Fecal Microbiota Transplantation: Present and Future

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Introduction

Fecal microbiota transplantation (FMT), also called stool/fecal transplantation or fecal bacteriotherapy, is the infusion or engraftment of liquid filtrate feces from a healthy donor into the gut of recipient to cure a specific disease. The concept of FMT for treatment of human intestinal disease was described approximately 1700 years ago by a Chinese medical scientist named Ge Hong.1 It was first reported in the English language by Eiseman and colleagues, who used fecal enemas to treat pseudomembranous colitis in 1958.2 However, it has only recently become popular with its success in treating refractory and recurrent Clostridium difficile infection (CDI).3 We review the evidence to support the use of FMT in treating a variety of disease.

Rationale for FMT

Although the exact mechanisms for the role of gut dysbiosis in disease development are not completely elucidated, alteration of metabolic activities induced by gut dysbiosis leads to weakened defense of the gastrointestinal mucosa, which in turn leads to intestinal permeability and toxic substances being absorbed into the systemic circulation. The main mechanism for the efficacy of FMT is likely to be the establishment of intestinal bacterial strains and antimicrobial components (adhesion, immunomodulatory molecules, bacteriocin, etc.) produced by these associated strains.4

Clinical applications

1. Clostridium difficile infection

FMT restores gut microbiota diversity via the infusion of donor feces into the gastrointestinal tract of a patient with CDI. In the past few decades, FMT has received considerable attention because of a convincing clinical trial of treatment of recurrent CDI. The first randomized controlled trial (RCT) of FMT for 43 patients with recurrent CDI compared FMT administered via nasoduodenal tube after 4 to 5 days of oral vancomycin with 14 days of continued vancomycin and with 14 days of vancomycin plus bowel lavage.5 Symptoms resolved within 3 months in 81% of patients receiving FMT, 31% of patients receiving vancomycin, and 23% of patients...
receiving vancomycin plus bowel lavage. The study was terminated early because of the low response rates in the comparator groups. The second unblinded RCT compared FMT given via nasogastric tube with FMT given via colonoscopy in 20 patients. Symptoms resolved completely for 70% of patients overall; outcomes were similar for the two methods. Most recent systematic review (2 RCTs, 28 case-series studies, and 5 case reports) showed that FMT was successful in 85% of recurrent CDI and 55% of refractory CDI compared with 30 to 80% success rates for medical therapies. Although FMT has a substantial effect and few short-term side effects for adults with recurrent CDI, there is insufficient evidence regarding FMT for patients with refractory CDI or for initial treatment of CDI. Considerations for future study in CDI include need for large, blinded RCT that would compare FMT with placebo in patients randomized after standard antimicrobial therapies, the best source and processing methods for donor stool, and the best timing for FMT after antimicrobial use.

2. Inflammatory bowel disease

The application of FMT for inflammatory bowel disease (IBD) was first published as a case report in 1989, in which the author himself confirmed ulcerative colitis (UC) for 7 years that was refractory to sulfasalazine and steroids. Six month after transplantation of a healthy donor stool by retention enemas, he remained symptom free. Most recent systematic review analyzed 18 studies (9 cohort studies, 8 case studies and 1 RCT) on FMT in patients with IBD, including 122 patients with IBD (79 UC, 39 Crohn’s disease (CD) and 4 unclassified). The results showed that overall rate of clinical remission after FMT was 45% (54/119). Recent two RCTs for FMT in UC showed contradictory results. Moayyedi et al. reported that FMT induced remission in a significantly greater percentage of patients with active UC (9/35, 24%) than placebo (2/35, 5%), with no difference in adverse events. Rossen et al. demonstrated that there was no statistically significant difference in clinical and endoscopic remission between patients with UC who received FMT and those who received their own fecal microbiota, although the microbiota of responders had distinctive features from that of nonresponders. Cui et al. recently published a pilot study in which they treated patients with refractory CD with a single FMT through the mid-gut. The rate of clinical improvement and remission based on clinical activity at the first month after FMT was 86.7% (26/30) and 76.7% (23/30), respectively. In addition, patients’ body weight increased. Further prospective studies are required to fully assess the safety and efficacy of the FMT in patients with IBD.

3. Functional gastrointestinal disorders

Pinn et al. reported the efficacy of FMT for the treatment of irritable bowel syndrome (IBS). They treated 13 patients (nine with IBS with diarrhea, three with IBS with constipation and one with IBS with a mixed bowel pattern), and followed up for an average of 11 months. Resolution or improvement of symptoms was reported in 70%, including abdominal pain (72%), bowel habit (69%), dyspepsia (67%), bloating (50%), and flatus (42%). In a case series of 45 patients with chronic constipation, who were treated with FMT via colonoscopy followed by a single fecal enema infusion the next day, 40 (89%) reported relief in defecation, bloating, and abdominal pain soon after FMT, with 18 patients reporting normal defecation during the follow up period (9-19 months). Although preliminary studies are promising, RCTs are needed to determine if FMT truly is an effective treatment modality for IBS or chronic constipation.
4. Extraintestinal disorders

FMT can also be used to treat diseases other than gastrointestinal disorders in which the gut microbiota is disturbed. There are preliminary reports on the use of FMT therapy in a wide range of disorders including Parkinson’s disease, fibromyalgia, chronic fatigue syndrome, multiple sclerosis, myoclonus dystonia, obesity, insulin resistance and the metabolic syndrome, and childhood regressive autism. Vrieze et al. performed RCT of FMT in 18 male patients with metabolic syndrome. In patients, who received fecal microbiota infusion from lean male donors, both insulin sensitivity and levels of butyrate-producing intestinal microbiota were markedly increased after six-week infusion, while no significant changes were seen in the control group.

Conclusions

FMT has been shown to be a highly successful treatment option for recurrent and even refractory CDI. The use of FMT as a treatment modality in other gastrointestinal diseases (IBS, chronic constipation and IBD) is only recently being explored, and future RCTs are necessary to better understand the role of the gut microbiota in the pathogenesis and effective treatment of these diseases. Many unanswered questions regarding FMT include an appropriate donor selection, standardized preparation and administration protocols, defined microbial restoration mechanisms, and long-term safety. More research is required in this field.

References

12. Pinn DM, Aroniadis OC, Brandt LJ. Is fecal microbiota transplantation the answer for irritable bowel syndrome? A single-cen-
