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Exploring New Developments in the Treatment of Recurrent C. Difficile

Dr. Buch:
Since our last discussion on Clostridium difficile, there have been a lot of new therapeutic developments. This is *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. And joining us to discuss these therapies is Dr. Paul Feuerstadt. Dr. Feuerstadt is an Assistant Clinical Professor of Medicine at Yale-New Haven Hospital. He is one of the leading authorities on Clostridium difficile.

Welcome back to the program, Dr. Feuerstadt.

Dr. Feuerstadt:
Thank you so much for having me. I'm excited to be here today.

Dr. Buch:
It's our pleasure. Dr. Feuerstadt, let's start our discussion by asking you why are we so concerned about recurrent Clostridium difficile?

Dr. Feuerstadt:
It's a really important question. C. difficile is a major problem in the United States. It's estimated that about 365,000 people will be diagnosed on an annual basis. And most importantly, of those that are completely normally treated, up to 35 percent will recur, and of those that recur, up to 45 percent will go on to recur, and then up to 60 percent thereafter, as patients get caught in this vicious cycle of recurrence after recurrence after recurrence. And those recurrences don't just mean abdominal pain and diarrhea. There's an impact on the patients psychologically. They have posttraumatic stress disorder for fear that they're going to get it again. Of course, there's a huge burden on the healthcare system. And I also like to think about recurrent C. difficile a little bit like hip fractures in individuals over the age of 65. Now in hip fractures in individuals over the age of 65, we know that their six-month mortality is really high. Well, with recurrent C. difficile, with each episode of C. difficile a patient gets, they're much more likely to result in colectomy or sepsis within 12 months, so there's a lot to this infection and the recurrence of this infection.

Dr. Buch:
And moving to therapeutics, please discuss the data comparing vancomycin versus fidaxomicin for recurrent Clostridium difficile.

Dr. Feuerstadt:
Also, a really important question for us as clinicians to think about, what really is the difference between vancomycin and fidaxomicin? Fidaxomicin is a narrow spectrum antimicrobial. So what does that actually mean? What that means is that fidaxomicin is a sharpshooter. It targets C. difficile and C. difficile alone. It is luminally active, so it isn't absorbed in appreciable amounts in our circulation. So it targets C. difficile, and it minimizes the effects on the microbiota within the colon. The reason that that's important is that antimicrobials treat one phase of C. difficile, the vegetative phase. That's the phase that releases toxins and causes symptoms. This is why when patients are on vancomycin or fidaxomicin their symptoms are well controlled. However, after the antibiotic is pulled off, the spore phase remains within patient systems, and it's the spore phase that needs to be eradicated by a healthy, diverse microbiota. Fidaxomicin preserves the microbiota that's present. How does that translate clinically? That translates clinically into lower rates of recurrences, and we see that within multiple clinical trials.

Of course, the pivotal clinical trial for this Tom Louie published back in 2013 in *The New England Journal of Medicine*. Within that manuscript, they showed when they compared vancomycin versus fidaxomicin head-to-head, initial treatment response was the same. It was about 88.2 percent for fidaxomicin, 85.8 percent for vancomycin. But when they looked at the 25-day recurrence rates, the time frame when most recurrences happen, recurrence rates in the vancomycin arm were 25.3 percent versus 15.4 percent in the fidaxomicin arm. So yes, what we theoretically see with preservation of the microbiota resulting in less rates of recurrence, we see that

in clinical trials, and there have subsequently been three prospective randomized controlled trials that have published similar results. So fidaxomicin continues even 10 years after the original pivotal data was published to be a safe and effective therapy preserving the microbiota and reducing rates of recurrence compared directly to vancomycin.

Dr. Buch:
Thank you. And the big question here for today is this. What should we know about the efficacy and safety of the new therapies for recurrent Clostridium difficile, and how do they compare with fecal transplants?

Dr. Feuerstadt:
The last 12 months have been pivotal in the world of C. difficile infection. Fecal microbiota transplant was essentially, we looked at a donor, we screened the donor, we said, "You're healthy." And then we gave the stool from that donor to an individual who had a disease, such as C. difficile, that we believed helped palliate the disease, and that worked. With C. difficile it was a lock and key effect. We knew the Bacteroidetes and Firmicutes were depleted. We assumed that the healthy donor had an appropriate amount of Bacteroidetes and Firmicutes, and we gave it. LBP is defined by the FDA as being not a vaccine, a biological that is made up of live microorganisms designed to prevent, treat, or cure a disease or condition. So we already see a much more sophisticated definition for LBP versus FMT.

There's a number of important differences between LBPs and FMT. LBPs have much broader donor screening and much less heterogeneity of donor screening. LBPs after donation have quality metrics of the consortium of microorganisms that are present that results in a more predictable efficacy and safety profile. LBPs are produced in a lab, in a much more controlled and safe environment. The data for LBPs are from randomized controlled trials versus mostly open-label or retrospective studies for FMT. And as an adjunct to that, the safety data for LBPs is much more hardy and robust because it comes from randomized controlled trials. So LBPs and FMT are really remarkably different.

In the last 12 months, there have been two FDA-approved live biotherapeutic products. The first is a product called fecal microbiota, live–jslm. We'll refer to it as RBL, and RBL is a single-dose broad consortium of microorganisms that's administered following a standard of care antimicrobial. It is rectally instilled. And what was the data for RBL? And the data for RBL came from something called the PUNCH CD3 trial, a prospective, double-blinded, randomized, placebo-controlled trial of patients with first recurrence and beyond, diagnosed with either the PCR assay or the enzyme-linked immunoassay. They were treated for at least 10 days of standard of care on a microbial, and then followed for eight weeks for recurrence in 24 weeks for safety. The overall efficacy for this product within that trial was 70.6 percent versus 57.5 percent in the placebo arm. Analyzed through a Bayesian analysis, the posterior probability of superiority was .991, and that result was the reason that the FDA chose to approve this product for the indication of prevention of recurrence of C. difficile infection.

As I mentioned earlier, this is a broad consortium of microorganisms. The second FDA-approved product is a product called fecal microbiota spores, live-brpk. We'll refer to it VOS. This product takes a completely different approach. It takes human-donated stool put through an ethanol purification process and just isolates the Firmicutes spores. It encapsulates those spores in four capsules that are administered as four capsules daily for three days, typically after a standard of care and a microbial, as well as a gentle bowel lavage. The study that looked into this was called ECOSPOR III. This was also a multicentered, prospective, double-blinded, randomized, placebo-controlled trial of patients with second recurrence and beyond diagnosed with either cell culture cytotoxin neutralization assay or enzyme-linked immunoassay. All received 10 to 21 days of vancomycin or fidaxomicin. They then had a washout period where they received nothing. Time for the antimicrobial to wash out of the patient's system. Then received a gentle bowel lavage with magnesium citrate and were randomized to either VOS or placebo followed for eight weeks for recurrence, 24 weeks for safety. The overall efficacy for VOS within this trial at eight weeks was 88 percent versus 60 percent in the placebo arm, a statistically significant difference, and that endpoint was the reason that that was approved by the FDA with the indication of prevention of recurrence of C. difficile infection. Neither product had concerning safety signals. The majority of the side effects were gastrointestinal in nature, including distension, flatulence, bloating, slight change in bowel habits. They were mild to moderate, and they largely lasted less than 10 days, so not a reason not to use these products.

Dr. Buch:
And one last question before we move on because some of the physicians out there and other providers may not have heard about bezlotoxumab. Can you comment with regard to that, and what your experience has been?

Dr. Feuerstadt:
Bezlotoxumab is a fascinating concept also. As I mentioned earlier, the standard of care antimicrobials control the vegetative phase. They control the symptoms. Bezlotoxumab and microbiota restoration therapy, they boost our immune system. The microbiota restoration therapy boosts the diversity of the microbiota. Bezlotoxumab boosts our ability to bind the toxin. It is a fully humanized

monoclonal antibody designed to bind toxin B in a specific way. It's a one-time infusion that's given during the standard of care antimicrobial. And within two pivotal trials both published in *The New England Journal of Medicine* in 2017, it showed through MODIFY I and MODIFY II that 90-day recurrence rates in a group that received placebo in addition to the standard of care antimicrobial recurrence rates were 28 percent versus 17 percent with bezlotoxumab or 26 percent for placebo versus 16 percent with the bezlotoxumab. So the number needed to treat from those trials was 10 to reduce one recurrence, but through subgroup analysis it was shown that in an over 65 population, the population that we in clinical practice see most often with C. difficile, the number needed to treat to reduce one recurrence was six with no significant concerning safety signals. So bezlotoxumab is an absolutely viable option as an add-on therapy in addition to the standard of care antimicrobial to reduce recurrence.

Dr. Buch:
Thank you. For those just tuning in, you're listening to *GI Insights* and ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Paul Feuerstadt about new developments in the treatment of recurrent Clostridium difficile.

Now, Dr. Feuerstadt, since we have so many treatments to choose from, how can we work with our patients to provide them with the best option?

Dr. Feuerstadt:
A wonderful question also. I believe that the best therapy is the therapy a patient is willing to take, and we now have a group of therapies that we can offer patients. So standard of care antimicrobial is nonnegotiable. All patients that have C. difficile or recurrent C. difficile will require a standard of care antimicrobial. The question is what form of therapy, if they need it, do we use to prevent future recurrence? And who is at greater risk of recurrence? And I like to think about those risk factors for recurrence into demographics, medication exposures, and environment. Demographic standpoint age over 65, any form of immune compromise. Medication exposures include acid suppressive therapy, specifically proton pump inhibitors, of course antimicrobials, and then the environment. People spend significant amounts of time in the hospital or skilled nursing facilities. Those are your high-risk patients for recurrence. I think it's a matter of sitting down and speaking with our patients about which modality they think would be best for them and what they're willing to do.

Dr. Buch:
And moving on to this question, what are the therapies that are in the pipeline?

Dr. Feuerstadt:
Another important question. So there's a number of therapies in the pipeline right now. There are a couple of early-stage antimicrobials, which I think is beyond the scope of our discussion today. Probably the biggest therapy in the pipeline I see right now is a product called VE303. VE303 is a different approach to microbiota restoration because VE303 is created in the lab. VOS and RBL rely on human donors to donate stool samples, and then it's processed. VE303 does not rely on that, and that's important for a couple of reasons. One is if there's another pandemic, which all of us hope there isn't, we would still be able to produce the product. Second, it costs a lot less money to not have to constantly screen donors. Third, there's more consistency associated with a synthetically produced product. And this is a product that has eight bacterial strains. It's an encapsulated product, and its phase II trial data came out in 2023, and it showed very encouraging results with an overall efficacy at eight weeks in the high-dose arm from the study of 86.2 percent versus 54.5 percent in the placebo arm, so patients receive standard of care, washout, and either high-dose, low-dose, or placebo. The low dose did not achieve statistical significance, so focusing on the high dose that is now ready to proceed to a phase III trial. So I think in the next few years we, hopefully, will be hearing about this product, and hopefully, this product will get FDA approval and will further revolutionize the fields and potentially bring down some of the costs because the cost to produce it theoretically would be much less.

Dr. Buch:
I want to thank my guest, Dr. Paul Feuerstadt, for educating us about this extremely important topic. Dr. Feuerstadt, I really enjoyed our conversation today, and thanks for being here.

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

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights, where you can Be Part of the Knowledge. Thanks for listening, and looking forward to learning with you next time.