Fecal Microbiota Transplantation in Inflammatory Bowel Disease Patients With *Clostridium difficile* Infection

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**G&H** What is the current understanding of the relationship between inflammatory bowel disease and *Clostridium difficile* infection?

**AG** There is a significantly increased rate of *Clostridium difficile* infection among patients with inflammatory bowel disease (IBD) compared with patients without IBD. A patient with underlying IBD has an approximately 5- to 8-fold increased risk of developing *C. difficile* infection compared with a patient who does not have IBD, as well as an approximately 10% lifetime chance of developing the infection. Over the past 20 years or so, there has been a significant increase in the rate of *C. difficile* infection and in the number of IBD patients who are hospitalized for *C. difficile* infection. In addition, recurrence of *C. difficile* infection can lead to significant issues with the care of underlying IBD, such as disease exacerbation and increases in the length of hospital stay, colectomy rates, health care costs, and, most importantly, the risk of mortality.

One of the challenges of managing these patients is determining whether *C. difficile* infection is causing their symptoms or whether the patients are just colonized with *C. difficile* bacteria, in which case the symptoms are being caused by the IBD. The symptoms of *C. difficile* infection commonly mimic those of an IBD flare.

**G&H** How is the cause of the symptoms usually determined?

**AG** Clinicians can use stool tests to try to determine whether *C. difficile* infection is present. Guidelines from the American College of Gastroenterology recommend that all patients with IBD who are hospitalized with a disease flare or who develop diarrhea in the setting of previously quiescent disease should undergo *C. difficile* testing. The problem is that the available stool tests frequently do not provide a clear answer. These tests are often reported in a confusing manner by the laboratory or misinterpreted by clinicians. Of the 3 widely available tests for *C. difficile* (glutamate dehydrogenase [GDH], toxin enzyme immunoassay [EIA], and nucleic acid amplification test [NAAT]), the most important test is the toxin EIA, which identifies the actual toxin that causes colitis and leads to symptoms.

The challenge is that many patients with IBD are inherently colonized with *C. difficile*, which can lead to a positive GDH and NAAT. Because these 2 tests cannot distinguish between a true infection and colonization, clinicians should rely on either toxin EIA or clinical judgment to decide the best course of action for their patient.

**G&H** Based on the research conducted to date, how effective is fecal microbiota transplantation for treating *C. difficile* infection in IBD patients?

**AG** Fecal microbiota transplantation (FMT), usually administered in just a single dose, has been shown to have a cure rate of over 90% for recurrent *C. difficile* infection. There have been a number of retrospective cohort studies over the last few years looking at the efficacy rate of FMT for recurrent *C. difficile* infection in patients who have...
IBD. These studies have largely shown that FMT is effective in this population, but with wide-ranging cure rates from 60% to 90%. At this year’s Digestive Disease Week meeting, results of the ICON study were presented. This was the first prospective study looking at patients with an underlying diagnosis of IBD who developed recurrent *C. difficile* infection and were treated with FMT. Of the 37 patients included in this study, 34 were *C. difficile*-negative at week 8, for a success rate of approximately 92%. This prospective study showed that FMT is a highly effective treatment for recurrent *C. difficile* infection in patients with IBD.

**G&H** Is there a risk of IBD flare following FMT in patients who have both IBD and *C. difficile* infection?

**AG** Several retrospective studies have demonstrated varying rates of IBD flare after FMT, from less than 10% to as high as 50%. The aforementioned ICON study assessed the safety of performing FMT in patients with IBD for the treatment of recurrent *C. difficile* infection. Of the 37 patients who were enrolled in the study, only 1 patient had a de novo IBD flare, and there were no serious adverse events. These findings suggest that FMT is safe in patients with IBD and does not appear to cause IBD flare at a significant rate. Thus, it is safe and effective to perform FMT in IBD patients with recurrent *C. difficile* infection.

**G&H** Does FMT treat the IBD in these patients?

**AG** There have been 4 randomized, controlled trials over the past several years that specifically looked at FMT for treating IBD, particularly ulcerative colitis. Although there does appear to be a signal that FMT can be effective at inducing remission in ulcerative colitis, a single FMT, which is what is used to treat recurrent *C. difficile* infection, is unlikely to improve underlying ulcerative colitis. The IBD trials all used multiple doses of FMT, with different delivery methods and dosing schedules. There are very little data on FMT in Crohn’s disease and no randomized, controlled studies to date. I counsel my patients that a single FMT is unlikely to affect their IBD for better or for worse.

**G&H** Are there any predictors of FMT success in patients with both IBD and *C. difficile* infection?

**AG** No, but there are several predictors of FMT failure. It has repeatedly been shown that a single FMT may not be successful in patients who are in the hospital with severe or fulminant *C. difficile* infection. Interestingly, several recent publications have shown that multiple FMTs can be effective in this cohort of patients. The use of antibiotics within several weeks after FMT is likely to lead to FMT failure. I recommend that patients defer any elective procedures that may require antibiotics for 8 weeks after FMT and strongly encourage antibiotic stewardship. As mentioned earlier, IBD does not appear to be a risk factor for FMT failure.

**G&H** Is there an ideal delivery method or stool preparation for FMT in IBD patients who have *C. difficile* infection?

**AG** A number of different FMT delivery mechanisms have been examined, including nasogastric tube, push enteroscopy, colonoscopy, flexible sigmoidoscopy, enema, and capsule. There has not been enough prospective analysis to determine whether one is better than others in patients with IBD. However, delivering the FMT via colonoscopy allows the clinician to directly assess the underlying colonic mucosa, which helps him or her decide how to treat the IBD moving forward. I use this opportunity to decide if IBD treatment escalation is warranted and frequently take biopsies to rule out cytomegalovirus infection.

As for different types of stool preparation, it has been shown that fresh and frozen preparations are equivalent. At this time, there does not appear to be any difference between aerobic and anaerobic preparations.

**G&H** Has there been any research on whether a single or pooled donor should be used in this patient population?

**AG** For patients with *C. difficile* infection, there are no data to suggest that a single vs pooled donor will affect the efficacy of FMT. However, for treating underlying IBD, there does appear to be a difference. A randomized, controlled trial published in 2015 by Dr Paul Moayyedi and colleagues used single donor FMTs for patients with ulcerative colitis. Only FMT from 1 of the 6 donors (donor B) led to a significant remission rate for ulcerative colitis, suggesting that some donors are more effective than others in treating ulcerative colitis. Subsequent trials in ulcerative colitis have all used pooled donors.

**G&H** How safe is FMT in patients with both *C. difficile* infection and IBD?

**AG** To date, FMT for recurrent *C. difficile* infection in patients with IBD has been safe, with no signature
for severe adverse events. However, the US Food and Drug Administration (FDA) recently reported that 2 immunocompromised patients developed bacteremia with multidrug resistant organisms (MDROs) traced back to the donor. The donor had not been screened for MDROs prior to donating stool, and the FDA has since mandated updated screening guidelines. These cases highlight the need for more safety data. The American Gastroenterological Association, in collaboration with the Crohn’s & Colitis Foundation and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, has established a national FMT registry database to assess both short- and long-term safety data over the next 10 years. I look forward to seeing the results and encourage all FMT providers to participate in this national registry.

**G&H Is FMT allowed outside of clinical trials for patients with C difficile infection who also have IBD?**

**AG** Under the FDA’s current enforcement discretion, which was enacted in 2013, FMT can be used to treat recurrent or refractory C difficile infection regardless of the patient’s underlying or comorbid diagnoses. However, if FMT is used outside of recurrent or refractory C difficile infection (eg, to treat IBD or other conditions), an Investigational New Drug application must be filed with the FDA. Ideally, such patients should be treated in the setting of a clinical trial.

**G&H Is FMT also being used as a first-line treatment for C difficile infection in IBD patients?**

**AG** At this time, FMT is not recommended as first-line treatment. A small trial from Norway published last year in the New England Journal of Medicine showed that FMT was not inferior to metronidazole as a first-line treatment for C difficile infection. However, there are not enough data to support using FMT in this manner at this time. Guidelines from across the world recommend using FMT in patients who have recurrent C difficile infection, but not as a first-line treatment. It is reasonable to consider using FMT in IBD patients with 1 recurrent C difficile infection because of the significant problems caused by recurrent infections in this patient population, including increased hospitalizations, cost of care, risk of colectomy, and mortality.

**G&H What questions remain regarding the use of FMT in this patient population?**

**AG** The ICON study was the first and only prospective study thus far of FMT for patients with C difficile infection and IBD, so further research is needed to determine whether the treatment effects are long-lasting. Because patients with IBD are frequently immunocompromised, we need additional safety data to better inform our patients and our practice. As recurrence in this population is so common, what is the role of adjuvant treatment with bezlotoxumab (Zinplava, Merck), a monoclonal antibody against toxin B, and could this therapy be combined with FMT to improve outcomes? If FMT was used previously, how should the patients be treated if their infection recurs? The majority of practitioners will treat these patients with antibiotics and see what happens, but perhaps if a patient required FMT previously and did well, FMT should be used at the next episode of C difficile infection. Also, beyond C difficile infection, what will be the role of FMT in IBD? More research is needed.

Dr Grinspan has served as a site investigator for Fisch Therapeutics and has received lecture fees from Merck and Takeda.

**Suggested Reading**


