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Curbing our Enthusiasm for Fecal Transplantation in Ulcerative Colitis

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Abstract: Given the known dysbiosis of gut microflora in inflammatory bowel disease, there has been great enthusiasm about the potential for fecal microbiota transplantation (FMT) as a treatment. This editorial accompanies a prospective series of five patients with ulcerative colitis who underwent FMT, but did not achieve remission. I discuss the important observations from this study and point out that the lack of clinical efficacy and observed side effects warrant caution in the ongoing pursuit of this treatment option.

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The complex causes of the chronic inflammatory bowel diseases (IBDs) known as Crohn's disease and ulcerative colitis (UC) remain unknown, but there has long been interest in the possibility that these immune disorders may be a result of alterations in the commensal gut flora. However, direct causality and proof of Koch's Postulates for an infectious cause of IBD (1) have been elusive. Instead, studies of the gut microbiome in IBD have identified a variety of changes in the intestinal bacteria in patients including decreased bacterial diversity, and more bacterial instability than is seen in healthy individuals (2). Newer hypotheses about the pathogenesis of IBD now involve a complicated interactive network between host genetic factors and the gut microbiome, which results in loss of the homeostatic mechanisms between mucosa and the microflora.

The observations of the altered gut microbiome in IBD have led to treatments directed at this component of the diseases, which would thereby downregulate the inflammatory process. However, there have been many challenges in achieving this goal, including the fact that it is not clear if the dysbiosis seen in IBD is related to the underlying cause of the disease or instead just a result of the active mucosal inflammatory condition (or even the treatments for it). In addition, it is also unknown what strategies should be employed to prepare the patient for gut microbial modification, what quantity and type of organisms should be used, and how the treatment might be delivered. Complicating matters further is the heterogeneity of disease genotypes and phenotypes, and that previous studies of probiotics and antibiotics in IBD (and specifically in UC) have had limited and non-durable success rates.

Despite the lack of data, theories of bacterial causes of IBD have "face validity" to many, and modern day charlatans make enthusiastic claims of the effectiveness of their supplements, probiotics, and dietary plans, and prey on the desperate and suffering patient looking for answers. Similarly, there is fervent interest in "fecal transplantation" (or fecal microbiota transplantation, FMT) for IBD by patients, who believe it to be a "natural" treatment (3). Many are certain this will be their cure, and will go to great lengths to find the treatment (and to pay out of pocket for it). Given the availability of the raw materials (stool from a donor), websites have sprouted (some with at-home FMT recipes and kits), weblog accounts of anecdotal success are multiplying, and patients are seeking providers who can deliver this treatment to them or just doing it themselves in their bedrooms and kitchens. Given this exuberance, there is a clear need for more research of FMT in IBD, and an even more pressing priority to ensure the safety of patients who are desperate and forgoing available standard of care medical or surgical therapies in favor of this unproven approach. To accomplish these goals, we need scientifically valid studies that answer important questions about the role of the microbiome in IBD, while simultaneously rigorously assessing the safety and limitations of transferring an entire community of organisms from one human being to another.

In this issue of the *American Journal of Gastroenterology*, Angelberger and colleagues (4) in Vienna present the results of such a study. They report a prospective study of FMT in five

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adult patients with moderate to severe UC, all of whom failed a variety of immune suppressive therapies (4). Although this is an uncontrolled study, it was carefully constructed and offers a great deal of information about FMT in UC, including some much needed answers regarding an approach to this treatment strategy for future investigation. The study authors tried to address many of the variables in performing FMT-donor selection, patient preparation, and most importantly, perform the first reported microbial analysis in FMT donor and IBD recipient in order to assess the durability of fecal transfer and glean information for additional research.

However, the intervention in this study was not only fecal transfer from a donor to recipient. Patients received 5–10 days of metronidazole, a cathartic colon preparation, pre-FMT probiotic administration, nasojejunal and enema administration of the prepared fecal material from one of two unrelated donors for 3 days, and concomitant proton pump inhibitor and imodium therapies. Safety, clinical efficacy, and bacterial compositions and changes were measured.

A strength of this study is that the authors identified phylotypes present in the post-antibiotic-treated recipients (pre-FMT) as a "risk" pattern of organisms (overrepresentation of *Enterobacteriaceae* and an underrepresentation of *Lachnospiraceae*) and phylotypes present in the donors that may provide clues for future work (*Faecalibacterium prausnitzii*, *Rosebura faecis*, and *Bacteroides ovatus*). However, none of the five patients in this study achieved clinical remission during the formal 12 weeks of follow-up, and only one had some clinical improvement. This was further supported by the fecal calprotectin levels in these patients, which decreased slightly, but still remained quite elevated.

Why did FMT fail in these UC patients? There are several possible explanations. First, it may be that modification of the bacterial species is not the right mechanism for treatment of UC. As theorized, UC may instead be a result of a more complex unregulated immune disorder, and the dysbiosis is a downstream result of the disease, rather than the cause. Second, the choice of patients may be the reason for this negative result. Patients with more severe disease and who already had demonstrated a more aggressive and medically refractory course may be the most difficult to treat with a microbial-based strategy. Additionally, there are other factors that may have affected the microbiome and lack of response to FMT in these patients, including the patients' dietary intake and the exposure to cigarette smoking (two of five patients were current smokers and two of five of these patients were ex-smokers). In addition, specific and unknown features of the donor fecal material, the mixing of two donors' samples in one of the patients, and additional variables, such as exposure to the antibiotics, probiotics, proton pump inhibitor therapy, or even the concurrent allowance of 5-aminosalicylate therapy may have affected the gut microbiome and the magnitude of treatment response.

In addition, and contrary to the apparent safety reported for FMT in non-IBD patients with recurrent *Clostridium difficile* infection, FMT in this study population was not without complication. All patients had transient fever and elevation of C-reactive protein (CRP), and diarrhea worsened the day after the procedure. Two of the patients in this study had ongoing and increasing elevation of their CRP compared with the post-metronidazole baseline level, suggesting that they may have become sicker after this treatment. In the follow-up phase, the authors describe a "collapse" due to orthostasis and, separately, an unexplained case of pancreatitis. These observations reinforce that administering a large volume of bacteria foreign to the recipient, especially in those with an impaired mucosal integrity, may have unintended consequences. A recent case report of relapse of UC in a patient who had been in remission and received FMT for *C. difficile* infection also demonstrates that an unintended consequence of FMT in IBD may be worsening of the immune response and disease severity (5)! Unfortunately, we are learning that FMT for IBD is not the panacea many hoped it would be. These findings and observations also support the current Food and Drug Administration position on FMT and its requirement for formal investigational new drug approval prior to any administration of FMT for clinical or research purpose (6).

Studying FMT in IBD is clearly quite complicated, and we certainly need additional careful studies like this one to inform us about how this may or may not be a path forward for our patients. Patient desperation is not the reason to provide patients with this treatment, and based on these results, the patient with moderate to severe colitis failing our current medical therapies and facing surgery may not be the best candidate for FMT. Future studies should identify a patient population who may be more likely to respond to this treatment, like the newly diagnosed patient or as the authors suggest, the patient with milder disease or who has had a medically induced remission. In addition, we must remember that it is our first responsibility to protect our vulnerable and sick patients. Clinicians who wish to provide "off-label" FMT to a desperate patient should think twice about it, and patients who have decided to pursue this on their own should beware the complexity, uncertain effectiveness and safety issues, and many unanswered questions. Angelberger and colleagues (4) provide a great deal of information to guide our future prospective research, but until then we must curb our enthusiasm for this "natural" treatment.

CONFLICT OF INTEREST

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