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EDITORIAL

FMT in IBD: What Have We Learned?

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Recurrent infection with the organism *Clostridium difficile* (CDI) is a major cause of morbidity and mortality, particularly in at-risk populations such the elderly, the immunosuppressed, and patients with inflammatory bowel disease (IBD) [1, 2]. The advent of fecal microbiota transplantation (FMT) under the hypothesis that *C. difficile* persistence is related to an altered gut microbiome offers a novel and effective solution to the treatment of recurrent CDI [3]. In the past, FMT was only practiced at a few centers in the USA, but it has since emerged as a standard therapy for recurrent CDI, now endorsed by treatment guidelines [4, 5]. Through the efforts of OpenBiome, a nonprofit stool bank, thoroughly screened donor material is readily available to providers, increasing the accessibility of this highly effective treatment. In the USA, FMT is performed under the Food and Drug Administration's policy of enforcement discretion for CDI [6], with efficacy rates of over 90% [7, 8]. Patients with IBD are not only at higher risk for CDI, which has been shown to result in higher rates of colectomy and death in this population [2], but may also be at higher risk for failing FMT [9].

In this issue of *Digestive Diseases and Sciences*, Meighani et al. [10] describe a retrospective cohort of twenty IBD patients who underwent FMT for treatment CDI at their institution. The heterogeneous population consisted of both inpatients and outpatients, with CDI ranging from mild to moderate, to more severe and severe complicated infections. They compared post-FMT outcomes in these IBD patients to outcomes of non-IBD patients who had undergone FMT for the same indication, reporting that the failure rate after FMT did not differ between patients with and without IBD, which differs from other published experience in which patients with IBD fail FMT more frequently [9, 11]. Furthermore, no complications secondary to FMT were reported, results in keeping with the published experience of other FMT centers [9, 12].

Testing for *C. difficile* in IBD patients with symptoms of disease flare is considered a standard-of-care [13]. One particular strength of this study was the methods used to diagnose CDI in these patients. *C. difficile* polymerase chain reaction (PCR) is a highly sensitive test, though it does not distinguish colonization from active infection with a toxigenic strain, problematic if PCR is the sole means of diagnosis. Their center utilizes a two-step assay, which has been recommended in recently published clinical guidelines [14], with the enzyme immunoassay for toxins A and B enhancing specificity. Rates of *C difficile* colonization at the time of hospital admission are as high as 10% [15] possibly much higher in patients with IBD [16]. This group counted both enzyme immunoassay (EIA) toxin-positive patients and toxin-negative/PCR-positive patients as failures, though it could be argued the latter were carriers. Since a strong physiologic basis is lacking for the supposition that CDI in IBD patients is not associated with pseudomembrane formation, it is plausible that these patients may be merely colonized in the setting of disease flare. Distinguishing colonization from active infection in this population, in whom symptoms can be confounded by baseline diarrhea, would help guide therapy and avoid courses of unnecessary antibiotics (or FMT) in favor of

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more aggressive IBD therapies in those patients who are toxin negative.

Methods used to administer FMT to the patients in this study varied. Though the majority (65%) were administered colonoscopically, one-third of patients had FMT administered by retention enema or nasogastric tube. Colonoscopic administration may be preferable in IBD patients in order to enable thorough mucosal inspection and assessment of disease activity at the time of FMT. In fact, unrecognized IBD may be a source of diarrheal symptoms in patients with recurrent CDI. Indeed, three patients in this study were newly diagnosed with IBD at the time of the FMT colonoscopy, cases that would have been missed if other delivery modalities had been utilized. The authors admit that the degree of IBD severity and previous treatments were unknown in many of these patients when initially evaluated in their tertiary referral center; many were assumed to be stable from an IBD standpoint. Though no disease flares post-FMT were reported in this study, up to half of patients with UC may experience a flare of their disease after FMT [9]. Since patients with more severe inflammation at the time of FMT may be more likely to flare or require intensification of their IBD regimen post-FMT, IBD patients should be counseled about potential disease deterioration as part of the informed consent process.

The optimal course of treatment for patients with IBD who are infected with *C. difficile* is another question. Though specific pre-FMT anti-CDI treatments are not described in this study, the IBD patients had been treated with a mean of two CDI treatment courses in the three months prior to FMT. Horton et al. [17] reported that treatment of ulcerative colitis patients with oral vancomycin shortened hospitalization length and reduced CDI-related readmissions. Since the novel antibiotic fidaxomicin is as effective as vancomycin, with a more narrow spectrum of activity, decreased rates of CDI recurrence may be expected if fidaxomicin is used as first-line therapy [18]. Given that CDI eradication in patients with IBD improves overall clinical outcomes, there is hope that FMT may soon be used earlier in the disease course for patients with IBD, even after a first-episode CDI. Our group is currently enrolling a trial (NCT03106844) aimed at assessing the efficacy of FMT at eradicating CDI in patients with IBD experiencing their first recurrence of CDI as well as assessing the IBD clinical outcomes post-FMT.

Since the IBD population is disproportionately affected by CDI, establishing the safety and efficacy of FMT in this unique population as well as developing a greater understanding of the impact of FMT on their underlying disease is imperative.

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