Intestinal Microbiota Transplantation for Patients With Inflammatory Bowel Disease Prevents Recurrence of *C. difficile* Infections but Not Recurrence of Gastrointestinal Symptoms

Lea Ann Chen, MD*

Patients with inflammatory bowel disease (IBD) are at increased risk for *Clostridioides difficile* infections (CDIs).¹ These infections can, in turn, complicate IBD—increasing the risk of treatment escalation, colectomy, and even death.^{2–4} The increased utilization of fecal microbiota transplantation for CDIs⁵ presents a unique opportunity to investigate the utility of this emerging therapy specifically for the IBD population and to glean additional insights into modulating IBD activity through gut microbiome manipulation. As current studies suggest that the beneficial effect of these transplants is likely mediated by the intestinal microbiota,^{6,7} rather than any other aspect of feces, the adoption of the more accurate and less sensational term “intestinal microbiota transplantation” (IMT) has been proposed.⁸

In this issue of *Inflammatory Bowel Diseases*, Tariq et al. present their retrospective analysis of a prospectively followed cohort of 145 adult IBD patients treated with colonoscopically delivered IMT for recurrent CDIs.⁹ Patients studied had at least 3 polymerase chain reaction (PCR)-confirmed CDIs with resolution of diarrheal symptoms on appropriate antibiotic treatment. Those who had CDI of their ileal pouch or who were too ill to undergo colonoscopy were excluded. After IMT, patients were evaluated at 1 week, 1 month, and 12 months, and those with diarrhea were offered repeat *C. difficile* testing.

The authors report an overall IMT success rate of 80% (116/145), on par with previously published data on IBD patients.^{10–12} Nonetheless, it should be noted that only 33% (48/145) of study patients achieved and maintained symptomatic remission after IMT. The remaining 47% of those

considered successfully treated consisted of 66 individuals who had continued or recurrent diarrhea after IMT but tested negative for *C. difficile* and 2 individuals who received empiric treatment for rCDI without confirmatory testing but then failed to respond to antibiotics (ie, interpreted in hindsight as IBD activity, not CDI). Though the study was not designed to address these topics, there were no differences detected in IMT efficacy based on IBD location or endoscopic severity of colitis.

One significant challenge in studying IMT in IBD patients relates to the difficulty of differentiating symptoms attributable to IBD from those attributable to CDI, particularly as individuals with IBD may be more likely to be colonized with *C. difficile*.^{13,14} The high concurrence of irritable bowel syndrome (IBS) and IBD^{15,16} and the possibility of postinfection IBS further complicate evaluations of IMT success. Although some measure of subjectivity cannot be avoided, the authors' standardized process for assessing IMT candidates, the preparation and delivery of the therapy, and the timing and nature of clinical follow-up allow for improved data reliability and decreased confounding. This combination of a disciplined approach and clinical expertise provides significant value to the developing IMT field.

Based on the authors' review of clinical documentation, they determined that 32 patients had ongoing IBD flares before IMT that persisted and 11 patients had new IBD flares after IMT. As the median time to these new IBD flares (range) was 15 (1–60) days after the procedure, it is difficult to determine whether these escalations in IBD activity were truly independent events or rather IMT-related. Combined, 29.7% (43/145) of the study population required IBD treatment escalation after successful clearance of their CDI, and no patients decreased or discontinued their IBD medications after IMT. In addition, 2 patients had severe self-limited abdominal pain that required evaluation in the emergency department (1 then had a brief stay in the intensive care unit). Overall, these data suggest that a single IMT does not improve the underlying course of IBD, but does impart risk for IBD flare.

Of note, the 29 patients with confirmed CDI after IMT were all re-treated with antibiotics. Interestingly, 65% (11/17) of those receiving vancomycin developed yet another CDI recurrence, whereas none of the 12 treated with fidaxomicin recurred. This is despite 26.2% (38/145) of the study population

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From the Division of Gastroenterology, Department of Medicine, NYU School of Medicine, New York, New York, USA

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Address correspondence to: Lea Ann Chen, MD, Division of Gastroenterology, Department of Medicine, NYU School of Medicine, 462 First Ave, 10E1, New York, NY 10016 (lea.chen@nyulangone.org).

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failing at least 1 course of fidaxomicin before initial IMT. These data suggest that fidaxomicin may be particularly effective in patients who develop rCDI after FMT and could be considered medical therapy before repeated IMT attempts.

Where do we go from here? Clearly more data are needed to understand how often the symptoms of abdominal pain and diarrhea in an IBD patient combined with positive *C. difficile* laboratory testing reflect colonization, true CDI, and/or an IBD flare. In fact, the authors note the importance of evaluating test results, symptoms, and prior responsiveness to antibiotics when assessing for rCDI, as 20% of their referred patient population received an alternate diagnosis.¹⁷ Similarly, it is important to determine the underlying etiology for the diarrhea that often remains after IMT and to identify clinical characteristics that may help distinguish symptoms of rCDI from IBD or IBS. These answers will help us appreciate the true safety and efficacy of IMT. To this end, a systematic and disciplined approach to evaluating suspected CDI and to the utilization of IMT will aid in separating signal from noise in investigative efforts. In addition, standardization of clinical documentation, such as the creation of templates for (electronic) medical records that could be utilized across IMT providers, would facilitate both retrospective and prospective studies.

As Tariq and colleagues have demonstrated, IMT can be an effective therapy for rCDI among IBD patients who are not responding to standard therapies. Their target—sustained CDI clearance (independent of symptoms)—is a high, yet reasonable, bar and highlights the great paucity of treatments to break or prevent the cycle of rCDI. Continued access to IMT for CDI indications, therefore, remains critical. To date, IMT is still considered an investigational therapy and has no Food and Drug Administration (FDA)–approved indication.¹⁸ Furthermore, IMT has known risks, as we were acutely reminded through the publication of 2 cases (1 fatal) of immunocompromised patients who acquired infections with extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* through IMT.^{19,20} Meanwhile, regulations and best practices associated with IMT are an area of continued flux,²¹ with the potential for additional changes after the FDA hearing on November 4, 2019,²² and the solicitation of public comments, which is scheduled to last through January 21, 2020.²³ Continued careful monitoring of prospectively followed cohorts, such as that described by Tariq et al. and the American Gastroenterological Association's national registry,²⁴ is therefore important to our growing understanding of IMT and to guiding the policies that will regulate the unique and emerging field of microbiome therapeutics.

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