# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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## Fecal Microbiota Transplantation for the Treatment of Inflammatory Bowel Disease

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**G&H** What is the role of the intestinal microbiome in inflammatory bowel disease?

**DR** For many years, it has been believed that the gut's organisms were somehow involved in inflammatory bowel disease (IBD). Throughout our history of looking for a cause of IBD, there have been repeated attempts to identify a specific organism or infection as the instigator. Even in the absence of identifying specific organisms, trials of administering broad-spectrum antibiotics to patients, under the assumption that there might be an organism driving the disease, have failed.

Nevertheless, there remains interesting indirect evidence that organisms may be involved in what causes IBD, both in the recent observations that patients with IBD have an imbalance in their gut flora, as well as the indirect evidence that, after surgery, patients with Crohn's disease benefit in the short term from antibiotics that prevent recurrence.

Now that improved tools are available to study the organisms that live in the bowel, there is great interest for new studies that will help us understand whether the gut microbiome will elucidate the causes of IBD or else simply tell us more about the effects of the disease processes on that ecosystem.

**G&H** When was fecal microbiota transplantation first used in IBD?

**DR** The idea that the ecosystem of organisms in the gut is imbalanced in IBD and that fixing that imbalance might in fact treat or even cure IBD is not new. There is a report of a physician who treated himself with fecal slurries delivered by enema in the 1950s. There are also case reports, primarily from the late 1980s and 1990s, that suggest some benefits with the use of fecal microbiota transplantation (FMT). However, most of the research in this area has occurred in the past 3 to 4 years, when physicians and physician-scientists have been more systematic in their attempts to use FMT as a treatment for ulcerative colitis and Crohn's disease. This research was, in large part, spurred by the understanding of FMT as an effective treatment for recurrent *Clostridium difficile* infection, which was becoming a significant health burden and a significant cause of morbidity and mortality.

**G&H** What have studies found thus far regarding the use of FMT for the treatment of Crohn's disease and ulcerative colitis?

**DR** The initial published experiences of FMT in ulcerative colitis were limited by being open-label cohort studies, primarily of sick patients who were failing medical therapies. Only more recently have placebo-controlled studies been performed. There have been 2 placebo-controlled studies, one from Amsterdam and one from Canada. Findings from the former study were negative, and findings from the latter study were initially reported as negative, but after a larger number of patients were included, actually demonstrated a statistically significant benefit for remission in the group receiving FMT compared with the group receiving placebo (water enema).

However, all of the trials have been limited because of their use of different types of patients (some being very sick and having failed many therapies vs some being less sick), delivery mechanisms (such as enema, colonoscopy, or nasogastric/nasoduodenal delivery), preparations, and posttransplant follow-up. Therefore, comparison of these trials in order to obtain a signal and understand where researchers might go forward with this information has been difficult.

Having said this, one of my postdoctoral students and I recently published a meta-analysis of the available FMT trials in ulcerative colitis and Crohn's disease. In the available studies, there does seem to be a group of patients who respond to this treatment strategy; it just is not clear whether these patients have a durable response. There are still many unanswered questions.

### G&H Which patients with IBD appear to respond to FMT?

**DR** In theory, and based on observation, it would seem likely that the patients who respond to FMT would have milder disease and a shorter disease duration. Likewise, it would seem likely that the patients who are failing all therapies, including corticosteroid-based therapies, are the ones who are least likely to respond to this treatment strategy. However, no one has yet done a good job stratifying these groups of patients. To test this hypothesis, my colleagues at the University of Chicago and I examined mild to moderate ulcerative colitis patients (ie, patients who were not very sick). Unfortunately, thus far our preliminary review of the results does not seem to support this hypothesis. Therefore, it is still unclear which patients would benefit most from FMT.

It may be that we are looking at this question the wrong way. Perhaps we should be assessing the microbiome of patients so that we can predict who is most likely to respond to therapy based on the types of organisms living in their bowel or based on a biomarker that we do not yet have. Ultimately, that is the direction in which most researchers think FMT should go—not just remaining a therapy in which stool is taken from a healthy donor and put into a patient's sick colon. Perhaps we should be doing a better job stratifying people by the types of organisms living in their bowel or the types of immune reactions that they have, and then performing more of a targeted modification of their gut microbiome.

### G&H How effective is FMT for the treatment of *C difficile* infection in patients with IBD?

**DR** This is an interesting question. FMT is known to work well in the treatment of recurrent *C difficile* infection in the non-IBD population, so it would be reasonable to think that this therapy also works well in the treatment of *C difficile* infection in IBD patients. Prior research from the Mayo Clinic and an abstract presented at this year's Digestive Disease Week have suggested that FMT has the same efficacy in eradicating *C difficile* infection in IBD patients as it does in non-IBD patients. However, it is important to keep in mind that these findings do not mean that FMT treats the IBD in these patients as well.

### G&H Are there any safety concerns associated with this treatment option?

**DR** Most patients who undergo FMT experience a short-term fever and mild elevation in their inflammatory markers when first receiving the treatment. However, these side effects do not seem to limit FMT's ability to treat these patients nor do they seem to discourage patients from going forward with treatment.

In addition, there have been reports—and my colleagues and I have seen such cases in our own experiences—that IBD patients become worse when receiving FMT; this treatment may cause unknown longer-term downstream effects in some patients. Therefore, there has been some interest in determining whether FMT is exposing patients to as-of-yet unknown immune proteins and other problems in the bowel that might cause new immune phenomena in the transplanted patients. It is important to remember that FMT is not just about transplanting the bacteria from one person's bowel to another person's bowel; this procedure includes transplanting all of the viruses, fungi, and proteins that are in a person's stool into another person.

### G&H Are there any regulatory challenges associated with FMT?

**DR** In the United States, the US Food and Drug Administration (FDA) regulates FMT through its vaccine and blood product division because the treatment is viewed as a biological substance. This decision is reasonable because stool actually is a biological substance. Because the safety of this procedure is still not fully understood, I think that it is also reasonable to require that an investigational new drug (IND) application be obtained from the FDA to study FMT in any condition other than recurrent *C difficile* infection. FMT is very effective at treating this infection, which has been acknowledged to be life-threatening and is rising in incidence in the United States. An IND application is encouraged when treating recurrent *C difficile* infection, but not required.

An interesting challenge has involved concern regarding the protection of donors. It is often thought that donating stool comes without any risk. However, screening potential donors for a variety of transmissible diseases

may reveal infections that the donors may not want their partners or stool recipients to know about. Thus, there is some concern from ethics committees regarding how to best protect donors in this process.

### G&H How are donors usually selected?

**DR** FMT donors are healthy individuals who have no gastrointestinal (GI) problems and ideally do not have a family history of specific GI problems. A variety of stool and blood screening tests are performed on the donor to look for potential infectious pathogens. In addition, donors cannot have recent exposure to antibiotics. There has been some interest in having donors be thin due to the possible association between the microbiome and metabolism, which could affect weight gain or loss. There has also been interest in whether donors might need to be gluten-free or have other dietary restrictions before they donate. None of these restrictions, however, have been proven as beneficial or necessary.

### G&H How is the transplant itself usually performed?

**DR** FMT can be performed by colonoscopy, enema, or nasogastric/nasojejunal delivery. The most common way is to perform a colonoscopy and then infuse a filtered version of the fecal material through the instrument port of the colonoscope using 60-cc syringes. An alternative method of administering FMT is via enema therapy. The aforementioned Canadian placebo-controlled trial of FMT in patients with ulcerative colitis used enema therapy. An ongoing trial in Australia is also using enema therapy, in this case every day, in order to test the theory that patients need to be treated longer to obtain a benefit.

A more recent advance has been the refinement of fecal material into a few specific organisms, which are combined inside a gelatin capsule, allowing for peroral delivery. The capsule dissolves in the patient's small bowel and delivers the necessary organisms downstream. This has been demonstrated to be effective for treating recurrent *C difficile* infection.

### G&H Is FMT currently being used in clinical practice or still restricted to the research setting for IBD patients?

**DR** For the treatment of IBD, FMT is restricted for use only in clinical trials, of which there are several currently ongoing. (All active trials can be found at clinicaltrials.gov.) As previously mentioned, in the United States, FMT requires regulatory approval, and several IND applications have been obtained. Some doctors perform FMT without regulatory approval, but I would caution both patients and doctors against this right now, before more is known about this therapy.

Separately, FMT is being performed for *C difficile* infection complicating IBD.

### G&H What are the next steps in research in this area?

**DR** The next step will be to focus attention on what is actually happening in the microbiome of individuals with IBD, rather than just administering transplants of feces. We also need to understand more about the dysbiosis that has been described and whether it is causative or just an effect. I am looking forward to research that measures the actual microbiome in patients with IBD—what it looks like, how it changes over time, how it predicts relapse, and how we might even discover specific strains of organisms that are driving some of the infections. Then, we can develop targeted approaches of management. It is important to find out if we can actually show that the gut microbiome changes when patients get transplanted, and, if it does change, how long the change lasts before the microbiome reverts back to being abnormal. With FMT, we are just assuming that the mixed-up mess that we find in IBD can be eradicated or rebooted by giving a patient healthy stool.

In addition to identifying specific organisms, it would be useful to find a biomarker that could predict which patients should receive FMT in order to develop customized treatment strategies for active disease or, where I think FMT might actually be more effective, for maintaining remission. In the future, I envision needing an immune-based strategy to induce remission, followed by targeted FMT to maintain or stabilize the microbiome.

*Dr Rubin has no relevant conflicts of interest to disclose.*

## Suggested Reading

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