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Beyond Antibiotics: Treatment Advances for Recurrent CDIs

Announcer:
You're listening to *GI Insights* on ReachMD, and this episode is sponsored by Nestlé Health Science, a leader in the science of nutrition and gut health. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *GI Insights* on ReachMD. I'm Dr. Charles Turck, and joining me to explore the latest treatment advances for recurrent Clostridioides difficile infections, or CDIs for short, is Dr. Paul Feuerstadt. He's an Associate Clinical Professor of Medicine at Yale University School of Medicine and an Attending Gastroenterologist at PACT-Gastroenterology Center. Paul, thanks for being here today.

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

Dr. Turck:
Well, to start us off, what can you tell us about microbiome-based therapeutics and other recent advances for recurrent CDIs?

Dr. Feuerstadt:
We're really at an exciting time right now; in the United States, C. difficile is a major problem. It's estimated that about 365,200 people get diagnosed with C. difficile each year. Huge number. The Centers for Disease Control and Prevention issued a threat level of urgent for this, speaking to the urgency behind this epidemic. One of the biggest challenges with C. difficile, though, is recurrence. Of those individuals that get treated completely correctly with either vancomycin or fidaxomicin, up to 35 percent will recure, and of those that recure, 40 percent will recur, and then 60 percent.

So all in all, shutting down C. difficile and shutting down that cycle of recurrence is really, really important. And there have been major therapeutic advances in the last 5 years in the world of the microbiota space. Essentially, two FDA-approved products that can be given after a standard of care antimicrobial can help shut down that cycle of recurrence.

Dr. Turck:
I was wondering if we could zero in on the similarities and differences between antibiotics and microbiome-based agents. First, how does each work to treat CDIs?

Dr. Feuerstadt:
Essentially, the standard of care antimicrobial—fidaxomicin or vancomycin—suppresses the vegetative phase, and then after you finish that antimicrobial, you supplement the deficiency in the microbiota, thereby minimizing the risk of recurrence. And in the last couple of years, there have been two FDA-approved treatments that supplement these standard of care antimicrobials; they take the form of fecal microbiota spores: live-brpk, which we'll refer to as VOS moving forward, and live-jslm, which we'll refer to as RBL moving forward.

Dr. Turck:
Yeah, I was wondering if we could visit the topic of safety looking at these two approaches: antibiotics and microbiome agents. Are there any common or major adverse effects we should be aware of?

Dr. Feuerstadt:
Safety's a really important factor here, and fidaxomicin and vancomycin are very, very safe. Neither of them are appreciatively absorbed within the system, so they essentially go through our digestive tract like a hollow tube. When we think about the safety of microbiota restoration therapy, I think we need to go back a few years because most people who associate FMT, or fecal microbiota transplant,

don't realize the safety associated with the FDA-approved products.

These FDA-approved products are very, very safe. Now, when we talk about adverse events associated with them, with VOS, it's most commonly distention, fatigue, constipation, chills, and diarrhea. The majority are mild to moderate in nature and were relatively short-lived, less than 2 weeks. Not a reason not to give the product. For RBL, it was abdominal pain, distention, constipation, nausea, as well as loose stools. With this, it was also mild to moderate in nature and short-lived. So again, as we think about these products, there's at least 6 months of safety data for both of these products in controlled trials as well as open-label studies.

Dr. Turck:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Paul Feuerstadt about antibiotics and microbiome-based treatments for recurrent Clostridioides difficile infections, or CDIs.

Now if we zero in on efficacy, Paul, how do these two approaches—antibiotics and microbiome agents—compare?

Dr. Feuerstadt:
So when we think about antimicrobials, it's important to realize that antimicrobials alone leave that deficiency in the microbiota, so when you supplement the microbiota, you drive up the efficacy.

So let's talk a little bit about the randomized control trial associated with VOS. With this trial, termed the ECOSPOR III trial, it was a prospective, double-blinded, randomized, placebo-controlled trial, where the diagnostics included cell cytotoxin neutralization and enzyme-linked immunoassay. So essentially, the patients in this study truly had C. difficile. There really weren't a lot of false positives. Patients received 10 to 21 days of vancomycin or fidaxomicin; they had a washout. A washout period is a period where we actually sit on our hands. We do nothing. That's a period where we allow the vancomycin or fidaxomicin to be moved out of the patient's body through bowel movements. That way, when we administer the microbiota restoration therapy, those antimicrobials are present in less frequency or not at all. And with VOS, we administer magnesium citrate to further wash out the vancomycin and fidaxomicin.

Then, VOS was administered or a placebo as four capsules daily for 3 days. The patients were followed for 8 weeks for recurrence and 24 weeks for safety. Overall efficacy on the VOST arm, at 8 weeks, was 88 percent versus 60 percent in the placebo arm—a statistically significant difference between the two. And at 6 months, efficacy for VOS was 79 percent versus 53 percent in the placebo arm. So patients weren't necessarily just responding for 8 weeks and then getting it again; they were responding in a very sustained fashion with a very consistent response rate.

Now the VOS product has undergone an open-label study as well. That open-label study included patients that were rolled over who had failed within their pivotal phase 3 trial, but also patients that directly entered the study. The patients that directly entered the study had broadened inclusion criteria, including a PCR assay, the most common diagnostic assay used in the United States, as well as first recurrence. First recurrence was not included in the randomized control trial.

Now within this study, 263 patients were included: 29 were rollovers from the phase 3 study, and 234 directly entered the study. 91 percent was the response rate at 8 weeks. Very impressive. And of those, 86 percent remained responsive at 6 months. So overall efficacy was 91 percent and then 86 percent at 6 months. So very consistent with the ECOSPOR III trial, and the safety was very consistent as well with the ECOSPOR III trial.

Now what about RBL? The RBL study was remarkably different. The RBL study was a prospective double-blinded, multicentered, randomized, placebo-controlled trial of patients with first recurrence and beyond. They could be diagnosed with whatever the local investigator decided they wanted to use. Also, the local investigator can decide on the treatment, so there wasn't a fixed treatment period, either. Within this trial, patients received at least 10 days of standard-of-care antimicrobial, the washout period, and then they were randomized to either receive RBL-1s or placebo. They were followed for 8 weeks for recurrence and 24 weeks for safety.

Within this analysis, they did something different. They did what's called a Bayesian analysis: an analysis that leverages data from another study—in this case, the phase 2 study because the same intervention was used, similar patient populations, and same follow-up. Since the consistency of the data in the RBL arm and the placebo arm were consistent across trials, it was truly a Bayesian analysis. The overall efficacy was 70.6 percent for RBL at 8 weeks versus 57.5 percent in the placebo arm. So we see a statistically significant difference with the posterior probability of superiority of 0.991, and that was why this product got FDA approved.

Now this product also has an open-label study that included 697 patients. The open-label study here included patients with IBS, inflammatory bowel disease, among other medical comorbidities trying to mimic the real world. Diagnostics: similar broad, treatment broad. Here, the efficacy within the open-label study was 73.8 percent, and of those that responded initially at 6 months, 91 percent remained responsive. Safety was consistent across the trials, as I alluded to earlier.

So what we're seeing here are really, really exciting products.

Dr. Turck:
Now what can you tell us about the efficacy of treating recurrent CDIs with antibiotics alone versus in combination with microbiome-based therapeutics?

Dr. Feuerstadt:
So therein lies what I was just talking about. That's an excellent question. Essentially, the placebo arms of the trials that I just quoted, the randomized controlled trials, are antimicrobials alone. And we see approximately a 57.5 percent efficacy or 60 percent efficacy in those placebo arms. Essentially, the placebos within those trials receive just standard of care with nothing else. So we understand how the microbiota-based live biotherapeutic products can further supplement the treatment efficacy and improve outcomes for our patients.

Dr. Turck:
Now given everything that we've discussed today, Paul, do you have any closing thoughts on how we can individualize treatment plans incorporating antibiotics and microbiome-based therapies?

Dr. Feuerstadt:
So that's a really important question, which is essentially: "Where does this fit?" "How do I use these products?" The older guidelines from 2021 say that microbiota restoration should be considered second recurrence and beyond, but we know that the VOS open-label study and the RBL studies both included first recurrence. And the American Gastroenterological Association issued guidelines on fecal microbiota transplant and microbiota restoration therapy in February of 2024. When they issued those guidelines, they essentially said that microbiota restoration therapy should be considered in those at greatest risk for recurrence, which fits with the FDA indication for both VOS and RBL. So now the bigger question is, "Well, that's a lot of lingo. What does that mean?" What that means is that first recurrence is absolutely in play for these patients. So the next question is, "Well, who's at risk?"

I like to think about the risk factors for recurrence into three buckets: demographics, medication exposure, and environment. From a demographic standpoint: age over 65, female gender, any form of immune compromise—chronic kidney disease, HIV, inflammatory bowel disease, inflammatory bowel disease on a biological agent, diabetes, medication exposures, those patients that get recurrent urinary tract infections, and those patients that get exposed to antimicrobials, like amoxicillin, ampicillin, clarithromycin, fluoroquinolones, cephalosporins, and piperacillin/tazobactam.

And then environment: people who spend significant amounts of time in the hospital and people who live in skilled nursing facilities have all those other risk factors, but also are surrounded by people that potentially could have C. difficile. So if you think about your patient, you can textualize those risk factors. If they have at least two of those risk factors, they most likely would benefit from microbiota restoration therapy earlier in the treatment algorithm with that first recurrence.

Dr. Turck:
With those final thoughts in mind, I want to thank my guest, Dr. Paul Feuerstadt, for joining me to discuss the use of microbiome-based therapeutics to treat recurrent Clostridioides difficile infections. Paul, it was great having you on the program today.

Dr. Feuerstadt:
Charles, thank you so much for having me. It's been an absolute delight being here.

Announcer:
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