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Editorial

Fecal microbiota transplantation as an alternative treatment for infection and inflammation

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Abstract

Our intestinal microbiota comprises 100 trillion bacteria, exceeding our own eukaryotic cells. While the microbiota has incredible health benefits, changes in the normal flora caused by inflammation, antibiotics or diet can negatively impact health and may contribute to diseases such as inflammatory bowel disease (IBD) and obesity. Using healthy microbiota to treat individuals with intestinal disease is not a new idea and fecal microbiota transplantation (FMT) has been used as a successful therapy in patients suffering from *Clostridium difficile* infection. Currently FMT is being considered as a treatment for patients with IBD. This editorial will discuss the history of FMT and implications for treatment of other inflammatory intestinal diseases.

Keywords
Microbiota, IBD, C. difficile, mucosal immunity

Abbreviation
FMT: Fecal Microbiota Transplantation

Our gut microbiota comprises 100 trillion bacteria, exceeding our own cells by ten-fold. The gut microbiota has several functions, including digestion, colonization resistance, maintenance of mucosal integrity, and priming of the mucosal immune response [1]. Disruption of the normal microbiota, or dysbiosis, can impact immunity and result in disease. This is best illustrated by *Clostridium difficile* infection (CDI), acquired when gut microbial diversity and number are reduced by antibiotic treatment. Antibiotic treatment compromises the ability of the natural microbiota to resist colonization by opportunistic pathogens, allowing resident *C. difficile* or ingested environmental *C. difficile* spores to dominate the intestinal tract, which leads to diarrhea and inflammation associated with pseudomembranous colitis. The close relationship between gut microbiota and disease is also apparent in IBD, such as Crohn's disease and ulcerative colitis, and alterations in the microbiota of IBD patients are well documented [2-11].

C. difficile is one of the most important causes of nosocomial infections. In the last 10 - 15 years, with the emergence of hypervirulent strains, there has been an increase in prevalence and severity of CDI [12]. Standard treatment for CDI involves antibiotics such as metronidazole and vancomycin. However, ~20 % of patients with an initial CDI are unresponsive to antibiotic treatment [13,14]. Furthermore, despite the recommended treatment, recurrence of disease is frequent [13-15]. There are now alternative antibiotics such as fidaxomicin, which has a CDI cure rate similar to vancomycin and shows improvement in its efficacy against recurrent CDI [16,17].

FMT is beginning to be recognized as an alternative to antibiotic treatment for CDI. FMT involves infusing bacteria from a healthy donor into the gastrointestinal tract of the patient to reestablish a normal gut flora by repairing or replacing the diseased flora [18]. In veterinary medicine, this process, called transfaunation, has been practiced for decades [19]. The first recorded performance of FMT in humans was in the 1950s in patients with fulminant pseudomembranous colitis later found to be caused by recalcitrant CDI, who showed "immediate and dramatic" responses [20]. Today there are more than 500 patients who have been treated for CDI with FMT with a cure rate of ~95% [21,22]. However, despite its efficacy, FMT has not become a widely used therapy for CDI, mainly due to the "yuck factor" and lack of data from randomized, controlled trials. Earlier this year, efficacy of FMT for recurrent CDI was confirmed by the first randomized, controlled trial [23]. In this study, FMT was significantly more effective in treating recurrent CDI than vancomycin alone or in combination with bowel lavage. Although the trial was not blinded and had a small group size, it provides impetus to address the other obstacles in adopting FMT as a routine therapy. As an example, there is growing interest in strategies to circumvent the direct use of feces by substituting it with purified intestinal bacterial cultures derived from a single healthy donor [24,25]. Additionally, the need to standardize the protocol for FMT is being recognized [26].

Although FMT has been reported mostly in the context of recalcitrant CDI, there are emerging applications of FMT. With the evidence that specific gut microbes can induce distinct immune responses in the host and that there is reduced diversity of the microbiota in patients with IBD [27-29], it is not far-fetched to think that restoring a normal microbiota will alleviate IBD. Indeed there are eight cases of ulcerative colitis and one case of Crohn's

disease in which FMT led to remission [30-32]. Though not identical to the human disease, there are animal models that mimic colitis and inflammation, which demonstrated that susceptibility to colitis and resistance to enteric infection are transferrable by FMT [33-35].

With FMT in IBD still in its infancy, there are lessons to learn from the more widely used FMT for CDI. First, it is necessary to have controlled and randomized clinical trials to address the efficacy of FMT in IBD. There are several uncontrolled clinical trials that are ongoing; however, there has yet to be a study with a control group. Second, a standardized treatment protocol needs to be established for stool processing, patient preparation (i.e. antibiotic treatment pre-transplantation), and delivery method. Lastly, the donor selection and screening process must be robust and well documented. This may be more important for treatment of IBD than CDI, as multiple infusions are typically necessary for the former [21], and consistency between the repeated infusions would be ideal. Current clinical trials will shed light on some of these considerations and will help shape future investigations on the therapeutic value of FMT for IBD.

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