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Exploring Updates in the C. Difficile Treatment Landscape

Dr. Nandi:
Clostridioides difficile, otherwise known as C. difficile infection, is that pesterous bacterium that continues to be a plague in 2023, but fortunately, we have wonderful new updates to share with you on this episode of GI Insights. Welcome to IBD Crosstalk for *GI Insights* on ReachMD. I'm your host, Dr. Neil Nandi. And joining me to discuss the latest updates in 2023 in C. difficile treatment and management is Dr. Monika Fischer. Dr. Fischer is a Professor of Medicine and the director of the IBD program and the stool transplant program at Indiana University.

Dr. Fischer, thanks for joining us today.

Dr. Fischer:
Thank you so much for having me.

Dr. Nandi:
This is a really exciting time, right? And, we have the first microbiome-derived therapeutic for the prevention of C. difficile that's been approved, RBX2660, otherwise known as REBYOTA. So, with stool transplant having been a standard regimen in refractory C. diff, how do you decide where to place this new arsenal or this new tool in the management of C. difficile?

Dr. Fischer:
So, REBYOTA is a great product. It has really excellent results in the clinical trial but we have to remember that it is an enema formulation. And I would decide where physician and this formulation based upon the route of administration that would be the most advantageous for my patient, and how I decide what would be the best route of administration will depend on the following. I would still prefer colonoscopy in patients who are younger, have no clear risk factors for developing C. diff. I want to rule out IBD, they have upper GI dysfunction dysmotility, or patients who have fulminant C. diff infection with ileus, hoping that very soon, we will have capsule formulation on the market. And as probably you can imagine, most patients would prefer capsule formulations simply because of the ease of administration. They don't require sedation. There are no procedure-related complications, and often, they don't need bowel prep or just minimal bowel prep and overall is more cost-effective. And what we have seen so far from clinical trials and cohort studies that colonoscopic and capsule administration were overall a little bit more effective compared to enema administration, and I think simply because there is a significant variability in patients' ability to hold the enema. Having said that I'm very excited REBYOTA is on the market and it is going to be available. Hopefully, insurance will pay for it and we will be able to offer this option to our patients.

Dr. Nandi:
Absolutely. So, let's say you have ruled out IBD. Let's say you have ruled out all these other things. Oral encapsulated is not aesthetically, preferable to the patient nor available. Are there a specific subset who you would be using the enema version?

Dr. Fischer:
I mean, anybody who would prefer that, honestly, but then also we have to consider that the provider's office has to be preferred to offer this option, so they will have need a room dedicated to the procedure. They will have a nurse who will administer the enema, will have to observe the patient, at least for a little while

Dr. Nandi:
You know, there was another tool that we've been using for the right patient which was antitoxin, bezlotoxumab, you know, which has been out on the market for several years, which was also for the prevention of recurrence of C. diff. How do you see bezlotoxumab in conjunction with the enema? You know, our positioning of these therapies is changing in real time. Are there particular patients in whom

you would be using the antitoxin?

Dr. Fischer:
Well, unfortunately, the insurance coverage for bezlotoxumab varied greatly between states. In state of Indiana we were not quite lucky in obtaining insurance coverage, so I don't really have much experience personally, but I know many colleagues of mine at other centers and states have. I think its use will be a bit limited, for reduced now that we have, the availability of REBYOTA. I think it will still have its role in patients who fail FMT or microbiome-based therapeutic products, so right now I still would prefer and want to use it in patients who fail an FMT twice. I think for patients who are very high risk for recurrence of C. diff, such as they had two episodes already within six months, they're immunocompromised, they have underlying IBD, it still will remain a reasonable option, and it certainly can be a concomitant therapy with the microbiome-based therapies.

Dr. Nandi:
And so I think you hit all the, the pertinent things, but probably the most salient is insurance access. You know, we've been able to get bezlotoxumab in my Northeast region, but again, it's about coordinating a timely infusion during antibiotic treatment. So it will be interesting to see, you know, how these therapies play out, in, in the management of C. diff, but it's exciting that we have better options than we have ever before.

Dr. Fischer:
Totally agree. And also, the limitation of bezlotoxumab was that you can only give it once, and you have to be careful in patients who have history of heart failure or have severe underlying cardiovascular disease because it can certainly precipitate heart failure, and it's not cheap, so I'm glad we have newer therapies.

Dr. Nandi:
A hundred percent. For those just tuning in, you're listening to *GI Insights* IBD Crosstalk on ReachMD. I'm Dr. Neil Nandi, and I'm speaking with Dr. Monika Fischer about updates in C. difficile treatment.

Now, Monika, let's talk about a couple of the most pertinent practical details of day-to-day practice that's relevant to GIs, primary care or any specialists with a patient who has C. diff. How are you managing proton pump inhibitors in your practice when it comes to C. diff?

Dr. Fischer:
So, actually, I do not recommend discontinuation as long as the patient has a valid indication for its use, so I really assess all my patients, especially recurrent C. diff, for the appropriateness of their PPI therapy. And if the PPI is unnecessary, then I discontinue, but if they have a valid reason, I continue. And why? Because the association between the increased risk of C. diff and, and PPI really comes from cohort studies, and we all know that there's a lot of heterogeneity, unknown confounders and really lack of dose response relationship in those studies. And even if you look at populations in those studies who have the highest risk of developing C. diff, so those are the hospitalized patients who are on antibiotics, the number needed to harm in these studies is quite high, somewhere between 30 to 50. And the most relevant or highest-quality evidence against discontinuing PPI in patients or worrying about PPI, and the development of C. diff comes from a large randomized controlled trial led by Paul Moayyedi that included 17,000 patients who were either on aspirin or rivaroxaban, and they were randomized to either taking pantoprazole or placebo. They were followed for three years, and at the end there was no significant difference in the incidence of C. diff associated with PPI compared to placebo. So there were only nine cases of C. diff in the PPI group compared to four cases in the control group, so that really convinced me that as long as a patient needs the PPI, I'm not going to worry about it, and I would rather use other methods and treatments to reduce the risk of recurrent C. diff.

Dr. Nandi:
Awesome. You mentioned antibiotics. We know that's a significant risk factor for causing C. diff. What is the role of probiotics? Every year it seems we have new meta-analyses that come out. What is the latest word, Monika, on the role of probiotics in primary or secondary prophylaxis?

Dr. Fischer:
I think finally we have a clear answer. I'd like to believe we do. At least two major society's guidelines, the ACG guideline from 2021 and the AGA guideline both agree that there is really no role for probiotics in the management of C. diff, neither in primary prevention nor in secondary prevention. Actually, these recommendations are based on the highest-quality evidence. ACG actually recommends against the use of probiotics for both primary and secondary prevention of C. diff. And again, the highest quality of evidence really comes from the PLACIDE trial, which was the largest primary prevention trial performed in the UK. We learned on nearly 3,000 patient experience that when they were treated with four-strain combination of certain lactobacilli and bifidobacteria, there was really no difference in antibiotic-associated diarrhea or C. diff development, whether they took probiotics or they took placebo. For another study showing no benefit of probiotics in primary prevention really comes from a more recent multicenter system by US study that implemented

prescribing a three-strain probiotic mixture to all hospitalized patients who were older than 50 and received a systemic antibiotic, and they followed them for 13 months among four hospitals and really found no value in giving them probiotics when they were treated with systemic antibiotics. For secondary prevention, we have the PICO trial, which was a small but very well done randomized trial, again trialing a four-train probiotic compared to placebo and found no difference in the rate of C. diff recurrence.

So, when you look at the highest-quality data of clinical trials, then overall the conclusion is that there is no role for probiotics, and we cannot forget that they are not risk-free. There are many case reports describing infection from probiotics in immunocompromised patients, and there is a small but a very well done study from Israel published in Cell a couple years ago that suggested that actually probiotics may impede normal recolonization following antibiotics compared to autologous FMT, which actually helped or facilitated a normal recolonization. And it's super expensive. I mean, it's estimated that we spend over $40 billion a year in the US on probiotics, right?

Dr. Nandi:
And, and unregulated and, and so—

Dr. Fischer:
Correct.

Dr. Nandi:
Unregulated.

Dr. Fischer:
And, I should have started with that. Totally agree.

Dr. Nandi:
So, Monika, looking to the future, right? Again, this is 2023, some great updates now, are there any new products or therapies on the horizon for C. diff that are not approved yet but in clinical development?

Dr. Fischer:
Yeah, and I'm very excited about at least two. SER-109 is coming. It's an encapsulated formulation of isolated Firmicutes spores, and they showed excellent efficacy, and their ECOSPOR III data showed that patients who had least had two recurrences had 88 percent response rate, meaning that at eight weeks they were C. diff free. And even their follow-up of open-label or ECOSPOR IV study showed higher efficacy, 91 percent of overall response at eight weeks, and patients who were treated after the first recurrence actually had 94 percent response rate. And importantly they followed these patients up to 24 weeks. There was no significant relapse, so the results were durable.

I'm also excited about Vedanta Biosciences' product that's called the VE303. They presented their phase 2 trial data DDW earlier last year, and they showed that they can achieve 86 percent success rate at eight weeks, and this product will be the first rationally selected bacterial strains that are clonal human commensal bacterial flora type bacteria, so we will exactly know what's in there, so that would kind of mimic the idea or perfect probiotic that finally will actually work for C. diff, and we will exactly know what's in there. So, I'm very excited about this.

Dr. Nandi:
It is exciting, Dr. Fischer, that we have so many products. This is a jam-packed, powerful audio session with so much great review of latest literature all thanks to you, Dr. Fischer, so thanks for being a lighthouse of information. Are there any last points you want our audience to take home?

Dr. Fischer:
So I'm hoping that in the future we will be able to use this product earlier in the treatment paradigm, so meaning we can position them earlier, because just extrapolating from the ECOSPOR IV data, so maybe if we can use these capsule formulations, you know, finishing our antibiotic treatment for even the initial or maybe the first recurrence of C. diff, then we can cure everybody 100 percent up front, and we wouldn't have to worry about recurrence.

Dr. Nandi:
And, honestly, I think we're going to get there. Thank you so much, Monika, for being on our program today.

Dr. Fischer:
Thank you. It was lovely to be on your show.

Dr. Nandi:

Absolutely. Any time. For ReachMD's IBD Crosstalk, I'm Dr. Neil Nandi. To access this and other episodes in this series, please visit ReachMD.com/GIInsights where you can be Part of the Knowledge. Thanks for listening.