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Calculating Clostridium Difficile: Diagnostic & Treatment Standards

Dr. Buch:
Clostridium difficile, also called clostridioides, affects 450,000 patients per year in the United States. In addition, 29,000 per year die within 30 days of their diagnosis. Diagnostic and treatment paradigms have changed. This is *GI Insights* on ReachMD. I'm Dr. Peter Buch and joining me, today, is Dr. Paul Feuerstadt. Dr. Feuerstadt is an Assistant Clinical Professor of Medicine at Yale New Haven Hospital. One of his prime areas of research is clostridium difficile. Dr. Feuerstadt has developed a useful resource called "Everything C. diff". Dr. Feuerstadt, welcome to the program.

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

Dr. Buch:
Let's jump right in. What are the risk factors for clostridium difficile development?

Dr. Feuerstadt:
Well, there are a number of different risk factors for clostridium difficile development. I like to think about them into modifiable risk factors and non-modifiable risk factors. Now, the non-modifiable risk factors are risk factors according to our demographics: age over 65, female gender, any form of immune compromise, chronic kidney disease, HIV, inflammatory bowel disease, rheumatologic disease, of course, any distant history of C. difficile infection. The modifiable risk factors include medication exposures, anti-microbials such as amoxicillin ampicillin, clarithromycin, fluroquinolones, cephalosporins, as well as acid-suppressive agents including histamine-blockers, famotidine, or proton-pump inhibitors, very, very large class of medications. And finally, the other modifiable risk factor is the environment. Do the individuals spend significant amounts of time in skilled nursing facilities or in hospital settings where they're surrounded by C. difficile leaving them at risk for this infection.

Dr. Buch:
That's great. Here's a two-part question. What tests do you utilize to diagnose clostridium difficile? And part two, what are the pros and cons of each test?

Dr. Feuerstadt:
That's a really important question that you're asking, and unfortunately, it's embarrassing in 2021 that I don't have a simple answer for you. There are three main tests that we use to diagnose C. difficile. The EIA, or enzyme-linked immunoassay, the GDH or glutamate dehydrogenase assay and finally, the nucleic acid amplification test or PCR. For those of us who've been practicing for more than ten years, we would remember a time when we used to send three consecutive bowel movements to diagnose C. difficile and that was the first generation of the enzyme-linked immunoassay. But that changed in 2009, when the second-generation test, the EIA became available. When that did become available, the, the test changed because we were able to have a higher sensitivity and it didn't require three consecutive bowel movements to diagnose this. Now, this test detects the toxin, itself. Meaning, it detects active C. difficile. Unfortunately, though, it has a moderate specificity. Therefore, as a stand-alone test in 2021, it isn't acceptable. What was added to it to make it a more accurate test is something called the GDH assay or the glutamate dehydrogenase assay. This is an enzyme that is diffusely released by clostridioides species, not specific to C. difficile, but clostridioides species, in general. Therefore, this test has a high negative predictive value. So, if the GDH is negative, it's unlikely that the patient has C. difficile. But if it's positive, there's a chance they have C. difficile. Most commonly, recently is the EIA and the GDH are ordered together. If they're both negative, you're negative, if they're both positive, you're positive, but if they're different or discordant, then we reflex to the PCR. The PCR detects the genes associated with toxin A or toxin B. therefore, the PCR is not detecting active infection, it can also detect somebody who is colonized,

meaning that they have the bacteria in their system, but they don't have active infection. When we use the precursor of the EIA and the GDH, in that situation, the PCR is the clincher. If you're positive, you're positive. However, when the PCR is used on its own, without the other tests, it's essential that we, as clinicians, clinically contextualize what we're sending. Specifically, patients should have three or more liquid stools in a twenty-four-hour period plus their stool should take the shape of the container in the specimen collection kit. If it doesn't, then the patient is probably colonized with C. difficile, however, if it does and the test is positive, then the patient most likely has active C. difficile. So, a long answer to a short question.

Dr. Buch:
How 'bout this one: how do we distinguish recurrent clostridium difficile from post-infectious colitis?

Dr. Feuerstadt:
Well, that's a really important question and I can tell you that I see quite a few patients that come to me with multiply-recurrent C. difficile infection and this is something that comes up all the time. How can we differentiate this? Now, as I just mentioned when we talk about diagnosis, a lot of institutions send off the PCR assay and that PCR assay will actually detect an individual who is colonized with C. difficile, not necessarily producing toxins and therefore, not necessarily having the active infection. Therefore, what we have to do is use our clinical intuition. We have to ask the patients about their baseline bowel habits before they had C. difficile. Then about their bowel habits when they had active C. difficile before antimicrobials and finally their bowel habits, currently. Typically, patients that have active C. difficile will have ten-plus bowel movements a day that are liquid. Patients with post-infection IBS will more likely have about half the number of bowel movements that they had when they had active C. difficile, therefore, about three to five bowel movements a day, plus, patients that have post-infection IBS will be more likely to have semi-formed stool, versus liquid stools. Finally, what are the criteria for IBS? Does the patient meet those criteria, specifically do they have abdominal cramps and do those abdominal cramps get better following a bowel movement or do they worsen following a bowel movement? If that symptomatology fits, the patient most likely has a post-infection irritable bowel syndrome. It's important that we ask the patients about the odor of their stool. If we were to ask a number of nurses who have experience and have been on the floors for a number of years, they can detect the odor of C. difficile when they walk on the unit of a hospital. Well, patients are similar. They know that the odor of their stool changed from their baseline to when they had C. difficile. If patients call and tell us that the C. difficile odor is back, that means it's much more likely that they have active infection. So, by quantifying the frequency of the bowels, the consistency of the bowels, the symptomatology in terms of abdominal pain associated with their bowels, and the odor of their stools, we can relatively easily dissect whether the patient has a post-infection IBS versus C. difficile again. And obviously, the treatments are very, very different for these two disorders.

Dr. Buch:
That's very helpful. I appreciate it. For those just joining us, this is *GI Insights* on ReachMD. I'm Dr. Peter Buch and joining me, today is Dr. Paul Feuerstadt, who is discussing clostridium difficile. Next is: would you comment on vancomycin and fidaxomicin for treatment of clostridium difficile?

Dr. Feuerstadt:
That's a wonderful question and very relevant to 2021 and beyond. Vancomycin is a mainstay therapy for the treatment of C. difficile and believe it or not, over the last 30 years, there've only been two prospective trials that have considered vancomycin head-to-head with metronidazole. The most recent of which, actually wasn't a trial that was designed to look at vancomycin's efficacy, it was designed to look at a product called tolevamer but none of us have heard of tolevamer because it's an ion-binder that did not have excellent efficacy to treat C. difficile. However, within that trial, there were two control groups: metronidazole and vancomycin. And then the study was conducted between 2005 and 2007 and during that time frame, vancomycin was, in fact, superior to metronidazole in treating C. difficile, which is where metronidazole got mostly left by the wayside back in 2017/2018 when the Infectious Disease Society of America issued their most updated guidelines. But the problem with vancomycin is that it's a broader spectrum anti-microbial. Specifically, it treatments C. difficile but it also alters the microbiota. By altering the microbiota, it leaves individuals at risk for recurrence of C. difficile. And in fact, patients who received vancomycin will have a recurrence rate of about 25% with initial infection and of those who recur, 40% will go on to recur after that and 50 to 60% will go on to recur thereafter, leaving patients, and providers for that matter, in this vicious cycle of recurrence and recurrence after recurrence. Fidaxomicin is a different kind of antimicrobial in that it just targets C. difficile. It's a sharpshooter of sorts. By targeting just the C. difficile, it maintains the microbiota that's present and minimizes the so-called collateral damage. By doing that, it's associated with reduced rates of recurrence and that was shown in two landmark studies published in 2011 comparing vancomycin with fidaxomicin head- to-head.

Dr. Buch:
Would you kindly update the audience regarding fecal transplants for clostridium difficile especially in this COVID-19 era?

Dr. Feuerstadt:
Wow, this is a really important question. In March of 2020, when COVID first came about, unfortunately, a lot things changed in all of

our lives. For those of us who treat C. difficile, the option of fecal microbiota transplant or now called microbiota restoration therapy, changed, as well. The stool banks that were providing stool to a lot of providers on a national scale, unfortunately, had to shut down by guidance from the FDA because the stools that were being donated were being donated post-December 1st, 2019. And the FDA required that any stool that was donated after December 1st, 2019 be discarded because it wasn't properly screened for COVID-19 and there was a risk of transmission. Therefore, over the last year or so, a lot of individuals who would've otherwise received fecal transplant or microbiota restoration, have not had access to this. But there is a silver lining. Within the future, hopefully over the next one to two years, we will see an FDA approved form of microbiota restoration therapy and those products were, over the course of the last year, in Phase 2 or Phase 3 trials, so that was available to the general public and now is available to the general public in open-label trials. Plus, as we've adapted, we've started to learn how to screen properly for COVID-19 within the stool and local centers and local stool banks have been able to such as the Mayo Clinic in Rochester, Minnesota.

Dr. Buch:
Where does bezlotoxumab fit into the treatment algorithm?

Dr. Feuerstadt:
Bezlotoxumab was a real important addition to our treatment algorithm for C. difficile that came about in around 2017. With the pivotal trials being conducted just before that. Bezlotoxumab is a fully-humanized monoclonal antibody that binds toxin B specifically, but as a clinician, well, we care somewhat about the mechanism, but how does it work? What it does is it decreases inflammation, and it is a one-time infusion given in addition to a standard of care antimicrobial. So, we give either fidaxomicin or vancomycin and in patients at greater risk for recurrence, we should consider using this. Within the clinical trials, patients that had one, two or three risk factors for recurrence for C. difficile did benefit from this product. In practice, many of us have been using this product for years and have found it to be very helpful in reducing recurrence and breaking that cycle that patients experience where they get C. difficile again and again and again.

Dr. Buch:
I imagine it's particularly helpful, these days, when we can't get access to fecal transplants.

Dr. Feuerstadt:
That's absolutely correct. Remember, the area that fecal microbiota transplantation fits into are patients who've recurred. And in those patients, it's important to understand that they have dysbiosis; they have a depletion of the diversity of their microbiota. I think it's important to take a step back and think about the two goals that we have as clinicians when treating patients with C. difficile. One is to get rid of the bacteria, but two is to make sure that the gut microbiota regrows. With initial infection, that's relatively easy because the gut microbiota is so-called "bent" but not completely broken. Once patients get to that recurrence, their microbiota is broken, therefore, we have to get rid of the C. difficile and if we don't use microbiota restoration therapy, we have to hope that it heals itself with treatment like this bezlotoxumab, this will decrease the likelihood of the C. difficile recurring, allowing the microbiota to restore itself a little bit easier and improving outcomes.

Dr. Buch:
Before we conclude, anything else you would like to share with our audience today?

Dr. Feuerstadt:
Yeah, I think it's really important, I had mentioned this before, that the microbiota restoration therapy space is really at the tip of the iceberg right now. We're about to see a lot of new developments. There are multiple products that finished Phase 2 and Phase 3 trials last year, most notably, a product called RBX2660, which is a full-spectrum microbiota formulation, an enema form of fecal transplant. There's a product called SER-109, which is just Firmicute spores in oral capsule formulation of microbiota restoration therapy and something called CP-101, which is a capsule formulation, as well, that finished a Phase 2 trial, the other products finished Phase 3 trials. Plainly stated, these are products that the FDA will be reviewing most likely in the next 12 months and we might see these broadly available, just like we discussed with bezlotoxumab. The difference between these products and the other data for fecal microbiota transplantation is that the other data for fecal microbiota transplantation were investigator-initiated studies, which were wonderful and showed excellent efficacy but were fairly heterogenous. With that heterogeneity, there was somewhat unpredictable efficacy and somewhat unpredictable safety. With these pharmaceutically-produced products, we have much more codified studies and much more codified safety and efficacy. So, I think over the next twelve to twenty-four months, it's gonna be very exciting to see these products become available to many more clinicians and hopefully we won't be hamstrung like we were with the COVID pandemic, since there will be a much more widely-available product or products for all of our clinicians to use to treat and break the cycle of C. difficile recurrence.

Dr. Buch:
That's all the time we have for today. I wanna thank Dr. Feuerstadt for sharing his insights with us. Dr. Feuerstadt that was a great

discussion today. Thank you so much.

Dr. Feuerstadt:
Thank you, so much for the opportunity. I appreciate it.

Dr. Buch:
For ReachMD, this is Dr. Peter Buch. To access this episode and others from *GI Insights*, visit ReachMD.com/GIInsights, where you can Be Part of the Knowledge. Looking forward to learning with you next time.