Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/gi-insights/properly-diagnosing-treating-c-difficile/14239/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Properly Diagnosing & Treating C. Difficile

Dr. Buch:
Evaluation and treatment of C. difficile is rapidly evolving. Welcome to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. Here to update us on C. difficile is returning guest, Dr. Paul Feuerstadt. Dr. Feuerstadt is an Assistant Clinical Professor at Yale New Haven Hospital. He has published extensively on C. difficile infection and has also developed an app called Everything C. diff.

Dr. Feuerstadt, welcome back to the program.

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

Dr. Buch:
To start us off, Dr. Feuerstadt, what is the best way to diagnose C. diff?

Dr. Feuerstadt:
You know, diagnosing C. difficile is so important because if we don't properly diagnose, then we don't properly treat. There's three main tests that we have. We have the EIA, or enzyme-linked immunoassay; the GDH, the glutamate dehydrogenase assay; and the PCR, the polymerase chain reaction. The EIA is the only test that detects a true active infection because it's the only test that is able to detect the toxin that's released by C. difficile, the toxin that stimulates the abdominal pain and diarrhea most commonly associated with it. So now you're saying, "Okay, great. Why don't we just use that test?" The answer to that is that that test has an unacceptably low sensitivity, so if it's positive, you can be confident that the patient is positive for C. difficile and an active infection, but if it's negative, you can't necessarily say that they do not have C. difficile.

And this is where the GDH assay comes in. The GDH assay is an assay that looks for an enzyme that's broadly released by Clostridioides species but not necessarily toxigenic C. difficile, so it has a high negative predictive value. If it's negative, it's incredibly unlikely that a patient has C. difficile. So now putting these two tests together, the EIA and the GDH, if they are both positive, you're positive; if they're both negative, they're negative.

But like many things in medicine, changes and differences in results happen, and frequently, these results will be so-called discordant. So how do we adjudicate those discordant results? That is where the PCR assay can come in in this algorithm. The PCR assay detects the genes that code for the toxin, not the toxin itself, but when it's adjudicating discordant results of EIA and GDH, if it's positive, then the patient is positive, but if the PCR is negative, the patient is negative. Unfortunately though, about 80 percent of all the tests available in the United States to diagnose C. difficile are PCR assays, and the PCR assay needs to be taken within clinical context. A patient should have at least three liquid bowel movements in a 24-hour period, the stools need to take the shape of the specimen container, and a patient shouldn't be on laxatives. If they meet those three criteria and the PCR assay is positive, then you can be confident the patient truly has C. difficile with a PCR being a solitary test.

Dr. Buch:

That's great. And just for further clarification, nuclear amplification tests, can you just explain how that fits in with the algorithm you just talked about?

Dr. Feuerstadt:
So the PCR assay is, in fact, a nuclear amplification test, and the issue with it is it has a tendency to overdiagnose C. difficile. It's estimated that a high percentage of healthcare providers have C. difficile colonized in their system, meaning the bacteria is present but it's not releasing toxin, not causing symptoms. The reason for that is that a healthy microbiota can keep that under control. So if you were to just do a PCR assay on a group of healthcare providers, a significant percentage of them would test positive, but we wouldn't treat those providers because those providers are in a steady state with their microbiota suppressing the infection. So that colonization concept is really important because when we see patients, if we overdiagnose or we over-send PCR assays, then we keep on treating with antimicrobials for C. difficile, and it isn't the C. difficile causing the symptoms.

Dr. Buch:
Thank you for that clarification. So here is one of the key issues I was looking forward to discussing with you. Different medical societies have conflicting guidelines. What's the best initial treatment for this infection?

Dr. Feuerstadt:
Such an important question. The Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, have the most recent guidelines and probably the most rigid methodology. They did a PICO analysis of the data, and the change was significant between the 2017 guidelines and the 2021. Within the new 2021 guidelines for treatment of initial C. difficile infection, there is now a preferred treatment, and that preferred treatment is fidaxomicin 200 milligrams twice daily for 10 days. An acceptable alternative is vancomycin 125 milligrams four times daily for 10 days. And in patients that have no access to either fidaxomicin or vancomycin, have a white cell count less than 15,000, and a creatinine less than 1.5 milligrams per decilitre, we can consider metronidazole 500 milligrams three times daily for 10 days. But as you can see, metronidazole has largely been removed from the recommendations for treatment of initial C. difficile infection.

Dr. Buch:
Thank you so much for that. When identifying patients at risk for recurrent infection of clostridium difficile, are there any reliable prognostic factors to consider?

Dr. Feuerstadt:
The risk factors and prognostic factors associated with recurrence really get grouped into three groups: demographics, medication exposures, and environment. From a demographical standpoint, age over 65. Any form of immune compromise—chronic kidney disease, HIV, inflammatory bowel disease, diabetes—all these factors should be considered. Medication exposures: antimicrobials are obviously the most important player here—amoxicillin, ampicillin, clarithromycin, fluoroquinolones, cephalosporins, piperacillin, tazobactam. But as a gastroenterologist, we also have to think about proton pump inhibitors and histamine blockers also are risk factors. And then finally, where does the patient reside? Are they in a skilled nursing facility surrounded by others who could have C. difficile and surrounded by other individuals who are at high risk for C. difficile that might be transcribing this? And are they also spending significant amounts of time in the hospital? The longer amounts of time in the hospital, obviously, also having other risk factors but also more likely to get exposed.

When we think about prognosis, we think about a white cell count greater than 15,000 or a creatinine greater than 1.5 milligrams per decilitre. Those two factors have very consistently been associated with worsened outcomes, including mortality and colectomy.

Dr. Buch:
Now, Dr. Feuerstadt, can you describe what is meant by the two-pronged approach to C. diff?

Dr. Feuerstadt:
So a two-pronged approach to C. diff is the next generation. We want to shift over from just antimicrobials alone, what I consider to be a little bit like the rotary phone, to the smartphone, the smartphone that does more, that we fully treat the infection. And the smartphone uses standard-of-care antimicrobials, which are non-negotiable. Patients will need either fidaxomicin or vancomycin. But the second prong of that approach is shutting down recurrence, and that takes the form of either bezlotoxumab, a fully humanized monoclonal antibody that's given as a one-time infusion during the standard-of-care antimicrobial or supplementing the deficiencies in the microbiota through microbiota replacement therapy or what is colloquially known as fecal microbiota transplantation.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Paul Feuerstadt about C. diff.

Now looking at future therapies, Dr. Feuerstadt, can you explain what RBX2660, SER-109, and CP101 are?

Dr. Feuerstadt:
You know, such an important question. As I mentioned before, the two-pronged approach uses a standard-of-care antimicrobial but also can use something else, and that something else for the last two decades has been fecal microbiota transplantation, a rudimentary approach essentially stating we take stool from what we perceive to be a healthy person and putting it into somebody who has C. difficile to supplement the deficiencies in the microbiota. A more sophisticated approach is a pharmaceutical approach. A pharmaceutical approach has rigid phase 2 and phase 3 trial data behind it, and eventually, will get an FDA stamp of approval.

The three products that you listed—RBX2660, SER-109, and CP101—are what we call LBPs, or live biotherapeutic products. These are FDA-overseen products, two of which are currently being reviewed by the FDA itself, and these products are forms of fecal transplant but much more sophisticated. RBX2660 is administered as a single rectal administration following a standard-of-care antimicrobial. And it is a broad consortium of microorganisms, so it includes a huge array of microorganisms. SER-109 says, "Do you know what? We don't need to give a huge array of microorganisms. Let's just give what is deficient." The deficiency that we believe is most important for C. difficile are the Bacteroidetes and Firmicutes. Well, SER-109 is an encapsulated formulation of Firmicutes spores. It's administered as four capsules daily for three days following the standard-of-care antimicrobial. And then finally, CP101 is a wide array of microorganisms in an encapsulated form, and it is given as 10 capsules on a single day following a standard-of-care antimicrobial.

Dr. Buch:
Do you recommend prophylaxis against C. diff for your patients?

Dr. Feuerstadt:
So again, a really important question. So patients who get C. diff; they get recurrences. What do we do next? Primary prevention. Most of the studies looking at either antibiotics or probiotics show that there's no benefit. In fact, there's actually probably harm. With regards to prophylaxing patients who have recurred, and you cure them, in the future, there's very nice data to show that if you give a low dose of vancomycin or potentially fidaxomicin with a concomitant antimicrobial, you can reduce future recurrence.

So how do I do that? I typically do that where a patient is cured, they call me, they say, "Look, I have a sinus infection," "I have a urinary tract infection," "I'm going to require this antimicrobial for this amount of time." I then will give a low dose of either vancomycin or fidaxomicin, either vancomycin 125 milligram twice daily for the duration of the other antimicrobial or fidaxomicin 200 milligram once daily for the duration of the other antimicrobial, and that is following the American College of Gastroenterology guidelines that were published in 2021, which made this recommendation, as well.

Dr. Buch:
That's great. Before we conclude, Dr. Feuerstadt, are there any other thoughts you'd like to share with our audience?

Dr. Feuerstadt:
Well, it's been so wonderful being here and discussing this topic. We are at such an exciting point for C. difficile. We are moving from just antimicrobials to antimicrobials and something else, and that something else, yes, can be bezlotoxumab but also can be live biotherapeutic products, hopefully, relatively soon. And the access and the safety associated with this methodology is going to be so much more reassuring for us as clinicians. The future is incredibly bright with regards to our treatment of C. difficile. We are almost there.

Dr. Buch:
This was an excellent review and look into the future of C. difficile therapies. I want to thank my guest, Dr. Paul Feuerstadt, for sharing his insights.

Dr. Feuerstadt, thanks so very much for joining us today.

Dr. Feuerstadt:
Thank you so much for having me. It's been a delight.

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 see you next time.