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Combating Clostridium Difficile in IBD Patients

Dr. Nandi:
Welcome to *GI Insights* on ReachMD. I'm Dr. Neil Nandi. On today's program, we will be reviewing insights into managing a dastardly difficult intestinal disease. It is none other than Clostridium difficile or C. diff. Indeed, C. diff is at the top of our differential when our Crohn's and ulcerative colitis patients flare. No doubt, you're used to sending off countless stool studies looking for a C. diff. But what do you do and how do you manage that positive immunoassay? Providing insights today on just this topic is none other than Dr. Jessica Allegretti.

Dr. Allegretti is the Associate Professor of Medicine and the Associate Director of the Crohn's and Colitis Center and the Director of the Fecal Microbiota Transplant Program at the Brigham and Women's Hospital in Boston, Massachusetts. Her innovative work in stool transplant was recognized with the Sherman Emerging Leader prize in 2020. We are very delighted to have her on our show. Jessica, welcome to *GI Insights*.

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

DR. Nandi:
We're really excited to get a deep dive into your mind and how you manage and approach C. diff and our IBD patients. And we'd love to learn more about your innovative research as well. Now to start off, can you please tell our audience what is the relative increased risk of C. difficile in IBD patients compared to the non-IBD patient population? How often should we be expecting this to occur?

Dr. Allegretti:
Yeah, absolutely. So our IBD patients are really a vulnerable patient population when it comes to C. diff infection. And so, if you have the non-IBD patient population, by comparison, our patients have at least a 10 percent lifetime risk of getting an infection at least once, which is substantially higher than the general population. And once they have had a C. diff infection, IBD patients are almost five-fold more likely to develop recurrent disease, which really can cause substantial morbidity for these patients. So it really is a risk, which is why whenever your IBD patients are coming in with, presenting with new symptoms, acute diarrhea, and they had been previously doing well, your first thought should always be to check for C. diff.

Dr. Nandi:
Absolutely. And I know that you have spoken on the podium at length about cautioning people about interpreting PCR versus immunoassay for colonization versus active infection. In a nutshell, how would you interpret or how would you caution our community about interpreting those results or when to order which test?

Dr. Allegretti:
Absolutely. In my personal opinion, this is the most difficult part of taking care of patients and diagnosing C. diff. The diagnosis really is, I think, one of those clinical conundrums, because the testing can be quite confusing. And if you're not used to looking at it every day, how to interpret it, I think can be quite tricky. I probably get 10 phone calls a day from my colleagues just about trying to understand C. diff testing. So I think the first thing I would caution any provider to do is know what test you're sending. You know, not all C. diff tests are created equal. And so you should know what you're sending and what that test actually means. And so if you haven't had a conversation with your micro lab ever, you know, talk to them, find out what tests you have available. What the sort of go-to is if you've never asked the question before.

Generally speaking, there are three main tests that you may see in any number of combinations or alone depending on where you are

practicing. And so I'll just walk you through them really quickly, the GDH test or glutamate dehydrogenase test, also called the antigen test-- so those three things all mean the same thing. It is an ELISA-based test that is very sensitive, and it is looking for that enzyme, glutamate dehydrogenase, which is an enzyme produced by all C. diff isolates. It is a first-pass screen; it is telling you are there organisms here. The second test is the toxin test, or the EIA toxin test, also an ELISA-based test, which is actually looking for the presence of toxin, A, B or both. And so the initial concern with this test, older iterations were that it was not very sensitive. And so for those of you practicing a while, you may remember when we used to have to send three consecutive school studies in order to diagnose C. diff. We obviously don't have to do that anymore because the testing characteristics have gotten a lot better.

But because of that initial concern for false negatives, many institutions went to PCR-only testing or PCR confirmatory testing. And this is where we start to get into some trouble because PCR testing can be called many things, PCR, DNA, toxin DNA. And so if you see the word toxin in it, you might think, 'Oh, it's great. It's checking for toxin,' but it is not. It is looking for the genetic material that codes for toxin. And so a PCR alone will not tell you really anything different than the GDH test does. It tells you about the presence of organisms, not about the presence of toxin.

And if there is one take-home point for this, please remember is that having C. diff in you does not cause disease; it's only when these organisms germinate and release toxin that causes the clinical illness. So being colonized is not a pathologic situation. Having presence of toxin is what really is critical here. So you have to understand what you're looking at and how to interpret it. Because if somebody is colonized with active diarrhea, you got to look for another source of their diarrhea.

Dr. Nandi:
Absolutely, indeed. And, you know, case in point, you know, most of us doctors are probably colonized. You know with C. diff, but we're not having active infections. So absolutely right. The difference between colonization and active infection is paramount because it can avoid unnecessary antibiotics. Now speaking of antibiotics, let's say you do have the patient who is, you know, true immunoassay, toxin positive, they have clinical C. diff and you need to treat them, what is your go-to antibiotic between vancomycin, fidaxomicin? When do you use each? And how do you use them in terms of dose and taper or pulsed dose?

Dr. Allegretti:
Absolutely. Thank you for not even listing metronidazole as an option because I would never choose it. I would never choose it, especially not for an IBD patient. And so really, my metronidazole has always fallen out of favor, as per the IDSA guidelines from 2018. And I can tell you, the ACG guidelines from this year should be coming out any minute, and they will mirror that sentiment. And so for me, it's a bit about price and payer. And so I would say I do like to use fidaxomicin, especially in my IBD patients, when possible. You know, if you look at the head-to-head data, it is better at preventing recurrences, especially when used early in the course. Although as many of you know, if you've tried to write for it, it can be prohibitively expensive, depending on the payer. And so it's still not my go-to primarily for that reason. I'm still primarily using vancomycin first line, because I still think vancomycin does still work well, although you get less specificity for C. diff killing, as you get a little bit more destruction of your microbiome, which I don't love. So I will use standard-dose vanco for a first episode.

There is some data from David Rubin's group that even for a primary episode of C. diff in an IBD patient you may have better outcomes if you go out to four weeks. So I would say if the patient was very tenuous, or, you know, they were a lot of other things going on with this IBD patient, I might consider a slightly longer course up to four weeks. Though I would say generally speaking, I'm still doing standard 14-day course of vancomycin, standard dosing.

I'll get on my soapbox here again and say there is never any reason to be using doses higher than 125 milligrams QID of vancomycin, the 250 and the 500-milligram dose have absolutely no utility in outpatient management of this disease. And so if the patient is not responding to standard dose vanco, you have missed the cause of their diarrhea, and you need to look for something else. The answer should never be increase the dose.

But when able, I do like to use fidaxomicin, especially in my IBD patients again, because of the head-to-head data.

Dr. Nandi:
For those just tuning in, you're listening to *GI Insights* on ReachMD. And I'm speaking with Dr. Jessica Allegretti on the management of C. difficile in IBD patients.

Now I know you're doing a very innovative study, the ICON study. Can you kind of give us some insights for our community as to what they can look forward to coming from your research?

Dr. Allegretti:
Absolutely. So the intersection between C. diff and IBD is really a passion of mine. You know, I think this is a really forgotten group of patients, if you will, because C. diff trials exclude IBD patients, and IBD trials exclude those with C. diff. And this is a really challenging

group of patients who are sick and really need help. So really understanding how to best treat these patients is really something I'm very committed to.

I am happy to report that we completed last year the first prospective trial looking at the use of FMT in this patient population. And the reason why this was important is because in multiple retrospective studies, there was a concern that FMT did not work as well as eradicating C. diff in IBD patients. And number two, there were subsequent reports of IBD flares in these patients post FMT. And so the question was being raised are we potentially harming these patients? And so knowing that really we needed prospective data to really answer these questions, we undertook this project. It was four different sites around the U.S. enrolling prospectively, doing a colonoscopic FMT and really systematically following IBD clinical scores, fecal calprotectins, and other markers of disease activity to understand what really happens with these patients.

This study has since been completed and has been published. And what we found was that actually these patients did much better than had been previously reported in retrospective data. We saw less recurrences of C. diff. And we really saw, you know, with a standardized definition, only one patient out of 50, who met the definition of IBD flare, meaning they had a Mayo score increase from 2 to 5 in this trial. Everyone else had either no change in their underlying IBD scores or improvement in their IBD scores.

And so I do feel that we have now shown that this is safe and should be offered in our patients. And as I mentioned, off of the tails of this positive trial, we are now subsequently looking at not only doing FMT in this patient population, but also combining it with bezlotoxumab to see if that not only improves efficacy, but also improves microbial outcomes. So I'm hoping to have that data for you sometime next year.

Dr. Nandi:
Jessica, this is very exciting. What you're doing is very innovative and practical. It's much needed insight, much needed research to get real treatments into the hands of our patients quickly. So I can't thank you enough. We have a lot of exciting developments to look forward to in the coming years from you, I know. Before we close, do you have any last remarks or pointers for our community?

Dr. Allegretti:
I would just say again, you know, the diagnosis is really critical. If you can take away one thing from this, it's really understanding what tests you're sending, how to diagnose these patients, and making sure you're making the correct diagnosis so we're not just putting patients in a C. diff box, and continually throwing more antibiotics at them when they might have something else going on. So understand your testing, look for clinical clues, such as, are they not responding to standard dosing of vanco? That's a clue that there's something else going on. And I know it's frustrating being an FMT practitioner these days, I feel all of you. I would say look forward to hopefully FDA-approved products in the near future. I would say if you're interested in learning more about FMT or how to do things like patient-directed screening, if you're trying to get that going at your center, my colleague Zain Kassam and I did just published a clinical primer on really everything you need to know about FMT, it's called the *6 D's of FMT*, it's available now. So we really wrote it to make it practical and handy for the practicing clinician. And so hopefully you find that useful.

Dr. Nandi:
That's a practical guide right there that you just promoted. And I do encourage our audience to go ahead and check it out. Jessica, thank you so much for joining us on the program and sharing your GI insights with our greater community.

For ReachMD. I'm Dr. Neil Nandi. To access this episode and others from *GI Insights*, please visit ReachMD.com/GIInsights, where you can Be Part of the Knowledge. Thanks for listening.