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## FMT & the Growing Treatment Landscape for IBD

Dr. Kahn:

Advancements in the field of gastroenterology have led to the development of more effective treatment options, such as fecal microbiota transplantation. Could this be the therapy patients with Crohn's disease and ulcerative colitis have been waiting for? Welcome to Crohn's and Colitis Foundation Perspectives on ReachMD. I'm Dr. Stacy Kahn, Director of the Fecal Microbiota Transplantation and Microbial Therapeutics Program as well as an attending physician at Boston Children's Hospital. Joining me today to discuss the role of fecal microbiota transplantation and the changing treatment landscape for IBD patients is Dr. Jessica Allegretti. Dr. Allegretti is the Associate Director of the Crohn's and Colitis Center, Director of the Fecal Microbiota Transplant Program, and an attending gastroenterologist at the Brigham and Women's Hospital in Boston, Massachusetts.

Dr. Allegretti, it's great to have you with us, and before we get started, I just wanted to take a moment to congratulate you on being awarded the 2020 Sherman Emerging Leader Prize for your work related to fecal microbiota transplantation, Clostridioides, and IBD.

Dr. Allegretti:

Thank you so much.

Dr. Kahn:

Now to start off, Dr. Allegretti, can you explain fecal microbiota transplantation, also known as FMT, to our audience? And can you help define it?

Dr. Allegretti:

Absolutely, and thank you so much for having me. I look forward to this discussion. So, fecal microbiota transplantation, which I will refer to as FMT going forward, is literally the installation of minimally manipulated microbial communities from stool of a healthy donor into a patient's GI tract, so that's really how FMT is distinguished from what we would consider defined consortia of microorganisms, otherwise known as a probiotic, you know, defined, microorganisms put into a capsule.

Dr. Kahn:

So given that FMT is regulated by the FDA and considered an investigational therapy, getting it can be pretty complicated. Can you tell us when FMT is recommended and how patients can be evaluated for FMT as a treatment?

Dr. Allegretti:

I think this is a really important question cause, again, given the state of the world, complicated doesn't even begin to describe this process currently. What's important to know about FMT is that it is actually not FDA approved for any indication. I think a common misconception by both, clinicians and patients is that it is FDA approved for the treatment of Clostridioides difficile or C. diff infection, but, in fact, it is not. The FDA holds a policy called enforcement discretion in which they allow us clinicians to use this therapy specifically for C. diff infections not responding to standard of care therapy, without obtaining an investigational new drug license from the FDA, which is a special license you have to apply for any time you're using an experimental therapy, but because this is felt to be really a lifesaving therapy for these patients, the FDA allows us to perform under this policy of enforcement discretion as long as we state that it is investigational and discuss the real and theoretical risks. This is an area that is constantly evolving and, in fact, the FDA is still I would say waiting to finalize their thoughts on this IND or investigational new drug license requirement, so, again, it's a very complex regulatory landscape for this therapy because it's not FDA approved yet. So, my recommendation for patients is if you are suffering with recurrent C. diff infection certainly you want to seek out expertise at a center that offers FMT like mine or Dr. Kahn's and really get consultation with an expert clinician who is familiar with this procedure because, again, navigating this landscape can be quite

tricky.

Dr. Kahn:

With that in mind, what are some of the risks and benefits of FMT?

Dr. Allegretti:

So, I would say, generally speaking, I think we all would agree that FMT is considered a safe and well-tolerated procedure. That being said, it is still, of course, as I just mentioned, an investigational therapy, so per that FDA mandate, we have to discuss the real and theoretical risks with our patients when we're doing good informed consent, and so the things I discuss with my patients are what I would consider the acute concerns – things like transmission of infections, bacterial, viral, or parasitic infections, because, again, we are using human stool that contains bacteria, viruses, fungi, etc. You always have to be concerned about transmission of infection. Now, I can tell you that up until fairly recently, there really had been no infections to date from well-screened material. However, there are a couple of things that I do want to point out that you may have seen in the press or read about. Last year there was a report of two patients who underwent an FMT as part of a clinical trial and unfortunately developed an infection with a multidrug resistant organism after the FMT, and it was later found to be that it was, in fact, from the donor's stool. Now, what I want to highlight about these cases is that this was not done under standard of care for seed of infection. These were done in the setting of clinical trials and what I do think this scenario really emphasizes is the importance of meticulous attention to donor testing and standardization of this process, which I think many of us are, are striving to do and are working towards that goal. The other concerns of note are these long-term concerns. Is it possible that we're predisposing the recipient to a disease that the donor will potentially develop in their lifetime? Remember that most stool donors are young, healthy individuals, and, in fact, they have to be very healthy. However, is it possible that we are transmitting a disease to the recipient that the donor may develop later in life and they haven't developed yet? Now with the NIH is sponsoring a national registry, and we are currently following patients for up to ten years to try to answer a lot of these questions. I can tell you in my own data set, which now is about eight years of follow-up data, we really have not seen any safety signals to suggest this, but I'm glad that the NIH and the AGA really feel strongly about collecting this data, and we will have more answers on this in the future.

Dr. Kahn:

For those just tuning in, you're listening to Crohn's and Colitis Foundation Perspectives on ReachMD. I'm Dr. Stacy Kahn, and today I'm speaking with Dr. Jessica Allegretti about fecal microbiota transplantation, or FMT for short. Now Dr. Allegretti, many of our IBD patients are interested in FMT as a treatment for their IBD. Can you tell us if FMT is safe and effective for patients with Crohn's disease or ulcerative colitis?

Dr. Allegretti:

Absolutely, I'd love to talk about this. So, I think it's, it's not surprising that IBD patients are interested in this therapy. IBD really does seem like the obvious next step with regards to exploration of this therapy after C. diff infection and so there has been a lot of work done in this space. I will always start with the caveat, though, is if you were listening earlier, remember that FMT is not FDA approved for anything, and so we or clinicians cannot offer this therapy to you to treat your inflammatory bowel disease. Currently, it can only be done in the setting of a clinical trial, so if this is something you're interested in, that's certainly where I would start um in speaking to your clinicians about that. With regards to safety and efficacy, there have been four randomized controlled trials looking at the use of FMT specifically to treat ulcerative colitis. Three of those trials were positive with regards to achieving the outcome of interest, which was clinical remission compared to the placebo, and so I do think this is an important first step in highlighting that there may be a subset of patients that do really respond well to this therapy for the treatment of their ulcerative colitis. I think the data on Crohn's disease is still a bit mixed in that we don't have any well done randomized controlled trials yet, so I think it's a bit harder to know where this is gonna pan out specifically for the treatment of Crohn's disease. One other thing I'd like to mention is that there has been a lot of data published on the use of FMT specifically to treat C. diff in IBD patients. Now, our IBD patients disproportionately are affected by C. diff infection, and so it's not surprising that this has been assessed in this patient population quite extensively. Now, there was some initial concern that the FMT might, in fact, be making the IBD worse in this patient population, and we saw many reports of IBD flare rates or IBD worsening in some of these smaller studies, um, so certainly this was an area that I felt was extremely important to investigate. I am happy to report that with support from the Crohn's and Colitis Foundation my group was able to perform a prospective trial where we actually performed FMT in patients with both IBD as well as recurrent C. diff and were able to follow them prospectively to really understand what was going on with their IBD course, and what we found was overwhelmingly patients either had improvement in their IBD disease activity or no change, and we really saw no worsening decompensation of patients' IBD when following it in that systematic way, so I think overall we can safely say that this procedure is safe in patients with IBD.

Dr. Kahn:

That's very good to hear. Are there other related conditions like PSC, or primary sclerosing cholangitis, that might respond to the FMT treatment?

Dr. Allegretti:

Yeah, so PSC is an area that I also became quite interested in because of its link to patients with IBD and it's thought that patients with IBD and PSC, there's certainly a link to this abnormal gut microbiome that we know our patients with IBD have that potentially perpetuates that liver inflammation we see in patients with PSC, and so we had hypothesized that perhaps by doing FMT in this patient population, we might be able to correct that dysbiotic state and improve that liver inflammation and therefore improve the liver tests we see in these patients, so my group performed the first pilot study of FMT in patients with both PSC and inflammatory bowel disease. This was a very small pilot study, so this was only done in ten patients but what we learned from this study is that this therapy was very safe in this patient population, we saw no significant adverse events, and really well tolerated, and we did see, decreases in the alkaline phosphatase of 30 percent of the patients in this study, and for those who aren't familiar, the alkaline phosphatase is one of the labs of interest we follow in patients with PSC, and we saw that in 30 percent of these patients that number decrease by 50 percent after the FMT, so we were certainly very encouraged by this data. I think this is a very small first step in understanding the use of this therapy in a condition like PSC but I think certainly encouraging.

Dr. Kahn:

And our last question for today is: Where is FMT research headed? What is your vision for the future of microbial therapeutics for our IBD patients?

Dr. Allegretti:

I definitely am very excited about the prospect of microbial therapeutics for the treatment of IBD. I certainly envision a future where this mechanism of action is just another mechanism of action that we have in our growing armamentarium of IBD therapeutics to treat our patients. I think the near future, what we're seeing even as of 2020, is there are now at least two companies, um, that have had top-line data that showed significant results in *C. diff* patients, and so I do suspect in the near future we're gonna have FDA-approved microbial therapeutics for the first time that we can use to start to treat our *C. diff* patients, and then certainly we will likely see extrapolation into our IBD patient populations. However, the more exciting part of this area of growth is that we're already seeing companies develop specific microbial therapeutics for IBD patient populations across the board, and so I do imagine that we will not be doing whole-stool FMT in its current iteration in the long term, but in the future we will have precise microbial therapeutics designed for our patients with IBD that we will be able to prescribe just like we can prescribe any of our other IBD therapeutics.

Dr. Kahn:

Well, this has been an extremely valuable discussion about fecal microbiota transplantation as an IBD therapy and an emerging new therapy for IBD. I'd like to thank my guest, Dr. Jessica Allegretti, for joining me today to discuss this treatment approach and provide a glimpse of the road ahead. It was great having you on the program, Dr. Allegretti.

Dr. Allegretti:

Thank you so much for having me. I always love chatting with you, Dr. Kahn.

Dr. Kahn:

Thank you as well.

Announcer:

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