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TOPIC HIGHLIGHT

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Restoring the gut microbiome for the treatment of inflammatory bowel diseases

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Abstract

Fecal microbiota transplantation (FMT) is considered to be a highly successful therapy for recurrent and refractory *Clostridium difficile* infection (CDI) based on recent clinical trials. The pathogenesis of inflammatory bowel diseases (IBD) is thought to be due in part to perturbations in the gut microflora that disrupt homeostasis. FMT restores essential components of the microflora which could reverse the inflammatory processes observed in IBD. Case reports and series for the treatment of IBD by FMT have shown promise with regards to treatment success and safety despite the limitations of the reporting. Future studies will determine the optimal delivery and preparation of stool as well as the conditions under which the recipient will derive maximal benefit. The long term consequences of FMT with regards to infection, cancer, auto-immune, and metabolic diseases are not known and will require continued regulation and study. Despite these limitations, FMT may be beneficial for the treatment of ulcerative colitis and Crohn's disease, particularly those with concurrent CDI or with pouchitis.

Key words: Crohn's; Ulcerative colitis; Microbiota; Fecal transplantation; Dysbiosis; Pouchitis; *Clostridium difficile*; Probiotic

Core tip: Advances into the understanding of the pathogenesis of inflammatory bowel diseases (IBD) have highlighted the importance of a dysbiosis in the intestinal microbiome. A perturbed microbiota with loss of colonization resistance is a main driver of *Clostridium difficile* infection and exciting new data exists that microbial restoration through the use of fecal microbiota transplantation (FMT) is highly successful. Therefore, it is logical to conclude that FMT will have therapeutic efficacy in IBD. Preliminary studies that have evaluated FMT for IBD are reviewed with an emphasis on subpopulations that may benefit the most. The limitations and unknowns for this novel therapy are also discussed.

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease, the two main classifications of inflammatory bowel diseases (IBD) are characterized by chronic intestinal inflammation resulting in recurrent episodes of disease exacerbations with associated abdominal pain, diarrhea, weight loss and rectal bleeding. IBD remains poorly understood and medical therapies continue to be inadequate. The current mainstays of conventional therapy for these diseases include 5-aminosalicylates (5-ASAs), corticosteroids, thiopurines, and anti-tumour necrosis factor agents. However, despite continued advances in therapy, a significant number of

patients remain refractory to standard therapies. Overall, 20%-30% of patients with UC will require a colectomy. At least 50% of patients with Crohn's disease will require surgical treatment in the first 10 years of disease and 70%-80% will require surgery within their lifetime[1].

The etiology of IBD is complex and several factors are believed to play a role in its development and progression. The host genotype is important and twin studies have shown concordance rates of 16% for UC and 35% for Crohn's disease[2]. However, these numbers also indicate that non-genetic factors play a substantial role in the development of IBD[3]. The most important of these is likely the intestinal microbiota (reviewed extensively in this issue of *WJG*). Humans have evolved with the microbes in the intestine which are known to provide critical functions to the host such as metabolism, digestion, development and maintenance of the immune system, and mucosal barrier function. The microbes exist in the various niches to carry out their function and are relatively stable over time[4]. In disease states such as IBD, the microbial balance that favored homeostasis is perturbed and studies that have analyzed the composition of the gut microbiome in IBD have found a loss in the richness and diversity of the bacterial components including under representation of the anti-inflammatory phyla *Bacteroides* and *Firmicutes* and a relative plume of pro-inflammatory *Proteobacteria*[5-7]. This shift in the composition of the microbiota ("dysbiosis") may favor the appearance of distinct pathogens that perpetuate the inflammatory response. In this regard, several studies have revealed an increase in adherent/invasive *E. coli* in the terminal ileum of patients with Crohn's disease and *Mycobacterium avium paratuberculosis* has been casually linked to Crohn's pathogenesis although a direct link has not been proven[8]. Opportunistic microbes such as *C. difficile* may also be able to establish pathogenicity in niches that may be present in the colons of IBD patients. Whether the dysbiosis directly leads to inflammation or is a consequence of an inflammatory environment is yet to be determined. Nonetheless, antibiotics and fecal diversion have been successful in treating various forms of IBD[9], and it is possible that restoring a healthy microbiota through Fecal microbiota transplantation (FMT) may prove to be more effective[2].

FMT has been suggested as a therapy for IBD, given the observed intestinal dysbiosis[10]. FMT has also been termed "fecal bacteriotherapy", "human probiotic infusion", "stool transplant," "intestinal microbiome restoration" and "fecal transfer" in the literature. FMT involves collecting stool from a healthy pre-screened donor and delivering a prepared slurry into the gastrointestinal tract of the individual with disease via nasogastric tube, EGD, colonoscopy, or enema[10]. Multiple studies have investigated the role of FMT for the treatment of colitis and diarrhea caused by the opportunistic pathogen *C. difficile*. The accumulated data suggests that FMT is a safe and highly effective therapy for *C. difficile* infections (CDIs) refractory to standard medical treatment with antibiotics[11-22]. In this review, we will discuss the literature on the use of FMT for the treatment of IBD with a focus on special populations of patients with IBD who are predicted to respond to this treatment. We also discuss the limitations of FMT and remaining questions for this exciting novel therapy.

PUBLISHED EXPERIENCE WITH FMT AS A THERAPY FOR IBD

There are currently no published clinical trials on FMTs in either UC or Crohn's disease. The literature consists of various case reports and case series, mainly in UC. The first report of FMT for UC was presented by Bennet and Brinkman in 1989[23]. Bennet, who had UC, self treated with fecal retention enemas. Six months after his experimentation, he remained symptom-free and off of medications. This report was followed by a case series, by Borody and colleagues in the same year, of 55 patients with a mixture of gastrointestinal disorders including UC, Crohn's disease (only one patient), and irritable bowel syndrome who were treated with FMT by retention enemas[24]. They reported that 20 of the 55 patients were "cured" after one FMT and 9 had significant symptom reduction. This study was very limited and did not provide details as to how clinical outcomes were measured and which patient groups may have derived the greatest treatment benefit. Furthermore, details were not provided as to the frequency and duration of treatment or the length of follow up. The one patient with Crohn's disease was reportedly symptom free after four months after suffering from steroid refractory disease[24]. In a later review, Borody reported that this Crohn's patient had relapsed at 18 mo[25]. Borody followed up this report up with another case series highlighting 6 patients with UC[26]. Each of the 6 had at least five years of disease and had either failed what was described as maximal medical therapy (steroids, 5-ASAs and mercaptopurine) or quickly relapsed upon withdrawal of medications. Each patient was confirmed to have active inflammation on colonoscopy and was negative for CDI. Prior to the treatment, each patient received antibiotics for 7-10 d in order to suppress the *Clostridia* (vancomycin 500 milligrams (mg) twice daily, metronidazole 400 mg twice daily, and rifampicin 150 mg twice daily). Each patient also underwent a one time 3 L lavage with an oral polyethylene glycol solution. These patients provided their own donors and received daily fecal retention enemas for five days. They were encouraged to retain the enemas for as long as possible (6-8 h). Each of these patients was in complete remission four months after treatment and remained off of IBD medications. In several of the patients, follow up colonoscopy revealed no active inflammation. The follow up time was variable but remission was reportedly sustained over many years (1-13)[26]. A recent systematic review on the topic found nine articles and 26 patients (18 UC, 6 CD, 2 indeterminate) who had received FMT for management of IBD, several of which are included

in the series described above[27]. Of these 26 patients, results were reported in 17. After FMT, 13/17 patients were able to cease all IBD medications within 6 wk and all had symptom reduction or resolution at 4 mo[28]. It is important to note that these cases varied significantly in the route of administration, preparation of stool, and screening protocols.

Angelberger *et al*[29] characterized the bacteria communities present both pre and post FMT in 5 patients with moderate or severe UC. They found that none of the 5 patients achieved remission by week 12 and response was only noted in one patient. In two of the patients, further deterioration of their UC was noted at 4 wk post FMT. Upon analysis of the microbial compositions, they found that the UC patients pre FMT displayed a low phylotype richness and an overrepresentation of *Enterococcaceae* and *Enterobacteriaceae* and an underrepresentation of *Lachnospiraceae*, *Ruminococcaceae* and *Bacteroidaceae* when compared to healthy donors[29]. They found that post FMT the microbiota of the patients became similar to that of the donor, however the duration of that change was patient dependent. The one patient with a clinical response maintained a similar microflora to the donor extending to 12 wk post FMT. However, the 2 patients who experienced disease deterioration showed increased microbiota dissimilarity by 4 wk post FMT. This small study raises several important questions such as what IBD phenotypes may respond best to FMT and how many infusions are necessary to establish a healthy microbiota and a sustained clinical response. Future studies for the treatment of IBD should carefully consider whether disease severity at the time of FMT affects treatment outcome, and at what point in the IBD disease process FMT may be optimal.

FMT FOR CDI IN PATIENTS WITH IBD

The incidence of CDI continues to rise[30]. First line treatment for CDI consists of antibiotic therapy, however recurrence rates have been reported between 15%-35%[30]. FMTs are best studied in CDI infections refractory to standard treatment. Current literature consists of multiple case series, systematic reviews and a recent randomized controlled trial[31]. Impressively, cure rates have been reported between 81% and 100%[30]. CDI infections are more common in patients with IBD, with a higher prevalence among patients with UC (3.7%) and Crohn's disease (1.1%) compared with the background general population (0.45%)[32]. While IBD itself is thought to be an independent risk factor for CDI, the increased prevalence has also been linked to immunosuppressive medications, increased antibiotic use and multiple surgeries and hospitalizations[33]. CDI may have adverse effects on the underlying IBD and so effective therapy to eradicate the organism is necessary to promote disease remission[33]. A recent systematic review identified eight articles that reported on 15 patients (9 UC, 6 Crohn's disease) who underwent FMT for recurrent or refractory CDI, however outcomes were only reported in 12 of these patients[27]. All patients had resolution of *C. difficile* as measured by stool specific testing. Several patients were noted to have fever and abdominal pain post FMT in this cohort but no major adverse events were reported. We will await the results of future trials to verify that FMT is a safe and effective therapy for IBD patients with *C. difficile*.

UC PATIENTS WITH ILEAL POUCHES

Up to 20% of people with UC undergo an ileal pouch anal anastomosis (IPAA)[34]. Over 60% of individuals undergoing an IPAA for UC have at least one episode of pouchitis[35]. This complication is uncommon in those undergoing IPAA for non-UC related reasons, such as familial adenomatous polyposis suggesting that genetic and environmental factors such as the composition of microbiota play a role in the pathogenesis of pouchitis[36]. Its development in relationship to microbiota likely has two sides: a dysbiosis which reflects changes in bacterial composition possibly at the core of the pathogenesis of UC as well as the emergence of pathogenic bacteria such as *C. difficile*[37]. Pouchitis often responds to a course of antibiotics but may recur and require multiple courses of the same antibiotic or a switch to a different antibiotic[34]. Various types of probiotic preparations have been demonstrated to maintain remission in pouchitis when used daily[38,39]. Unfortunately, pouchitis becomes a chronic, refractory condition in 5%-30% of patients undergoing IPAA for UC[40] and more effective therapy is needed. Because dysbiosis likely propagates pouchitis in IBD and bacterial manipulation with antibiotics and probiotics has proven to be successful, it stands to reason that FMT will prove to be a successful treatment for many pouchitis patients. There is currently no published literature or ongoing trials exploring this possibility.

LIMITATIONS AND UNANSWERED QUESTIONS FOR FMT

Screening

The process of screening the donor stool and what tests should be ordered prior to FMT continues to evolve. Ideally, experts from gastroenterology and infectious disease can form a consensus regarding the appropriate screening of donor stool. In our practice, we ask the donor initially about high risk sexual behaviors, whether they have been diagnosed with any gastrointestinal diseases such as IBD, colon polyps, or irritable bowel syndrome, and whether or not they have taken antibiotics within the previous 3 mo. We then screen both the donor and recipient's blood for Hepatitis A (IgG and IgM), Hepatitis B (HBsAg/Ab and HBc), Hepatitis C (Ab), HIV-1/2 (Ab and viral load), and Syphilis (TP-IgG). The donor's stool is screened for *C. difficile* (by culture), routine stool bacterial culture, Giardia antigen,

Cryptosporidium antigen, and test for ova and parasites. More extensive screening protocols have been used in other studies that include additionally screening the donor for strongyloides, CMV, HTLV 1 and 2, EBV and Entamoeba histolytica[31]. Given regional and geographic differences, we recommend consulting with an infectious disease specialist and infection control in order to determine the appropriate screening tests for an individual practice setting.

Whether or not the efficacy of FMT is improved with a related donor *vs* unrelated donor is not clear at this time. One recent systematic review suggested that stool from a related donor resulted in a higher resolution rate (90.5%) for CDI than an unrelated donor (84%)[30]. However, other studies where universal donor pools were used have yielded similar overall results[30]. Identification of individual bacterial components within the donor microbiota which could potentially influence efficacy are being investigated[41].

Patient preparation

Most published reviews have recommended large-volume bowel lavage before the procedure, regardless of upper or lower tract administration in order to mechanically reduce *Clostridial* organisms that are still present[30]. This concept has never been tested formally. For recurrent *C. difficile*, reports generally have recommended discontinuing antibiotics 1-3 d prior to the FMT[13,30], however this has also not been compared to continuing antibiotics up until the day of the procedure. At our Institution, we have patients discontinue antibiotics the night before the FMT.

Stool delivery

Another issue that will need clarification through future study is the mode by which the stool is delivered to the bowel. Although the efficacy of FMT has been shown to be similar when delivered by endoscopy, nasogastric tube, enema or colonoscopy, it is possible that one method may be superior to another in IBD. The type and location of IBD may drive this decision. Upper gastrointestinal delivery of stool may be more efficacious for patients with small bowel Crohn's disease *vs* delivery by colonoscopy for patients with colonic disease. Lastly, tolerability and relative safety of each procedure will have to be considered when deciding between upper gastrointestinal delivery *vs* lower. In this regard, belching, nausea and abdominal cramps have been reported with upper gastrointestinal administration on the day of the procedure in 8/16 patients, however these symptoms resolved upon follow up[31]. Although no major adverse events have been reported with any intestinal administration of stool, the safety of the proposed procedure should be considered at the time of treatment. Although colonoscopy is generally considered to be a safe treatment in the setting of active IBD, the perforation rate may be increased and other modes of stool delivery should be considered in patients with moderate or severe inflammation or stricturing disease. Lastly, it is possible that FMT delivered by retention enema is effective in a subset of IBD patients and would obviate the need for an endoscopic procedure and hospital visit.

Processing and storage

Another unanswered question is whether donor stool may be frozen and then thawed prior to FMT. This has obvious practical implications but whether or not the key components of the stool will be adequately preserved is not known. The University of Minnesota reported similar *C. difficile* cure rates among patients who received fresh *vs* frozen (minus 80 degrees Celsius from 1-8 wk) specimens (n = 33)[42]. In this series, 10 patients had underlying IBD. Interestingly, only 4 patients required a second FMT for recurrent symptoms and 3 of them had underlying IBD[42]. Stool frozen at -80 ℃ therefore may be equally effective for FMT as fresh stool, however the viability of organisms after exposure to atmospheric oxygen may be an important consideration. Facultative anaerobes in stool may be inactivated by oxygen and thus transplants under anaerobic conditions may be more efficacious[4].

It is conceivable that oral preparations that mimic human stool may be manufactured in the near future. Although probiotics have yielded modest treatment effects in certain populations of IBD[43-46], it is likely that the various probiotics lacked critical organisms and possibly other factors that help successfully restore the gut microbiota back to health.

Long term complications

Whether or not FMT may exacerbate underlying bowel disease in some patients may be an important question. A case of a UC flare after FMT for CDI was recently reported[47]. The patient had quiescent disease for twenty years and was not on immunosuppressive medications. He developed symptoms nine days after the FMT. *C. difficile* testing was negative and sigmoidoscopy revealed the appearance of inflammation and ulceration that was not present on the FMT colonoscopy.

There is a theoretical concern for the transmission of infections that may have escaped the screening process[48]. A recent case series reports two patients who experienced gastroenteritis only 2 d and 2 wk after FMT respectively. Both patients were found to be *C. difficile* negative by PCR but norovirus positive. The donor stool however was negative for norovirus and the authors concluded that there was not direct transmission from donor to patient.

Whether or not FMT may influence non-gastrointestinal diseases in the long term such as metabolic disease, obesity, and cardiovascular disease is not known at this time[49-53]. This may be the reason why several regulatory agencies such as the United States Food and Drug Administration have asked for more research on FMT

before this can be recommended as a first line treatment.

Regulation

While initial reports of FMTs for IBD are promising, several unresolved issues remain. Treatment of IBD with FMTs may be considered investigational and so many health care providers may not cover the cost of the procedure (colonoscopy and stool preparation). This is the case in the United States where the Food and Drug Administration has required that providers who would like to perform FMT must file an "Investigational New Drug" application. Many patients may end up having to pay the hospital charge for this treatment out of their own funds. This burden may be greater when it is possible that patients with IBD may require several treatments. Nonetheless, it is conceivable that long term costs may be reduced if FMT leads to treatment success and the patient is able to avoid expensive medical therapies, hospitalizations, or surgeries.

CONCLUSION

FMT is now considered to be a highly successful therapy for recurrent and refractory CDI based on recent clinical trials. The pathogenesis of IBD is thought to be due in part to perturbations in the gut microflora that disrupt homeostasis. Therefore, it is logical to extend the successes of FMT in CDI to the treatment of IBD. Case reports and series for the treatment of IBD by FMT have shown promise with regards to treatment success and safety despite the limitations of the reporting. While several questions remain unanswered such as the long term consequences of FMT on the recipient, this therapy may be beneficial for the treatment of UC and Crohn's disease, particularly those with concurrent CDI or with pouchitis. The study of the gut microbiome has opened an exciting new world in medicine raising as many questions as it seems to answer. It is nonetheless here to stay with additional data from randomized controlled trials much needed. Synthetic and multi-microbial stool substitutes are an inevitable advance that we are likely to see in the near future.

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