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The Changing Landscape of *Clostridioides difficile* Infections

Announcer:
Welcome to CME on ReachMD. This activity, entitled "The Changing Landscape of Clostridioides difficile Infections" is provided by Prova Education and is supported by an independent educational grant from Merck.

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Dr. Garey:
Did you know spores of C. diff are ubiquitous? They're all over the place. If you look down at your shoes, one of those two shoes will have C. diff on the bottom of them. So if you're a little lonely watching this webinar by yourself, look down and C. diff will be smiling up at you. Not only that, but given the best treatment today, unfortunately in about 20% of patients, C. diff will come back. Dr. Rao, what do you think?

Dr. Rao:
Yeah, I think that's right. And even just as striking, about 1 in 20 to 1 in 10 patients with C. diff will be admitted to an ICU, have a colectomy, or even die from the disease. And despite this, we lack the tools to identify which patients will have a good outcome and which will have one of these adverse outcomes. Predicting severe outcomes and recurrence is an active area of current research.

Dr. Garey:
Today on Clinical Countdown – The Changing Landscape of C. diff Infection, we're taking a closer look at appropriate personalized treatment plans for patients with and without risk of recurrent C. diff. You ready for this, Krishna?

Dr. Rao:
Yeah, let's do it.

Dr. Garey:
Dr. Rao, please start us off with some nuts and bolts. How do we diagnose this disease state, and how do you assess disease severity?

Dr. Rao:
So the diagnosis of C. difficile infection is made by identifying the appropriate clinical syndrome plus evidence for toxigenic C. diff in the stool. The clinical syndrome can vary. On the more mild end, you have the typical diarrhea – more than three bowel movements of loose stool per day, abdominal pain, as well as sometimes fever. However, on the more severe end, you can have ileus, peritonitis, megacolon, even sepsis. And occasionally, this can be a little bit tricky to diagnose. Sometimes people just come in with some white count elevation or leukocytosis, along with mild abdominal distension and ileus, but this is more rare. Generally speaking, C. difficile infection is not a subtle clinical entity. It's important to recognize severe C. diff as well, including symptoms such as fever and acute kidney injury, as these patients can progress to adverse outcomes, such as ICU admission, colectomy, or death. More fulminant disease can lead to sepsis or even megacolon.

However, it's equally important to distinguish colonization from true symptomatic infection. You know, 15 years ago, we went from

having very poor tests and not much knowledge about C. difficile to now, the situation where our tests are exquisitely sensitive with these PCR-based assays. So now we're actually, I think, swinging in the other direction, where we're often overtreating people and overdiagnosing C. difficile, and actually treating what is colonization, not true symptomatic infection. It's not recommended to do that, and treating colonization may actually not improve outcomes, exposes people to antibiotics needlessly, and may even worsen the shedding of spores and spread of the disease.

So guidelines have shifted to recommending some measures to try and improve your specificity and diagnose true infection versus just colonization. And these measures could be as simple as the lab rejecting formed specimens that are sent to them. It could be implementing multistep testing, where you pair a very sensitive test with a more specific test. Or it could be more innovative techniques, such as electronic health record-based alerts for patients where you're trying to order a C. difficile test but they just got laxatives or they just started tube feeds or they just received oral contrasts – situations where some loose stools may not be unexpected.

Dr. Garey:
Yeah, that's a great overview, thanks. I want to just pick up on one point and expand upon it a bit, and that's the laxatives. So in a hospital, obviously there's a ton of different reasons why you might have diarrhea. One of them is C. diff. And in the most recent version of the IDSA guidelines, they really did harp on make sure you rule out other causes of diarrhea, and specifically, in one of the figures, they really highlight overuse of laxatives or just even use of laxatives causing diarrhea and then testing for C. diff.

Dr. Rao:
Very nice. So, Kevin, I'd like to dive deeper into the management of C. diff in adult patients. Can you walk us through some of the best practices for treating patients? And also, how do the guidelines put up by the IDSA, or Infectious Diseases Society of America, come into play here?

Dr. Garey:
Science has been amazing with C. diff, too. The Human Microbiome Project – the appreciation that C. diff is caused by good bugs in our gut – a healthy microbiome prevents C. diff. So could we invent more narrow-spectrum antibiotics that don't cause the dysbiosis that vancomycin causes, oral vancomycin. And hence fidaxomicin came along, that showed a lower recurrence rate compared to vancomycin. Along with that, Human Microbiome Project came. Why not just restore the microbiome? And that's where fecal microbiotic transplantation came from. Extending that into antimicrobial stewardship, maybe we should just prevent overuse of antibiotics in the first place. It's really been a wonderful merging of science with clinical practice. A better appreciation of our immune system, and how we neutralize the toxins, specifically toxin B, to prevent the disease from coming back by using our own immune system, led to the development of bezlotoxumab, a humanized monoclonal antibody that is specifically designed to prevent recurrence.

Dr. Rao:
Wonderful. I agree with all of that. I would just further underscore that the treatment of recurrence is a special topic and requires some different strategies than the initial infection. So for a first recurrence, if the initial episode was treated with metronidazole, then the recommendation is to use vancomycin. Otherwise, the options are vancomycin taper and a pulse or fidaxomicin. If there is yet another recurrence, so now this is the second recurrence after that first episode, then there is four options, and the guideline promotes all of them equally and doesn't distinguish between them. So you could either do another vancomycin taper and pulse, you could do vancomycin for 10 days followed by rifaximin, you can do fidaxomicin, or the fecal microbiotic transplantation, as you mentioned, Kevin.

Dr. Garey:
Yeah, you know, I think that's great. And you know, with the recurrent and the highlight of recurrence, we've changed our mindset with C. diff. It's not just about stopping that diarrhea anymore. So, it's stopping the diarrhea and preventing recurrence, and then extending that. It might be preventing it in the first place, and I wanted you to comment on that for a few minutes as well.

Dr. Rao:
Yeah, you know, I think preventing the initial episode is really best done by avoiding antibiotic use to begin with. That's the primary thing that causes this dysbiosis state you were mentioning, where the microbiome has been disrupted. However, in many cases, you can't avoid an antibiotic. And so if one must be used – as you mentioned, we're learning a lot more now about how these impact the gut microbiome and how that relates to the pathogenesis of C. difficile. It turns out not all antibiotics are made equal. Some of them, especially the narrow-spectrum antibiotics, are less disruptive. And other ones, the broad-spectrum antibiotics, are quite a bit more disruptive. And it's not surprising that when the research has been done into this, it looks like the broad-spectrum antibiotics, the more disruptive ones, are the ones that carry the highest risk of C. difficile infection.

We also do have a lot of data associating gastric acid suppression with C. diff risk, but this is observational, and we don't yet know if actually holding or reducing gastric acid suppression has a beneficial effect on risk of C. diff. That said, most patients I've encountered on a proton pump inhibitor, for example, don't actually have a good indication to be on one, and there are other adverse health effects

from that class of antibiotics as well, such as increased risk of osteoporosis and pneumonia. So, many times, I end up stopping it anyway.

The other strategy you can take is to prophylax during the other antibiotic treatment, with an antibiotic with activity against C. difficile. So normally, we would think about vancomycin or fidaxomicin here. This hasn't been studied very well. The only one that has some randomized control trial data is fidaxomicin, but that was in a special BMT population. So it's not clear if those trial data are generalized to a more general inpatient or outpatient population.

Bezlotoxumab, which you mentioned earlier, Kevin, is a monoclonal antibody that targets toxin B, and it's a good option. And it does appear to be very effective, with around a 40% reduction in subsequent risk of recurrent C. difficile. But it's very expensive. And people have looked at other, more experimental treatments such as nontoxigenic C. difficile, and looked to see if being colonized with nontoxigenic C. difficile is protective. There are some promising phase 2 clinical trial data, but as of yet, there is no FDA-approved products, and the observational data haven't really been well validated.

Dr. Rao:
Yeah, that's good. That a huge topic, and to summarize it that quickly – nice job, I'll say. I'd like to expand upon maybe one of those issues, I think an important one, and that's prophylaxis. A lot of interest in it, and it makes a lot of sense. We don't want to get to disease state in the first place. But unfortunately, a lot of people use vancomycin, oral vancomycin. So oral vancomycin has potent activity against C. diff; that's great. However, with prophylaxis, you're not killing the bug; you're trying to prevent it from showing up. So oral vancomycin has just as potent activity on most of the other good bugs that live in your gut. It causes a very profound dysbiosis that has been shown to easily help grow and germinate C. diff. It causes enough dysbiosis to cause that. So we're using an agent that has a risk factor for the disease to prophylax the disease. That's a very, very tough one to figure out.

I will actually go back to bezlotoxumab again for a second, Krishna. It doesn't cause any dysbiosis. All it does is neutralize the toxins. You would regrow your microbiome, if something comes along, voila! Bezlo would be there to neutralize the toxins. Not proven, obviously yet. It's proven to prevent recurrence, and I wonder if we could ever stretch that into a primary prevention model. That would require more study.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Kevin Garey, and here with me today is Dr. Krishna Rao. We're discussing the changing landscape of C. diff infection.

Krishna, brace yourself. We're about to start the lightning round. This should be very quick. Succinct question, and then answered within about 30 seconds. So if you're ready…ready, set, go!

Dr. Rao:
All right. So, as I stated above, you know, I think we need better tools to risk stratify patients for adverse outcomes, both for the more fulminant and severe disease, that leads to ICU admission, colectomy, or even death, but also for recurrence. Even though recurrence happens very frequently, it's just very challenging to identify who is going to recur and who is not. And this is important because we need to do this in order to adjudicate treatment decisions effectively and not waste a treatment that's more expensive, more invasive, potentially more experimental, on someone who wouldn't have benefitted from that. But unfortunately – there are many researchers, myself included, working on this problem – but it's yet to be solved.

Dr. Garey:
So, I want to pick up on the prevention of recurrent C. diff aspect in my lightning round. The therapy is exploding. We can neutralize the toxins with bezlotoxumab. We can stop the dysbiosis by choosing a narrow-spectrum antimicrobial, like fidaxomicin. We can augment and restore the microbiome with fecal microbiotic transplantation, and second-generation probiotics, let's call them. How we are actually going to use all of those different treatment strategies, that are all going down very different avenues, is really what we have to come to grapple with from the medical community. Is one enough? When do we choose one or another? And do we start considering combination therapy within this disease state?

Dr. Rao:
Just like many other things this year, C. difficile has also been hit by the COVID epidemic and affected. We've interestingly seen a decline in C. diff, which is not surprising, as many people are staying home and distancing, and to a large degree, C. difficile is a transmissible infection. And in fact, we haven't published these data yet, but my lab has been surveilling patients in the hospital over the last few months, and we've seen our C. difficile asymptomatic colonization rates only at about 4%, whereas in the hospitalized population, you expect double or triple that amount at a minimum. And it might be that people are staying home and not only not getting C. difficile, but not even passing it among each other to the level of asymptomatic colonization.

Dr. Garey:

Well, this has certainly been a fascinating educational conversation. Before we wrap up, Dr. Rao, can you share with our audience your one take-home message?

Dr. Rao:
Sure, I think it's important to remember C. difficile infection is a dangerous disease. It definitely causes a lot of burden to the US healthcare system, lots of morbidity, mortality, readmission. But we have effective treatments when it's recognized and managed early. So being vigilant, recognizing it, and starting treatment immediately is very important. However, overtreating it is also a problem, and that should also be avoided.

Dr. Garey:
Yeah, that's a great take-home message. I guess for me, C. diff is such a multifaceted disease as well. It's a spore that's ubiquitous in the environment that we're trying to prevent getting into a patient – infection control. And then we're trying to limit the antibiotics so that we don't have a dysbiosis that allows that spore to germinate. Now despite those best efforts, we're still going to have patients with C. diff that we're going to have to treat. And knowing that it's correct the dysbiosis or restore the dysbiosis, it's kill the bug with the appropriate antibiotic, as well as thinking about augmenting the immune response. It's that multifaceted approach to C. diff that I think is really going to help us learn how to treat this disease state better.

Dr. Garey:
Unfortunately, that's all the time we have today. I want to thank our audience for listening and thank you, Krishna, for joining the conversation. Your wisdom is always terrific to hear from.

Dr. Rao:
Thanks, Kevin. It was my pleasure, and great to talk with you, too.

Announcer:
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