrowth” and then do you change the treatment at all?

And what would that indicate to you - that clue - that they may have a fungal overgrowth?

Dr. Rezaie: Yeah, I mean, one of the situations is that, well, the breath test is negative. Remember, fungi don't produce hydrogen or methane or even hydrogen sulfide. I can’t pick them up on a breath test, right?

They produce carbon dioxide, but how am I supposed to pick for carbon dioxide because I'm producing it myself. It's hard to differentiate a microbial co2 from human co2. It's essentially impossible. I generally prefer to do endoscopy and do a small bowel aspirate and do fungal culture and see if the patient has small intestinal fungal overgrowth, because even though it's there, it's definitely less common than Small Intestine Bacterial Overgrowth.

The advantage of aspirate is that it tells me what type of fungus it is, because the treatment and the dose of treatment may be different. For example, Candida albicans and Candida glabrata can go abroad and are more resistant. Definitely, that's my preferred route.

But you have to be practical. Sometimes you have patients that are not responding to a usual SIBO treatment, and other protocols, whatever treatment that you have done regarding abdominal pain and abdominal bloating and distension. And that's the time that we may consider

empiric therapy, although obviously that's an off label therapy. But after reading out the risks and benefits of the treatments that we use,

Shivan Sarna: What are some of those therapies?

Dr. Siebecker: That is what I was going to ask, and specifically, what if you get Candida glabrata? Which is more resistant? What do you find works for that?

Dr. Rezaie: Well that's another interesting thing that you said, because when you have you do grow it. Then you ask the microbiology lab "Okay, can you tell me what this is sensitive to?" And even when they say, for example, "it's sensitive to fluconazole." But then they tell you what is right. For example, if they said the usual dose may not work, you need to double or even triple the dose.

And The microbiology lab is able to tell you 'it's usually fluconazole sensitive' but it needs a higher dose than Candida albicans. And that's not something unknown. We do know that based on the cases of when patients have Candida fungemia when the Candida is in the blood, for example, you suddenly have endocarditis. It's a well known fact that if it's glabrata, you need a higher dose of antifungals to treat.

Shivan Sarna: I know, some people may not realize the scope of conversation that we need to reveal here about how you developed that special scope that doesn't get contaminated. Could you clarify that for everyone, because it's breaking news, really?

Dr. Rezaie: Yeah, absolutely. Let's talk about how we ask for it from the small bowel. You go for endoscopy, you're under anesthesia, we go with the scope through the mouth. In the back of the throat usually there's much saliva there, so we actually aspirate that amount of saliva sitting there if it's too much, and suction it because it can go to your lungs so we don't want the patient to aspirate that.

Then we go into the esophagus. If there is a little bit of a gunk and a little bit of saliva we suction it. And then we go to the stomach. If there is an excessive amount of fluid, again with suction That stuff doesn't come back to your esophagus, go to your lungs, and you aspirate.

That's a complication that can happen with the endoscopy. We counteract that by suctioning whatever we see. This leads to that suction channel of the endoscope becoming totally contaminated. By the time that you get into the small bowel, it has just gone from the throat all the way to the stomach. That suction channel is already contaminated.

If I go with this model, with that suction channel, all that stuff is going to come into that collection tube that I have. And when I send it to a microbiology lab it is going to grow all sorts of things, including respiratory tract bacteria, which is the same as gut microbiome; we do have respiratory microbiome, and that's not abnormal.

If I pick up, for example, some Haemophilus, and also saliva has a lot of bacteria: Porphyromonas, Solobacterium, Haemophilus, Corynebacterium, Cellulosimicrobium, Streptococcus and Campylobacter and all that. It's the native bacteria in the gut. The next round of improvement was okay, let's send a sterile catheter through the channel that has an open tip, and it goes to the small bowel and leads suction with that. The problem is that while you're pushing that catheter in and the tip is open, obviously some of this stuff will go in, so it decreases the amount of contaminate in question, but definitely doesn't eliminate it.

Now the second iteration - and the most revolutionary part - is that now we have two catheters inside of each other, and there is a membrane at the tip. When we go through first, we go through the small bowel. And then when we're in the small bowel, finally the inner tube comes out and advances into the small bowel and starts suctioning and that kind of eliminates the contamination risks.

This was a lot of work. The problem is that when you put too many plastic tubes, which catheters are made out of, on top of each other, they don't move right. You're inside the scope, you have a bent scope, it just doesn't move right; the friction of two plastics on top of each other just doesn't move well. There was a lot of engineering that we went through to make that happen, with different types of material going in each catheter, the inner and outer sheath, to make it able for that catheter to slide through that.

That's how we do the aspiration now to decrease the chance of contamination. And that's why some of the aspiration studies in the past don't correlate well with breath testing, because they're contaminated. So Mayo Clinic, for example, just published a Brian Lacy published paper two years ago that showed that single lumen technique has a 19.6% to 20% false positivity rate.

One fifth of your samples are saliva, so it's not accurate. That will skew your results significantly. This double catheter eliminates that issue.

Shivan Sarna: What are the chances of the double catheter going global? I was talking to a local gastroenterologist here and he said "it'd be so great if I had one of those" you know, it's not mainstream yet.

Dr. Rezaie: The main issue is actually mass producing these very delicate catheters. I'm not gonna promise, but I will have it - unless something goes unusually wrong - available probably in winter 2024.

Shivan Sarna: Oh, that's fantastic. May we have the name of the catheter?

Dr. Rezaie: The catheter, we call it Endo Lotus. Because you know, we call a lotus catheter because the way I designed it at the tip, it has a capillary. The inner catheter has multiple capillary tubes. I was inspired by how trees suck water from the ground all the way to 60 meters high up. Capillaries, they suction and things come up. And the small bowel is a very dry sort of

organ. Interestingly enough, especially after the fasting that you need to do an endoscopy. The inner catheter has multiple capillaries just like the roots of trees, and it goes through and it kind of sucks and wicks that fluid out into the catheter.

That also helps us because sometimes we go in there and it's bone dry, but we can always work out of it. Which this catheter will be able to do so I called it Endo Lotus, because if you cut the roots of a lotus … they're not capillary. It's more like air pockets but that's how it looks like at the tip, like a horizontally cut root of the lotus.

[29:24]

Shivan Sarna: Well that's beautiful, almost like a honeycomb. That's so cool. Exactly. Yes.

Dr. Siebecker: Additionally while you're talking about that and about the disconnect that had existed between culture testing … the gold standard, which now you've significantly improved with this technique, and various forms of breath testing. Can you comment about glucose breath testing versus lactulose? We often see in the studies that glucose can look better in studies, but in practice, we find lactulose works better for many of us. Can you discuss all this and then the culture lineup?

Dr. Rezaie: I can't agree with you more. Obviously, people like glucose, because the idea is that it does not reach the colon. On the other hand, lactulose has a chance of reaching the colon eventually, because it doesn't get absorbed.

You may pick up the colonic fermentation if you continue the test for a long time, so it was just a battle of specificity and sensitivity of these two. One main issue was that a breath test kept being compared to aspiration and aspiration has two issues: Number one, contamination and 20% of the times your gold standard has false positives. I mean, that's essentially a tenuous standard.

The second issue is that aspiration goes and aspirates a 5 to 10 centimeter segment of the small bowel. When we take that sample and try to extrapolate that data to six meters of small bowel, 20 feet of small bowel … that's just naive to think that that's a completely perfect representative sample, right?

It has a false positive rate because of contamination, and it does have a false negative rate because of the sampling error, right? Those are the problems with the aspiration.

Now, you want to compare that to breath testing. Obviously, when you compare, and try to use sensitivity and specificity for a test, a gold standard needs to exist. And well, the gold standard doesn't exist in this situation. It's just an agreement that exists between the two.

If anything, these two tests are complementary, rather than one of them being gold standard and the other one, not. But the reason why is the glucose research field and all, it works, but then

when it comes to the clinic, we're the positive ones. I think it's because when we do it within the clinic, patients are fasting.

I will give you an example. When a patient is hypoglycemic, what do we do? We give them glucose tablets. And right away, within minutes, the glucose goes up, the glucose gets absorbed, starting from the mouth, all throughout, right?

Glucose, when it gets absorbed, obviously, the concentration of that decreases significantly. And that is important, driven by the glucose level of that patient that is doing the glucose testing. And obviously, it's a little bit on the lower side, because they're fasting for 12 hours, or at least eight hours, right? So glucose is continuously being absorbed.

One big problem with glucose is that as it travels through the small bowel, if it reaches there, it significantly decreases in terms of how much glucose is in there. You have no idea, for example, in your genome, how much your glucose is being exposed to the bacteria, which is a problem, if you're looking for hydrogen production, using glucose, right?

That's why, I think, it fails in clinical practice, because the glucose absorption among patients is highly variable, and how much glucose reaches the small bowel and how much of it reaches the jejunum and ileum is going to be highly variable.

In clinical practice, we need to use laterals, and that's the reason why now, if there's a fair criticism to that, that somebody with rapid small bowel transit, then laterals can reach to the colon, and then hydrogen production occurs, and you pick up colonic fermentation as small bowel fermentation, and somebody with ultra rapid small bowel transit.

But there are a couple of things that need to be considered here. The very elegant study was done in 1989 - and we won't be able to do this anymore - they used to give catheters with a weight filled with mercury in them to people; people would swallow it.

And this would travel and they would do X rays on them until they're like, oh, it's in the cecum. Think about it, a catheter sitting in her mouth, it's gonna illuminate and it's full. Well, mercury, if that opens up, like, you know, things that won't happen again. What they did is that they put that into the cecum. And they started putting lactulose in it at a rate of 15 grams per minute.

And they just waited to see how long it would take for the hydrogen to go up in your breath. It takes about 40 minutes for the hydrogen to go up by 20 parts per million in the breath, even when you're just continuously infusing the lactulose into cecum. That just tells you that there is a lag between exposure of the lactulose to the bacteria, even in an area where an amount of bacteria is just sitting there, like the cecum. It takes that much time to produce hydrogen. That's why 40 minutes is there, right? And unless your small bowel transit is like 10 minutes. Think about it. It's 20 feet, right? For something to go through a lumen in 10 minutes, and that lumen is six meters, that’s very fast. Is it possible? Yes, it is possible, but it's rare. You're not going to get

those false positive tests. The thought of false positivity in lectures is a little bit exaggerated. And that's why I just use the actuals in my clinical practice. And then I think you do too, because otherwise, I'm gonna miss a lot of Small Intestine Bacterial Overgrowth patients that otherwise will get to the next doctor and get antidepressants baby, right.

Dr. Siebecker: Okay. I have another question for you, Ali.

Okay. So on one of your studies, there was something that was just, you know, tucked away in there one sentence that came out in Digestive Disease Week that was a bit shocking that I'd love for you to talk about, and that is that you identify lactobacillus as a small intestine microbiome disruptor.

Dr. Rezaie: Yes, it was a surprise to me too. I just wanted to tell you, because, you know, traditionally, we considered lactobacillus as the healthy type, right? So like something that you can find in yogurt, something that you can find all over, right.

The role of, for example, lactobacillus and vaginal microbiome, is it's proven right? But there's a difference between gut microbiome and vaginal microbiome, especially in terms of pH. That's actually a prime example of one bacteria being helpful in one area is not necessarily helpful in other areas as well.

What we saw essentially - and granted, this is an association, meaning that we saw that then lactobacillus was going up the network of bacteria, or breaking - The network of bacteria is sort of like a design, essentially, it looks at interaction of multiple bacteria, and builds a complex network.

And the complexity of the networks is counted, similar to any other network by how many lines, how many dots are there that we call nodes, and how many lines are connecting these nodes together. The complexity of this network significantly improved when it was reduced, improving people who have excessive amounts of lactobacillus, to our surprise.

Now, it is possible that there is somebody else that is decreasing everything, including the network and pushing the lactobacillus up. I don't know. But definitely there was this association that we observed, but that's one thing that we keep, we need to keep a lookout to see if it gets reproduced in future studies.

Dr. Siebecker: Yes, we have so many studies and even patients who do take lactobacillus orally and benefit, not everybody does, but even people with Small Intestine Bacterial Overgrowth. What patients may do when they hear about this is they may go oh, my gosh, I have to stop taking lactobacillus acidophilus.

Dr. Rezaie: I don't think we're there yet. It's just obvious any discovery happens at one point and then needs to be reconfirmed and then further down and remember the lactobacillus family. It's not like a tiny family.

There's a ton of different strains. And I wouldn't be surprised that some of them are helpful, and some of them are harmful. This is not at a point that you would make any clinical recommendation based on, this is just a finding.

Dr. Siebecker: Great, thank you for clarifying that. Another one that was interesting that you found? Well, you've been able to identify Klebsiella as one of the main overgrown bacteria in hydrogen sulfide Small Intestine Bacterial Overgrowth.

And I was fascinated that in one of the studies, you found that even when it was present at sub-Small Intestine Bacterial Overgrowth levels, that it was involved in pathology. And if you would just talk about that, that would be interesting.

Dr. Rezaie: Yeah, absolutely. This goes back to your point about disruptors. There are literally bullies and microbiomes, just like when you have bullies in the school, and so one bully can disrupt the whole school, as opposed to a few calm guys that just behave abnormally. That's essentially the same thing as Klebsiella.

They do have the capability of affecting the fungi, the other bacteria, they produce biofilms. They mess things further up, and others that are even emerging that they can affect the permeability of the gut. Essentially, they can wreak havoc in the small bowel. And on top of it, they produce a lot of transmitters.

Classic production of histamine by Klebsiella is a problem, right? That's one thing. They can even have systemic effects, these bacteria, and that's, obviously, why I was saying that it's exciting times, because now instead of talking about big groups of bacteria, now we're getting focused and focused on focused on different specific disruptors and see that if we can suppress those, would that be enough to regain the microbial balance.

Because think about it, the more tailored and more precision that we have there, we can have more precision medicine therapy for that approach, as opposed to empiric sort of, for example, antibiotic therapy. That's why it makes it very interesting.

And also, it makes it possible that, okay, I found this specific bacteria, let's see what it produces that it can suppress, rather than killing it, to make the balance better. That's obviously another sort of interesting door that it opens.

Dr. Siebecker: Have you been looking into those kinds of treatments?

Dr. Rezaie: Well, no, I think about it this way. There is, for example, histamine, right? That has been produced, so should be a target intraluminal history. That's one pathway, right? Serotonin as being produced by a lot of bacteria, should we target intraluminal serotonin.

Having said that, it is easier said than done. Suppression of intraluminal biomarkers is extremely hard, because no medication is just going to get distributed evenly throughout the guts, right? That's a problem. But those are what are being opened as potential therapeutic pathways.

Dr. Siebecker: Well, on that note of treatment, can you share with us what antibiotics or antibiotic combinations you're currently using for the different types of Small Intestine Bacterial Overgrowth and Intestinal Methanogenic Overgrowth?

[44:05]

Dr. Rezaie: Antibiotic use in practice, and to be pragmatic, is obviously driven by many factors: a patient's patient preference, and obviously testing the results, and also a patient's symptomatology, and - sadly enough - insurance; what gets covered what doesn't get covered, right?

That's real life, right? For treatment of somebody who is treatment naive for Small Intestine Bacterial Overgrowth now don't antibiotics. In the past, I definitely reached for Rifaximin first, which is the safest drug that is out there and it has very little systemic absorption. The safety of it from hepatic encephalopathy IBS trials, is that it's very good.

The problem is cost, right. That's one issue that we have with it. But you know, that's the ideal world right? That's why I reach for other treatments for hydrogen predominant bacterial overgrowth.

I used to use Ciprofloxacin a lot. But the problem with Ciprofloxacin is the black box with the arthritis that can happen. It's rare, but when it happens, that's a problem. And because of that, I do use doxycycline as one of my other options that are used. There is data on metronidazole as well, but you know, metronidazole is not a well tolerated medication; some people get nausea with it but a lot of people do tolerate that. Those are some of the options that I use in terms of Intestinal Methanogenic Overgrowth.

Obviously, we target hydrogen production. The botanicals are not capable of producing methane. And then we target managers themselves. You need some smelting to suppress the hydrogen production, something similar to Rifaximin and then something to suppress management. Neomycin is one option. There were some shortages in Neomycin so we had to switch to Flagyl.

But now Neomycin is becoming more available, which is good news. I like Neomycin because it's, again, poorly absorbable. You know, whenever we can avoid systemic absorption of the antibiotic, I think we should do it for sure. Why? Because that's more of a tailored management. Essentially, my treatment becomes Rifaximin plus Neomycin. If Rifaximin is not an option, then I have tried a super Flagyl as a combination.

I have tried augmenting as well, which is essentially amoxicillin and clavulanic acid together That that does have an effect on both of them. Those are the treatments. When it comes to

hydrogen sulfide. I do try Rifaximin. I do sometimes combine it with Bismuth if the patient is not constipated or doesn't get constipated with this, but some people are sensitive to Bismuth and get really constipated.

But there is data to say that it does suppress the hydrogen sulfide. I just thought that those are very slow because I don't know if some people are very sensitive to Bismuth.

This establishes common disorders of 262 milligrams. I usually try one tablet twice daily and work my way up to see what's working because, you know, I don't want to cause the patient to say "Well, thanks for fixing my diarrhea, but I haven't had a bowel movement for weeks." That's not a good outcome. That's how I approach it. Yeah, that was great.

Dr. Siebecker: It was amazing. Well, of course, a page full all day. Limit it. Okay, there's two more I just really wanted to get to and we may only have time for one.

I know you did a study on artificial sweeteners and I know a lot of our patients are very interested in that. The description was that you took folks who use carbohydrate-based artificial sweeteners. And then versus aspartame, which is non carbohydrate.

Can you tell us anything about it? I mean, I'm a little concerned people are gonna go, "oh, no, I can't use this sweetener" and again, we're not there yet.

Dr. Rezaie: We're definitely not there yet. Remember, they probably have looked at the literature. Artificial sweeteners are kind of under fire in multiple fields in the field of endocrinology and the field of aging and the field of diabetes. But remember, the people who take artificial sweeteners, they're taking it for a reason, right?

Because of that reason, whether it's because of obesity or because of diabetes, or it's because of other medications that they're on. And for that reason, their microbiome is already different, because they're different from the others, right?

That's one thing to look at, because for example, they read like studies that showed that okay, for example, coffee improves mortality. Essentially it has multiple studies that show that in Annals of Internal Medicine. But if you sweeten that coffee with more than a tablespoon of sugar or you use artificial sweetener, does that effect go away?

But the thing is: who puts artificial sugar in their coffee? Somebody who wants to avoid calories, right? Because of that, well, of course, if you compare a diabetic versus a non diabetic patient, the rate of mortality because of heart disease is going to be different, right?

It's not because of that sugar and all the artificial sweeteners specifically, right. But what's interesting is that these studies try to get rid of these confounders as much as they can, but it's never 100%. That's why I think you're not there in terms of saying that, "Oh, no, do not touch any artificial sugars because they cause all sorts of troubles."

At least from the gut microbiome standpoint, these are just hypothesis generating studies and findings that instigates further studies to see whether these are true or not. These are, again, not at the level that we make clinical recommendations.

Shivan Sarna: Thank you Dr. Siebecker for the excellent questions and co-hosting with me. Thank you, Dr. Rezaie, we really appreciate you. Godspeed in your work; we're praying and sending good vibes to everyone over there.

Dr. Siebecker: Thank you so much for all the work you do and all the answers to these questions.

Dr. Rezaie: You're welcome. Anytime.

Shivan Sarna: Oh, good. He said anytime Allison, anytime.

Dr. Siebecker: Can I meet with you after the American College of Gastroenterology meeting in the fall?

Dr. Rezaie: Yeah, sure. Post-Vancouver. All right.

Shivan Sarna: Thank you so much.

Dr. Rezaie: Thank you. Bye