



**Article:**

Eric M Ransom, et al.

*Fecal Microbiota Transplantations: Where Are We, Where Are We Going, and What Is the Role of the Clinical Laboratory?*

Clin Chem 2020 <https://doi.org/10.1093/clinchem/hvaa021>

**Guests:** Dr. Eric Ransom is a clinical and public health microbiology fellow at Washington University in St. Louis. Dr. Andrew Reinink is a physician and researcher at the University of Minnesota--Minneapolis VA Medical Center.

Bob Barrett:

This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Fecal microbiota transplantation is a medical procedure by which intestinal microorganisms are transferred to a patient as a therapeutic. These procedures are most commonly used for medically refractory or recurrent infections of *C. difficile* that usually develop after broad-spectrum antibiotic usage that disrupts the normal intestinal microbiota, creating a niche permissive for *C. difficile* to flourish and cause toxin-mediated illness. However, questions remain regarding the effectiveness, safety, regulatory oversight, and best practices in fecal microbiota transplantation.

A Q&A feature appearing in the April 2020 issue of *Clinical Chemistry* examined these very questions. Five experts with different roles in the field including infectious diseases, laboratory medicine, industry, and public health shared their thoughts on this important topic. Dr. Eric Ransom was a co-moderator of that Q&A feature. He is a clinical and public health microbiology fellow at Washington University in St. Louis, Missouri. He is joined in this podcast by one of the expert panelists, Dr. Andrew Reinink, a physician and researcher at the University of Minnesota, Minneapolis VA Medical Center, and we'll start with you, Dr. Reinink. What are fecal microbiota transplantations and under what circumstances are they considered for therapy?

Dr. Andrew Reinink: Your listeners have probably heard of *C. diff*, or what's more formally called *Clostridium difficile*. This microbe can infect the bowel and cause a range of symptoms from diarrhea to life-threatening conditions like toxic megacolon. A *C. diff* infection can usually be treated with oral antibiotics; unfortunately, this approach doesn't work for everyone. Fecal microbiota transplantation is an alternative method for treating *C. difficile* infections. Right now, the only current indication for fecal microbiota transplantation, or FMT, is to treat or prevent recurrences of *C. diff*. But there are three specific *C. diff* scenarios where FMT is used. They are fulminant *C. diff* where there is severe, worsening colitis that doesn't respond at all to antibiotics; there's refractory

C. diff where symptoms don't resolve despite adequate antibiotic therapy; and recurrent C. diff, C.diff that initially responds to antibiotics, but recurs within a short period, usually less than three months after antibiotics are stopped. FMT is, right now, the accepted treatment following an antibiotic course for the second recurrence of C. diff, although many physicians use it after a first recurrence. At this point, FMT should not be used as first-line treatment of a routine non-recurrent C difficile infection because the majority of these patients are able to reconstitute their colon microbiome without FMT.

Bob Barrett: There must be some risks with these procedures. What are those risks and how can they be mitigated?

Dr. Andrew Reinink: The risks of FMT are primarily first, the documented risk of transmitting a pathogen to the recipient, and secondly, the more theoretical risk that some other undesirable trait that's mediated in part through the microbiota will be transferred, such as susceptibility to an autoimmune disease. These risks are mitigated primarily through comprehensive donor screening and restricting FMTs to only indicated cases. Donor material, stool donations, are also selected and screened quite carefully for patient safety. You may have heard, there's been two FDA safety alerts in the last year regarding documented transmission of pathogens. The first was an ESBL producing E.Coli in two patients in June 2019 in the setting of the clinical trial; the second Enteropathogenic E. coli and Shiga toxin-producing E.Coli in March of this year. We also have to talk about COVID. On March 23, the FDA advised to only use stool collected before December 1st of 2019, until comprehensive donor screening and stool testing for COVID as well as informed consent changes can be implemented.

Bob Barrett: Okay. Well, Dr. Ransom, let's bring you in here now. How are donors for fecal microbiota implantation selected and screened?

Dr. Eric Ransom: It's a great question. This actually changed quite a bit over the years. Believe or not, donors were initially selected based pretty much solely on their physical proximity to the patient. The logic here was to find somebody with the most similar intestinal microbiome, somebody eating the same foods and having at least somewhat of the same lifestyle. Now this largely resulted in spouses, close relatives, and a roommate being the donor. Now, while this still occurs from time to time, the field has largely moved away from this and towards commercial suppliers, or what we call fecal banks, somewhat similar to a blood bank. Regarding the screening, there is no official or nationalized screening process. So it's highly variable across the different institutions. With that being said, a lot of programs do kind of track some similar

things. For example, donors undergo health and lifestyle screenings to make sure things like HIV and hepatitis won't be transmitted during the transplant. Some programs do have a little bit more aggressive screenings. They may exclude somebody for recent antibiotic use or somebody with a history of GI conditions or even somebody with an abnormal body mass index. Now that's for the donor. The actual material itself is also screened. This varies by institution, but what we're normally looking for is to exclude any pathogens like Salmonella and Campylobacter or even C. diff. You certainly wouldn't want to transplant somebody with the organism you're trying to get rid of.

- Bob Barrett: That makes perfect sense. Does the clinical microbiology laboratory play a role in this process and if so, what is that role, how?
- Dr. Eric Ransom: Yeah. This really depends on the institution and how they're getting their donor material. A few centers are still mixing and preparing their own donor material for transplant and for those facilities, the micro lab is still heavily involved in product preparation and in the screening process, but this is becoming less and less common all the time with the rise of these commercially available products through fecal banks. Nowadays, most local laboratories are not involved at all or maybe will do some minor screening just prior to transplant.
- Bob Barrett: Is there any regulatory oversight of these procedures, and are those regulations effective?
- Dr. Eric Ransom: Yeah. This is actually pretty fascinating. The FDA oversees this product because they view it as a drug. What is interesting, though, is that unlike most drugs, there's no standard formulation or known composition of the microbes. So, because of this, it's made FDA approval quite challenging and nothing is actually been approved to date but given that there's so much clinical evidence and the effectiveness of fecal transplants and there's this huge unmet need in the field, the FDA has decided to apply what they call enforcement discretion. So for now, investigators use investigational new drugs or INDs. This is a way for the FDA to track individual cases and to generate some monitoring data for the hopes of in the future coming in and actually approving a product.
- Bob Barrett: Okay. Well, Dr. Reinink, we'll give you the last word on this. How do you see fecal microbiota transplantations evolving over the next five or even 10 years?
- Dr. Andrew Reinink: That's a great question. You've seen tremendous change over the last 10 years. It will be fascinating to see where the field goes over the next 10. For C difficile, there's great interest in what's known as synthetic FMT with defined

microbial consortia. That's a set of specific strains of bugs that can be replicated where each dose is the same and not containing the entire breadth of the fecal microbiome, just the few strains that we think modulate the protective effects or therapeutic effects in *C. diff*. The first trials of this approach though haven't succeeded. The upside of this is it would mitigate many of the current risks of FMTs since there's a lot fewer unknowns as far as number of strings, number of traits that might be passed through, but since FMT still is a little bit of a black box, it's going to be really tough to get the right strings in there. And that's what a lot of companies, a lot of researchers are working on right now.

Another frontier is personalization, matching the specific microbial or metabolomics profile the donor to the needs of a recipient. Maybe one person is recurring because they don't have adequate conversion of bile acid and secondary bile acids, maybe another one has different metabolites than the microbiota supplies that isn't in their native microbiome. So the vision is that maybe we'll have a series of defined microbial consortia that we could pick based on what the needs of the patient are. There's also a vast amount of research going on right now for FMT and other methods of microbial supplementation and manipulation for other conditions that might be mediated through or caused by or triggered by the gut microbiome. It's not entirely clear whether this is going to be through FMT or more narrowly targeted approaches. The areas of active research include inflammatory bowel disease, irritable bowel syndrome, and liver disease including non-alcoholic fatty liver disease, hepatic encephalopathy. There are also ongoing trials for even some neuropsychiatric conditions including autism. So it's going to be interesting to see how this field evolves.

Bob Barrett:

That was Dr. Andrew Reinink. He is a physician and researcher at the University of Minnesota--Minneapolis VA Medical Center. He was joined by Dr. Eric Ransom from Washington University in St. Louis, Missouri. They are two of the participants in the Q&A feature in the April 2020 issue of *Clinical Chemistry* on fecal microbiota transplantation. I'm Bob Barrett. Thanks for listening.