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The Gut Microbiome: An Evidence-Based Approach to Managing Recurrent C *difficile* Infection

Announcer:
Welcome to CME on ReachMD. This activity titled: The Gut Microbiome: An Evidence-Based Approach to Managing Recurrent C. Difficile Infection, is provided by Partners for Advancing Clinical Education, and is supported by an educational grant from Ferring Pharmaceuticals Incorporated. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Banty:
I'm pleased to welcome our first speaker, Dr. Colleen Kelly, an Associate Professor of Medicine in the Division of Gastroenterology at Warren Alpert Medical School of Brown University in Providence, Rhode Island. She's here today to discuss the role of gut microbiome in C. diff infection.

Dr. Kelly:
Good morning. Thank you for joining us. I'm Colleen Kelly, coming to you from Providence. We know C. difficile is a bacteria. And its present two forms, there's a spore form; this is the contagious agent. This is generally spread by fecal oral transmission, so these spores are ingested. And then due to some kind of trigger, they begin to grow and develop into a vegetative form. And these vegetative forms will sometimes be triggered to produce a toxin. And there's two different types of toxins; toxin A and toxin B. But these toxins infect the cells of the colon, causing a lot of tissue injury and recruitment of inflammatory cells to the colon and a variety of a spectrum of diarrhea severity.

And the thing that we're going to talk a little about today, as we move on, is how do we treat vegetative forms of C. diff versus preventing infection and preventing reinfection and targeting the spores? We know some people can be asymptomatically colonized with C. diff, and this can be tricky in sorting out do they really have a C. diff infection? And how can we modify our management of these patients to avoid the infection itself and also reinfections?

So, we're going start with C. diff risk factors. And these should be pretty familiar to everybody. We know the large majority of C. diff infections happen after antibiotic exposures, that's one of the major risk factors. But we also see it more in patients over age 65, and certainly in those who've been recently at a home or a nursing home. But it's important to keep in mind that about a third of these cases are now community acquired. And it's scary that I'm actually seeing cases in patients who report no antibiotic exposure and no contact with the healthcare environment. So that can happen. It's also more common in patients who are immunocompromised, and anyone with a previous history of C. diff infection is at risk to develop it again.

Another thing to keep in mind, for those of us that treat inflammatory bowel disease is that C. diff is very commonly implicated in flares presenting with diarrhea. Individuals with IBD, ulcerative colitis, or typically Crohn's colitis, have a nearly fivefold risk of developing C. diff during the course of their lifetime. And in these patients, it's more likely to be community onset, they're likely to be younger and to suffer C. diff recurrences. Also, these patients are more likely to need escalation of their IBD therapies or hospitalization. And if someone's hospitalized with a flare of IBD, and they're found to have C. diff, during that hospitalization, they have four times higher mortality and increased rates of colectomy, compared to those with IBD alone.

So, the first question is, in making an accurate diagnosis of C. diff, it's really important to test the right patient. So, this is very important; C. diff is an acute illness, it's not a chronic diarrhea. So, we talk about an acute onset or recent onset of diarrhea, defined as greater than or equal to three unformed stools in a 24-hour period. We should not be testing asymptomatic patients or those who've taken laxatives, a lot of hospitals will have protocols to not run a test in someone who's recently received a laxative, and it should never be

used as a post-therapy test for cure. This is one of those things that I hope you can take away from this today. We still see it done, people will finish a course of therapy for C. diff, and their doctor will say, 'Let's see if it's gone. Let's do a test.' It's not advisable to test in those scenarios.

And then the next question is what test to use? And unfortunately, there's no way to make this really simple. It tends to confuse people and part of it is you when you get a test report, you need to know what type of test your lab is using. And the three that you're going to see most commonly, number one is the glutamate dehydrogenase. This is an enzyme immunoassay. And what GDH is, it's an enzyme and it's produced by all C. difficile strains. So not all C. difficile strains make toxin. So even non-toxigenic strains will produce GDH. It is a very sensitive assay, so if there is a C. difficile in the person's colon, it will pick up on the GDH assay. However, it is not specific, it is also picking up non-toxigenic strains. So, you'll never see the GDH as a standalone test, but it's a pretty quick, pretty cheap test that labs will use to screen. So, if it's negative, it usually means that C. diff is not there.

Another test is the C. diff PCR. And this is widely used, most hospital laboratories. And what it's testing for is the gene on a C. diff bacteria that makes it capable of producing toxin B. So, it's testing for the presence of a toxigenic strain. Because it's a PCR and it amplifies DNA, it's also very sensitive. But it's also not specific, you can see this positive in up to 5% of people walking around feeling perfectly healthy, because colonized people, even people colonized with a toxigenic strain that's not making toxin, will be positive on this PCR.

And then the third type of test is the toxin A and B enzyme immunoassay. And this actually tests for the presence of a toxin being produced by the organism. So, if you're finding toxin in the stool in a patient with diarrhea, you can be very certain that their symptoms are due to C. diff. So, it's a very specific test. However, the sensitivity is variable. And for those older people in the room like myself, you may remember before the PCR, you had to send two or three of these toxin immunoassays to be sure to get an accurate result. So, sensitivities are in about the 85% range.

But it's really important to remember that no test stands alone and that clinical presentation matters, testing the right people, and really keeping your thinking cap on. So, the IDSA guidelines recommend that PCR-only testing is acceptable, so it can be used as a standalone test.

The ACG, or American College of Gastroenterology guidelines, which I was the chief author, recommend for best accuracy using multistep or algorithmic testing. And I'm going to take you through this approach. So, in this, you would start with a highly sensitive test, be it the GDH or the PCR. If it's negative, the patient doesn't have C. diff, you can stop. If it's positive, you would then proceed to the more specific test, being the enzyme immunoassay for toxin. If that's positive, C. diff is confirmed, and you treat. If it's negative, there are a couple of possibilities. It could be early in the infection and the toxin assay hasn't triggered positive yet, it could be a false negative, or the patient could be colonized and having diarrhea from another etiology. So, you really have to think it through.

The most important thing I want to point out though is if you really suspect the patient has C. diff infection, if they have risk factors, if they have a severe colitis, white count, things that go along with C. diff, you want to treat if you have a high clinical suspicion, regardless of what that testing shows, because we really don't want patients being undertreated.

And then when you're approaching a patient with C. diff, you've got to think of what category of infection this is. As I said, there's a spectrum in the diarrhea severity, and a spectrum in outcomes. So, we divide, similar to the IDSA guidelines, ACG guidelines, divide C. diff into severe, and fulminant. And it's actually pretty easy. The difference between a severe infection and a non-severe infection is the presence of a white blood cell count greater than 15,000 and a serum creatinine 1.5 mg/dL or greater or an increase in their baseline creatinine by 1.5-fold. These are markers of severe infection and increased risk of poor outcomes. And then you have fulminant infection, those patients meet the criteria for pretty severe CDI, but they're also very sick. They're usually in the intensive care unit, hypotensive, they may need pressors, they'll have an ileus and sometimes it's toxic megacolon.

So, another subtype of C. diff is recurrent C. diff. And this is defined as patients will have a good response and get formed stools during treatment. But following a successful course of that anti-C. diff antibiotic therapy, they will recur with diarrhea again, and symptoms very similar to what they presented with previously. This typically occurs within 8 weeks, and about 99% of recurrences happen in that timeframe. And there's a couple of reasons why we see recurrent C. diff. There can be the persistence of these spores in the colon of the patient. Spores are not penetrable by antibiotics. So, they wait it out. And when the patient's done with their vancomycin, they then convert to a vegetative form and start multiplying. Some patients with impaired host immune responses to C. diff will have higher rates of recurrence. There is reinfection from the environment, these spores can live on household surfaces for months. So, I do tell patients who have had a C. diff infection, any bathroom surfaces they used when they were sick, they're going to want to clean those with bleach spray. But one of the bigger and biggest reasons for recurrent C. diff is this concept of decreased microbiome diversity or dysbiosis. And a C. diff recurrence is a big problem. Multiply recurrent infections are up over 200% over a decade.

So, some individual risk factors for C. diff recurrence that might make you think this is likely to happen in your patient, host risk factors, more common in people who are older, who have compromised immunity or chronic renal failure. Also, the severity of the C. diff episode, so patients who have a severe episode are more likely to suffer recurrence than those who've had a non-severe episode. If they have ongoing exposures, like they are living in long-term care, or they keep having antibiotics for chronic UTIs or something like that, that again puts them at risk. And then pathogen-specific factors, there are strain types of C. diff that just seem to be more virulent and more likely to recur. This isn't something you're likely to have access to at the time of care, more for research purposes, but strain type does matter. And one of the biggest risk factors for recurrence is prior C. diff recurrence. So, after you treat an initial episode of C. diff, you've got about a 25% chance that the C. diff is going to recur within 8 weeks. And that's what I tell patients with that first infection. If they've already had a recurrence, and you're treating them again, the chances of it coming back a second time are about 40%. And then if they're in that cycle and they get another course of antibiotics, the likelihood of them having a second recurrence or a third episode is over 50%. And C. difficile patients, and you probably have taken care of people like this, who did fine on vancomycin, but as soon as they finish the course anti-C. diff therapy, they're again very sick within an 8-week period of time.

So, I'm going to hand it over to the moderator again to do this case study.

Dr. Banty:
Thank you. So, our first case study is a 66-year-old woman who presents with several days of severe watery diarrhea and crampy abdominal pain. She has 8 to 10 explosive watery bowel movements a day with incontinence and nocturnal bowel movements. Her history is notable for a recent episode of diverticulitis for which she was hospitalized and treated with Cipro and Flagyl. Stool is positive by both PCR and toxin EIA for C. diff. What risk factors does the patient have for developing C. diff infection? And –

Dr. Kelly:
So, this patient is a recipe for C. diff. She's over 65 years old. She has recently been hospitalized, so contact with a healthcare environment, and treatment with pretty broad-spectrum antibiotics for that episode of diverticulitis.

Dr. Banty:
How do her white blood cells look to you as far as for maybe classifying disease severity?

Dr. Kelly:
Okay, so we remember the difference between non-severe and severe is that white blood cell count of 15,000, hers is 12.5. So, also looking at her creatinine there of 0.84. By both of those criteria, she meets a non-severe infection. So, some key takeaways from what I just told you. The risk factors, advanced age, immunocompromised state, recent stay in a nursing home or a hospital, and antibiotic exposure, modifiable things here, always minimizing antibiotic exposure and being careful in any use of antibiotics, are these really necessary. Variability in testing exists, but it's really important to use your clinical judgment in conjunction with these imperfect tests to determine who really has a C. diff infection and who may have diarrhea from something else and just be colonized with a positive PCR.

We're going to stratify all disease by severity. And when we get into treatment strategy, we'll see how we utilize that. And patients with recurrent C. diff are at very high risk of developing further recurrent episodes. So, the takeaway here, C. diff recurrence is an important problem. And patients with risk factors for recurrence or history of recurrence should be on your radar early.

So, to really understand C. diff treatment and reason for recurrence and how we treat recurrent infection, we really have to understand the role of the gut microbiome and the impact of dysbiosis. So, Microbiome 101 here, just a few definitions. Microbiota, those are the micro-organisms that live in an established environment such as the colon. The microbiome is sometimes used interchangeably with this, but it really is the genetic material or the genes carried by these micro-organisms in that environment. Dysbiosis is a derangement of the normal microbiota. So, altered levels of bacteria or more bacteria there than should be of various subtypes. And then the metabolome, this is the functional properties of these gut microbiota. So, what they're able to do, the proteins they're able to produce or actions they're able to take in the gut.

So, the human gut microbiome is vast and diverse. There's up to 1,000 different species in the average colon. Not just bacteria though; we see viruses, bacteriophages, fungi, archaea. But in general, for most healthy people, it's dominated by four big phyla or broad types of bacteria. This is demonstrated on the graph on the right here, each of those numbers at the bottom of the graph represents an individual patient. But you can see most of them have this abundance of Firmicutes in blue and Bacteroidetes in orange. And these are gram-negative organisms and gram-positive organisms that are capable of producing short-chain fatty acids. And they're all anaerobic, so they like to grow in conditions where there's very little oxygen. Compare that to the little green stripe at the top, those are Proteobacteria. These are things like E. coli, Salmonella, Shigella, we think about these bacteria when we think about the colon, but they're usually present in under 5% of the total bacterial load. They're just easier to grow in culture than the anaerobes. And then Actinobacteria, these are a soil bacteria in gray.

And what happens in recurrent C. diff? We get a couple of things. This dysbiosis, that is defined by altered diversity. So, in a healthy person, lots of diversity, lots of different bacteria present all operating in harmony in that state of health. In patients who have recurrent C. diff and have dysbiosis, the diversity, so the different types of organisms are much lower and there's less of them. And looking to the right here on this slide, you see how a healthy gut looks, each of these stripes being a different patient sample, and you see again, that broad band of blue and green representing the Bacteroidetes and the Firmicutes, those anaerobic organisms, compared to patients with recurrent C. diff, who have big swaths of red, those Proteobacteria, are not supposed to be dominant, but in these recurrent C. diff patients, they are.

The takeaways from this, microbiota are the micro-organisms, the microbiome is the genetic material on the micro-organisms. Gut microbiota has a delicate balance of hundreds of bacteria dominated by Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. And patients with recurrent C. diff have a loss of diversity and abundance of these phyla. And the takeaway from this, maintenance and restoration of the host microbiome is pillar to the recurrent C. diff prevention and treatment. I'm going to get a little bit into the guidelines for treatment now.

So, when you think of treatment, you have to think of what are you at – what phase of the organism are you actually treating. And all the antibiotics that we have are active against that vegetative phase. And we know that ternidazole, vancomycin, and fidaxomicin, those are the three mainstays of C. diff treatment. And the way they differ from each other, number one, cost; metronidazole is about $10 a course, vancomycin about $200 a course, and fidaxomicin is a couple thousand dollars a course, so much more expensive. And fidaxomicin has an advantage of being a little more narrow spectrum, so it targets more C. diff and less of those other beneficial bacteria that we're trying to keep around. Vancomycin is also more widely accessible by patients, and it has less side effects than metronidazole. Metronidazole people will have nausea or a kind of metallic taste in their mouth or can get a neuropathy. And also, there's been an emerging resistance to metronidazole, so you're seeing it used less.

The spore phase, on the other hand, is impenetrable by these antibiotics. So again, the spores are not affected by the antibiotics. And we just need to have a healthy diverse microbiome in place, so that when the antibiotics are stopped, those spores can be prevented from activating and becoming vegetative.

So, the IDSA and ACG guidelines are here. And this is a complicated table with tiny print that you can refer to later. But the main thing to keep in mind is that for our first episode of C. diff, you have recommended to use either fidaxomicin or vancomycin. And the IDSA guidelines favor fidaxomicin because it's more narrow spectrum and it might not set people up for cycles of recurrence. ACG permits the use of metronidazole in select patients. And we know patients who are young, healthy, not a lot of comorbidities, this is the first infection that's non-severe, you can use metronidazole, but you want to be prepared to change it after a couple of days if they're not getting better.

Dr. Banty:
Okay, let's look back at that case. Our patient was treated with a course of fidaxomicin, and her stools became formed within several days. Symptoms of diarrhea returned 11 days later, which she described as the same as before. Stool testing was again positive for C. diff. The second episode was then treated with a 6-week course of vancomycin with a tapering schedule. Stools remained formed while she was taking the vancomycin. Ten days after she finished her last dose, she again experiences diarrhea with the same urgency and crampy pain. The on-call doctor recommends she initiate vancomycin for a presumed third episode of C. diff infection. So, Dr. Kelly, what would you recommend for this patient at this point?

Dr. Kelly:
So, at this point, this is a third episode, a second recurrence, we know that after this vancomycin course, her chances of it coming back were 50/50. And so, at this point, I would offer this patient a fecal microbiota transplant, FMT, or one of the new live microbiota products that are becoming available.

I'm going to go back to that table comparing the IDSA and the ACG treatment recommended guidelines for recurrence. So, for a first recurrence, this is a second episode, the big takeaway is do something different. If they were treated with fidaxomicin for that first episode, then try a vancomycin in this tapered-pulsed regimen. If they already had vancomycin and you haven't used fidaxomicin yet, then fidaxomicin should be your agent. But both guidelines suggest that this is the time to pull out the vancomycin, once someone's had just one recurrence before they get in this cycle of multiple recurrences.

Vancomycin taper-pulse doses, there really is no exact right answer there. People sometimes we'll extend them over weeks and months. I usually try to keep it to 6 weeks, I treat a patient with a 10-day course of four-times-a-day vancomycin 125 mg, and then we will extend it for another 4 weeks. We can either drop it down to twice a day, once a day, every other day, then off; all sometimes to make it easy on the patient to do the 10-day course. And then I'll just say take one dose every third day for the next 4 weeks. The idea with the pulse dosing is those little spores that are waiting out your antibiotic and impervious to it, will start to wake up during the 2 days when they're

not receiving vancomycin, and then you hit them with another dose on day 3. So, that's the logic between these regimens, but there really isn't any, you know, exact right answer in how you do that.

And then as far as adjuvant therapy, again, we're getting to bezlotoxumab here. This is another point where you're going to want to really assess whether or not this patient is appropriate for bezlotoxumab. Again, it's a monoclonal antibody. We recommend it in people who are older, so over 65, who are at high risk of recurrence, so someone who's had a severe infection, who's already had a recurrence. And you want to not use it in people who have a history of CHF or heart failure, there's a warning on that because in clinical trials, there was a higher rate of CHF exacerbation in the patients treated with bezlotoxumab. And you don't have to wait till the first recurrence, you can use bezlotoxumab if after even a first episode you suspect that this patient is at really high risk for recurrence. But again, keep in mind it's only about 10% effective over placebo, so you have to treat 10 patients with bezlotoxumab to prevent one C. diff recurrence.

So back to our guidelines. So, after you've started to get into this multiply recurrent pattern, it's your second or third recurrence, your third or fourth episode, what do you do? Well, both guidelines recommend at this point considering fecal microbiota transplant. It's important to keep in mind this is not a primary treatment, you still have to treat the infection, the urgent and acute episode as it arises. So, if someone calls having diarrhea, it's not immediate fecal transplant; it's 10 days, at least, of another therapy, fidaxomicin or vancomycin, followed by FMT to keep it from coming back.

So, what is FMT? Basically, you're taking fecal material from one healthy donor, containing all of that array of microbiota, putting it into the colon somehow of a recipient who's sick and having recurrences of C. diff. And there's probably a lot of different ways that works, by restoring those short-chain fatty acid-producing anaerobes, you get a more kind of homeostasis of the gut. There's different microbes that actually produce antibiotics, they're called bacteriocins, that may have efficacy against the C. diff. The primary mode of efficacy, though, and we think is related to the role in bile acid metabolism. So, primary bile acids are produced by the liver, they go to the colon, and are converted to secondary bile acids by gut bacteria. Those secondary bile acids actually impair the growth of C. diff, and are resistant to C. diff. But if you don't have those good abundant bacteria and microbiota, you get a buildup of primary bile acids in the colon, and those are actually used in culture media to grow C. diff. So, it's almost as if the colon becomes a culture dish for recurrent infections.

So does FMT work? Absolutely. The first study, this was a landmark study in 2013 *New England Journal*, it was a Dutch study, and they had patients who had at least one recurrence and were at high risk for relapse. They were treated either with a standard course of vancomycin with or without a bowel lavage, or short course of vancomycin to get the infection under control followed by FMT. And the way they delivered it was through a nasoduodenal tube. And the study was actually stopped early because it was so apparently better than the vancomycin standard treatment, in that 81% of these were cured with no relapse after just a single FMT.

In a meta-analysis in 2017 of 37 similar studies, efficacy and clinical resolution of recurrence was seen in 92% of patients treated with FMT. But as we've done more studies and randomized controlled trials, FMT overall efficacy has ranged from 67% to 82% overall.

This is hot off the press. This is the most recent Cochrane Review of only randomized controlled trials, so things with the highest level of evidence, and FMT was found to prevent recurrence. As you see here, the list of trials, mine being one of them, Kelly-2016, FMT was delivered in different ways and different regimens, but for the most part, appeared effective, favoring FMT over control or placebo. And the number needed to treat here to prevent one C. diff was only 3.

Early on, when I first started doing FMT in 2008, I would just ask for a family member or close friend to come in and be screened as a donor. I said, 'Bring in somebody healthy, clean living, and we would do some serologic and stool testing, use that stool.' But as time has gone by, we've found ways to make this much safer for patients and much more convenient for providers. And that's through the use of stool bank. So, stool banks centralize that process of identifying good quality donors and can process the material, shipping it out for use, where it can be stored frozen until it's available - until it's needed. It is less expensive than donor-directed screening, where you're having to order each of these tests on an individual basis, when you can screen one donor and then get multiple stools from that donor and multiple treatment courses. And there have now been consensus guidelines that have best practices for stool banking. So, these people are healthy, no risk factors for disease transmission, no underlying conditions that might be associated with gut microbiota alterations, and they're tested for wide ranges of infectious agents.

FMT, there's different routes of administration. And so, as we talked about, a nasoduodenal tube or nasogastric tube was in that initial study. Patients hate NG tubes, so I don't think that has really caught on much here in the States. Also, I worry about aspiration. So, you're putting a large amount of fecal material into someone's stomach or proximal GI tract, and then vomiting it or aspirating and is bad. So, I don't usually do it this way or recommend that. Retention enemas, this is easy, you don't need a medical doctor degree to do a retention enema. You put the donor material in, and patients hold it in for some period of time. This can be a little tricky. Patients

maybe who are older with some fecal incontinence might not be able to tolerate it, you may need repeated doses for best efficacy. As a gastroenterologist, I've mostly used the colonoscopic approach. So, this has the advantage where you can examine the colon, make sure nothing else is going on, particularly in patients with IBD where you might want to assess that, and then you put the donor stool right through the scope. But more recently, we're seeing the emergence of oral capsules, where they'll put these microbiota into capsule form and administer it to the patient. In some studies, it's looking about equal in terms of efficacy to colonoscopic administration without the procedural cost or risk.

And what are the risks? Really, we're putting a lot of bacteria into somebody, so there are risks of infection. This does appear to be pretty low and pretty rare. But a few were publicized that were pretty scary. In June 2019, two immunocompromised adults who were actually being treated as part of a clinical trial for a non-C. diff indication, they got drug-resistant E. coli infection that came from the donor and one of the died. Right around the emergence of COVID, we saw some E. coli transmission through donor stool from a stool bank. And then when COVID hit, we knew that we were seeing SARS-CoV-2 detected in the human stool, and since there was no - it wasn't clear that it couldn't be transmitted this way, the FDA kind of put a hold on FMT during that time. And then most recently, the monkey pox alert last year, so donors are now tested for that as well.

So, some key takeaways from this, fidaxomicin is preferred over vancomycin once you start getting recurrent episodes. Preventing C. diff recurrence can be done through addressing modifiable risk factors such as antibiotic use that is ongoing. And considering adjuvant therapies; one of those being bezlotoxumab in people after, as they're going through standard of care antibiotics. This is people who have age over 65 and other risk factors like severe infection or immunocompromised. And FMT should be considered in patients after a third episode of C. diff, or a second recurrence. In partnership with patients, healthcare providers should focus on preventing these recurrences when you're thinking about treatment regimens.

We're going to wrap it up with these new and emerging microbiota therapies. Well, FMT is great, but there's problems with it right? It can be difficult to figure out where to get a donor, and the way the FDA has positioned FMT, it's made it a little difficult for some patients to access it. So, we've seen an emergence of these live biotherapeutic products, or LBPs, that are based on this idea of restoring the gut microbiota through replenishing those good bacteria. And these products, it's important to know they aren't for use alone for a C. diff infection; they're adjuvant therapy following a standard-of-care course of antibiotics. So, if I'm going to be going for an FMT, I usually will treat the patient with vancomycin. We do vancomycin for a 10-day course, and then usually take a little break, 2 to 3 days, and then administer FMT. It's before the recurrence has a chance to happen, and it gives time for the vancomycin to wash out of the body. But it works by restoring diversity.

There are a couple of recently approved products I'm going to tell you about, and another that's in phase 3 clinical trials. So, the first one was approved earlier this year, it's fecal microbiota live-jslm, that is the generic name. In clinical trials, it was RBX2660, and its trade name is REBYOTA. Its clinical trials - first of all, it's administered as a rectally administered product. So, it is ordered, shipped to the hospital or to the practice, it is then thawed and can be used, given as a single-dose enema to patients. In the trials, you can see their randomized controlled trials showed 70% resolution of C. diff after treatment is RBX2660 versus 57%, those were patients who just got the standard antibiotics alone. In their open-label study, those who achieved treatment success, which was about 78%, were followed for 6 months, and over 95% of those patients, on average, did not suffer another recurrence. So, it seems to be a long-lasting solution.

The second agent, which has also now been approved and should be available in June, is fecal microbiota spores live-brpk, so that's the generic name. It's in clinical trials SER-109. And you may have seen it advertised as VOWST, that's the trade name. This is a little different. It is sourced from human donors, just like REBYOTA, but the stool is treated with ethanol to kill off a lot of the bacteria and only keep non-C. difficile spores. So, it's a distilled FMT. Those spores are then put into capsule form, and they're given as a dose. It's a 3-day dosing regimen, they take three capsules a day, for 3 days. There is a bowel prep to kind of wash residual vanco out and allow those spores to engraft better. In their clinical trial, ECOSPOR III, they had really high rates of resolution, 88% compared to 60% of people who just went through the course of antibiotics alone. And again, those seemed to be across all subjects, not just those who've had multiple recurrences, but on the right there, even patients who've had a first recurrence, or have a low likelihood of recurring again after receiving a dose of these capsules.

And then the final product, this is entering phase 3 trials right now, so it's not available, but it's VE303. This experimental agent is actually different in that it is bacteria, but they're not sourced from human donors. It's eight species that are grown in culture. And they were chosen because they are thought to be the beneficial bacteria that everyone needs in the colon that are going to prevent the C. diff from coming back. So, in there, they recently published in *JAMA* last month, the results of their phase 2 study. And this looked at high-dose VE303 versus low-dose VE303 versus placebo. And this was an efficacy and dose-finding study, and they showed that 86% of patients who received the high dose, this is a 14-day regimen of 10 capsules a day, achieved cure, compared to those who received placebo. And the low dose was not better than placebo. So, they're going on with a higher-dose regimen for their phase 3, and hopefully that will get done over the next year or so.

So, this is just for your reference to compare these LBPs at a glance, the ones that are currently available, fecal microbiota live-jslm and fecal microbiota spores live-brpk, so one is a directly administered product, the other is a capsule product. The main differences also for the for the REBYOTA product, you do not need to do about purge or a bowel prep; whereas that is recommended that you give some type of a bowel prep, it could be a bottle of magnesium citrate or a couple of glasses of MiraLax, it doesn't have to be the same bowel prep that you would do for a colonoscopy, where it's just like a complete bowel prep, but just something to have them having a bowel movement to wash some of that residual vancomycin out of their system so that it's not impairing the growth of those bacteria that you're trying to get in there. And then the VE303 that is not yet available.

I'm going to actually get into some implementation considerations for fecal microbiota live-jslm. So, it is covered by Medicare Part B and 96% of commercial insurance, so they have good coverage, and you should be able to access this now. And if you look at their website, again, the company – the trade is owned by Ferring, REBYOTA, they can help you out with coupon cards and helping lead you through the process of ordering and using the material. It is handled by specialty pharmacies and distributors and shipped directly to healthcare facilities. And you have to refrigerate it once you get it. You can throw it – it doesn't have to be in a deep freezer, it can be in any refrigerator, where you store vaccines and such and used within 5 days. It's not readily approved by all hospital formularies yet, and there's some question by clinics who might not feel that they're set up for enema administration and they're developing protocols around that, and some are considering using infusion centers instead. I think you should really still have the risk discussion with patients about infection and be cautious in someone who is severe immunocompromised because this is donor stool. And those infectious risks are very similar to just conventional FMT.

Okay, so key takeaways here, these LBPs, this is the next generation of FMT. And they're important because they've undergone FDA, overseen in clinical trials, they're available, they're covered by insurance, and all of that stuff. Antimicrobials will always be needed prior to an LBP, so it's not a primary treatment of the C. diff, it's to prevent an additional recurrence. Fecal microbiota live-jslm and fecal microbiota spores live-brpk are now approved. And the phase 3 trial of VE303 is starting up. But the bootcamp take-away today, the data for LBPs is more regimented than FMT, there is extended follow-up, and closer looking at side effects and microbiome analysis to explain the mechanism of action.

So hopefully, there's some questions here I can answer.

Dr. Banty:
A number of people are asking about what your thoughts are on the use of probiotics or diet to prevent risk of C. diff infection or a recurrence?

Dr. Kelly:
That's a great question. The ACG guidelines don't recommend using probiotics. And we took a really deep dive into this when we were working on the guidelines, because if we're going to recommend things to patients, things that could be expensive, we want to recommend things that work. And the best quality evidence we have shows that probiotics really don't work that well for either prevention of C. diff in the first place; so, this is primary prevention, someone who's getting an antibiotic and you're trying to keep them from getting C. diff, or someone who's already had C. diff, and you're trying to prevent it from occurring again, that's secondary prevention. In neither of those, is it highly effective. There's just a lot of questions that - more questions than answers there. So, I was seeing patients that come in, they might have $100 worth of probiotics that they're taking, I try to redirect them, you ask about diet, I do ask. They're older, they're frail, they're maybe not eating well, if you were trying to encourage the growth of those good bacteria, we want to make sure that they're eating enough high-quality foods. I tend to recommend a fiber supplement. This isn't based on a lot of data, other than that, we know those short-chain fatty acid-producing bacteria love to gobble up dietary fiber. So, sometimes I'll give them the little fiber wafer cookies or gummies. And these also have an ability, besides being a prebiotic and good for the bacteria, they also have a little bit of a binding quality. So, as people are getting over a C. diff infection, and they have that little kind of IBS diarrhea tendency, it tends to regulate the stools a little bit, so I push them more towards fiber than probiotics.

Dr. Banty:
Great. Sheila's wondering if there's a population of patients where FMT is contraindicated, and if some people might need multiple FMTs?

Dr. Kelly:
Yeah, so multiple FMTs. So, about 10% of people who have an FMT will fail, and they'll have another recurrence. So how do I treat FMT failures? One, I take a step back, I say, why did they fail? Did they fail because they're getting treated for recurrent UTIs? And is that a discussion I should have with an ID doctor or their urologist? Or is there any other reason? If that's possible, I tried to address it. If I can access bezlotoxumab, I've been, for FMT failures, giving a dose of bezlotoxumab while they're on their vancomycin, and then followed

up with an FMT. And so far, I'm 100% on that, I've been able to cut off all cycle recurrences with that one-two punch. But again, that has a lot of expense, so I don't go there unless I have to.

Another time where you might need multiple FMTs, using the C. diff in the acute setting – or sorry, using FMT in the acute setting in patients with severe fulminant disease who are hospitalized and approaching either death or colectomy, there is some data for using multiple FMTs in that scenario. Again, that's probably limited at this point to Centers of Excellence or places that have a lot of experience in FMT, but of course, reaching out to one of those centers if you have a patient like that to guide you through if it's something that you're interested in.

Dr. Banty:
Great. Thank you. And thank you, Dr. Kelly, for an amazing presentation.

Dr. Kelly:
Thank you for having me.

Announcer:
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