Fecal Transplant in Inflammatory Bowel Disease

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KEYWORDS

• FMT • IBD • Ulcerative colitis • Crohn disease • Fecal transplant • Dysbiosis

KEY POINTS

- Patients with IBD have differences in the composition of their microbiome compared to healthy individuals, but it is unclear whether this dysbiosis is a cause or consequence of chronic inflammation.
- Studies have explored whether manipulation of the gut microbiome through FMT might be an effective treatment for IBD since it has proven to be so effective CDI.
- Two of the three RCTs published on the use of FMT in UC achieved their primary end point of clinical remission; no RCTs have been done in CD patients.
- Hopefully the numerous ongoing trials investigating FMT in IBD will help clarify the efficacy of this modality as a treatment option.

Crohn disease (CD) and ulcerative colitis (UC) are chronic relapsing and remitting inflammatory diseases of the gastrointestinal tract that affect both the pediatric and adult populations. The incidence of inflammatory bowel disease (IBD) is increasing in the United States. There are currently about 1.6 million people in the United States living with IBD, with as many as 70,000 new cases of IBD diagnosed each year.[1] The incidence of IBD is also increasing in Asia, Africa, the Middle East, and South America, which may, in part, be caused by the rapid industrialization of these countries over the last 20 to 30 years.[2] The exact pathogenesis of CD and UC is still unknown but it is postulated that environmental factors and a dysregulated immune response to microorganisms in the gut in genetically susceptible individuals underlie the development of IBD.[3–5] The current treatment paradigm is based on the goal of altering the dysregulated immune response and decreasing inflammation in the gut by targeting various proteins in the inflammatory cascade. Although the available drugs have the potential

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to significantly improve patient symptoms, they are limited by their cost, side effects, and inconsistent efficacy.

THE MICROBIOME IN INFLAMMATORY BOWEL DISEASE

The gut microbiome has become an exciting new frontier for medical research not only because of the role that it may play in gastrointestinal disease but also for its potential activity in nongastrointestinal systemic disease, the obesity epidemic, mental health, and colon cancer.[6] This development has coincided with increased public interest in complementary and alternative medicine treatment options, including prebiotics and probiotics, as shown by a global probiotic market size in excess of $36 billion in 2015 that continues to grow.[7] Advances in DNA sequencing technology have allowed researchers to begin to characterize the exceedingly complex nature of the intestinal microbiome in both healthy and diseased patients. Patients with IBD have qualitative and quantitative differences in the bacterial species that make up their microbiomes compared with healthy individuals.[8,9] Certain bacteria, like *Fusobacterium*, *Escherichia*, and the Proteobacteria, are increased and other bacteria, like *Bacteroides*, *Bifidobacterium*, and *Clostridium* groups IV and XIVA, are decreased in patients with IBD and mouse models of colitis.[9,10] There is some evidence suggesting that variability in expression of NOD2, the first identified CD susceptibility gene encoding antimicrobial defensins, alters the bacterial milieu of the microbiome.[9,10] At this point, it is unclear whether the dysbiosis seen in IBD is a cause or consequence of chronic inflammation.[10] Most of the studies involving the composition of the microbiome so far have investigated its bacterial composition, although, as technology improves, studies are beginning assess the fungal and viral, especially bacteriophage, composition of the microbiome as well.[10]

At present, the most effective therapy available involving manipulation of the gut microbiome is fecal microbiota transplant (FMT) to treat recurrent *Clostridium difficile* infection (CDI). In FMT, stool from a healthy screened donor is administered to a recipient with the goal of restoring gut microbial diversity toward that of a healthy person. The first fecal transplants were performed in China in the fourth century to treat food poisoning and severe diarrhea.[11] The first known data on the use of FMT in the United States were published in 1958 by Eiseman and colleagues[12] in Denver, who administered fecal enemas to 4 patients with antibiotic-resistant pseudomembranous enterocolitis. The first case report of successfully treating CDI with FMT was published in 1983, with several subsequent case reports and retrospective case series reporting that FMT seemed to be an effective treatment in recurrent CDI.[13–15] The first randomized controlled trial to assess FMT for the treatment of recurrent CDI was published by van Nood and colleagues[16] in January 2013. Their study was stopped early after interim analysis showed a cure rate of 81% with a single nasoduodenal infusion compared with 31% of patients who received vancomycin alone and 23% who received vancomycin plus a bowel lavage. The overall cure rate after 1 to 2 FMTs was a remarkable 94%. Subsequent clinical trials of FMT for severe or recurrent CDI have shown cure rates as high as 100%, with a mean cure rate of 87% to 90%.[17] In the spring of 2013, the US Food and Drug Administration (FDA) announced that it was classifying stool used in FMT as a biologic drug, and therefore only physicians with an approved investigational new drug application could use FMT to treat patients. Later that summer, in response to outcry from patients and providers, the FDA changed their position to one of enforcement and discretion, stating that physicians could perform FMT specifically for cases of CDI not responding to standard therapies provided patients were given informed consent indicating that FMT is an experimental therapy.[18]

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