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Fecal Microbiota Transplantation

Past, Present and Future

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Abstract and Introduction

Abstract

Purpose of review: Fecal microbiota transplantation (FMT) re-establishes a balanced intestinal flora with resultant cure of recurrent *Clostridium difficile* infection (RCDI). FMT has also been used to treat other gastrointestinal (GI) diseases including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and chronic constipation and a variety of non-GI disorders. The purpose of this review is to discuss the intestinal microbiota and FMT treatment of GI and non-GI diseases.

Recent findings: It is known that an imbalanced intestinal microbiota predisposes to CDI, IBD and IBS. The complex role of intestinal microbiota to maintain health, however, is a newer concept that is being increasingly studied. The microbiome plays an important role in cellular immunity and energy metabolism and has been implicated in the pathogenesis of non-GI autoimmune diseases, chronic fatigue syndrome, obesity and even some neuropsychiatric disorders.

Summary: FMT is a highly effective cure for RCDI, but increased knowledge of the intestinal microbiota in health maintenance, as well as controlled trials of FMT in a wide range of disorders are needed before FMT can be accepted and applied clinically

Introduction

Fecal microbiota transplantation (FMT), or infusion of a fecal suspension from a healthy individual into the gastrointestinal (GI) tract of another person to cure a specific disease, is best known as a treatment for recurrent *Clostridium difficile* infection (RCDI); FMT, however, also has been used successfully for inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), idiopathic constipation and a variety of non-GI diseases. Recent studies have shown that the intestinal microbiota plays an important role in immunity and energy metabolism and that an imbalance in our commensal intestinal bacteria can predispose to disease development.[1] Re-establishment of the wide diversity of intestinal microbiota via infusion of donor feces into the colon is the proposed mechanism by which FMT results in clinical improvement in patients with RCDI.

FMT is by no means a new therapeutic modality, however, it did not receive public attention until recently, after several studies were published showing that stool is a biologically active, complex mixture of living organisms with great therapeutic potential for *Clostridium difficile* infection (CDI)[2–4] and perhaps other GI[5–8] and non-GI disorders.[9,10] The revelations about the human microbiome being published by the Human Microbiome Project consortium is bringing the strength of science to clinical observation, thereby enhancing our understanding of the complexities of our intestine and stool.[11] The administration of human fecal suspension by mouth for patients with food poisoning or severe diarrhea was first reported in fourth century China by Ge Hong.[12] In the 16th century, Li Shizhen described use of a variety of stool products for treatment of diarrhea, fever, pain, vomiting and constipation.[12] In the 17th century, FMT was used in veterinary medicine and later termed 'transfaunation'.[5] The first use of fecal enemas in humans for the treatment of pseudomembranous colitis was reported in 1958 by Eiseman *et al*.[13]

Fecal Microbiota Transplantation Methodology: Route of Administration

Until 1989, retention enema was the most common technique for FMT,[14] however, alternative methods have been used subsequently, including nasogastric tube (1991),[15] colonoscopy (2000),[16] and self-administered enemas (2010).[17] To date, over 400 cases of FMT have been reported worldwide including approximately 75% by colonoscopy or retention enema, and 25% by nasogastric or nasoduodenal tube, or by EGD.[18,19] Although there is no consensus, the colonoscopic approach is favored over fecal enema for RCDI because enemas only reach the splenic flexure,[16] whereas with colonoscopy, the entire colon and ileum can be inoculated and disease extent and severity can be elucidated.[18]

Fecal Microbiota Transplantation Methodology: Stool Preparation

Patients undergoing FMT for RCDI typically remain on their CDI antimicrobials until 2–3 days prior to FMT. A bowel preparation is administered to all patients the day before the procedure, regardless of route. Donor stool is most often used within 8 h of passage, however, frozen stool samples from standardized donors have been thawed and colonoscopically administered 1–8 weeks after passage for treatment of RCDI with similar success rates to fresh stool.[19] The patient's relationship to the donor does not appear to affect outcome.[20,21] The amount of stool used has varied, however, in a recent review, relapse was four-fold greater when less than 50 g of stool was used.[20] Stool is most commonly suspended in nonbacteriostatic saline, however, water and other diluents (e.g., yogurt and milk) have been used without consistent differences in resolution or relapse rates.[20] Donated stool is mixed with diluent to a consistency that can be injected via the biopsy channel of a colonoscope. Before aspiration into a syringe, the suspension is filtered through gauze pads or strainer to remove large particulate matter. The volume of stool suspension used for FMT has varied from 200 ml or less to 500 ml or more, and it appears there is a trend toward improved outcome with larger volumes.[20]

Fecal Microbiota Transplantation Methodology: Donor Screening

In general, donors are excluded if they have taken antibiotics within the preceding 3 months; are on immunosuppressive or chemotherapeutic agents; have known or recent exposure to HIV; hepatitis B or C; have a current communicable disease; are morbidly obese; have IBD, IBS, atopy, chronic diarrhea or constipation; GI malignancy or polyposis; participate in high-risk sexual behaviors; use illicit drugs; have a history of recent incarceration or travel to areas with endemic diarrhea. Donor blood testing should be performed for HIV, hepatitis A, B and C; donor stool testing includes culture, C. difficile toxin, ova and parasites, Giardia antigen, cryptosporidium antigen and *Helicobacter pylori* antigen if the oral route is to be used.[14]

Treatment of Gastrointestinal Diseases: *Clostridium difficile* Infection

The incidence of CDI has increased to epidemic proportion over the past 10–15 years. In the United States, from 1996 to 2003, CDI doubled from 98 000 to 178 000 cases and 31–61/100 000 hospital discharges,[22] whereas the unadjusted case-fatality rate rose from 1.2% in 2000 to 2.3% in 2004.[23] It is now estimated that between 500 000 and 700 000 cases of CDI occur annually in US hospitals and long-term care facilities with an estimated hospital excess cost of care of approximately 3.2 billion dollars.[24]

Currently, first-line treatment for CDI includes cessation of the culprit antibiotic, if possible, and treatment with metronidazole or vancomycin (or fidaxomicin) depending on disease severity.[25,26] Most patients with CDI initially respond to this treatment, but recurrence rates are 15–30%.[27] Patients who have one recurrence have up to a 40% chance of a second recurrence, and after their second recurrence, up to 65% of patients will suffer a third.[28] Recurrences are usually treated with additional courses of metronidazole, oral vancomycin or prolonged vancomycin in pulsed-tapered regimens.

The high recurrence rates of CDI prompted the need for alternative therapies, for which FMT offers a rational and straightforward approach. It is now accepted that disruption of the normal balance of colonic microbiota from antibiotic use or other insult results in CDI. Patients with RCDI have decreased species richness and a reduction of

Bacteroidetes and *Firmicutes* phyla in their stool as compared to patients with just one episode of CDI or antibiotic-associated diarrhea.[4] FMT likely provides therapeutic benefit by reintroducing a balanced microbiota via donor feces.[29] Studies using terminal restriction fragment length polymorphism analyses and gene sequencing techniques have shown that the bacteria of the recipient's stool closely resembles that of the donor about 2 weeks after FMT and is dominated by *Bacteroides* spp;[2,3] this alteration persists for more than 30 days after transplantation.[2,3]

Current literature on FMT for RCDI is predominantly comprised of single center case series and case reports,[30–41] a meta-analysis[42] and one systematic review.[20] In all, about 92% of patients were cured of their RCDI, with a range of 81–100%.[20,30–42] A multicenter long-term follow-up study of patients who underwent colonoscopic FMT for RCDI reported an astounding overall ultimate cure rate of 98%.[21] Patients in this study had symptoms for an average of 11 months before FMT and most (74%) reported resolution of diarrhea within 3 days.[21] Immediate symptom resolution and long disease-free intervals after FMT for RCDI also have been reported in other studies,[5,20,31,32] and may result from the durable effect of FMT on re-populating the colon with normal commensal organisms.[2,3]

A systematic review of FMT, including all methods of administration and comprising 317 patients from eight countries and 27 case series and reports, reported an overall cure rate for RCDI of 92%.[20] FMT via colonoscopy or enema has proved more successful for RCDI than the nasogastric route; the latter gives an overall resolution rate of 80%.[20]

Perhaps surprisingly, FMT has been found to be quite acceptable to patients. In the recent multicenter study, 97% of patients with RCDI reported willingness to undergo another FMT if they were to have a repeat CDI episode, and 53% stated that they would choose FMT as first-line therapy before antibiotics.[21]

Treatment of Gastrointestinal Diseases: Inflammatory Bowel Disease

Specific infectious agents, such as *Mycobacterium paratuberculosis* and invasive E. coli, have been etiologically linked to Crohn's disease, however, isolation of a causative pathogen is awaited in ulcerative colitis.[11] An alternative hypothesis, now widely accepted, suggests that IBD results from continuous antigenic stimulation by nonpathogenic commensals, leading to an exaggerated sustained immune response in genetically predisposed hosts.[11] Dysbiosis, or dysregulation between protective and injurious commensals, is the mechanism by which intestinal flora are thought to lead to IBD.[43] First, patients with IBD have an abundance of Enterobacteriaceae and paucity of *Faecalibacterium* prausnitzii.[11] Second, IBD patients also have 30–50% reduction in the biodiversity of their intestinal microbiota, attributable to decreased *Firmicutes* (specifically *Lachnospiraceae*) and Bacteroidetes.[43,44] Third, patients with IBD are more likely to have been prescribed antibiotics in the 2–5 years preceding their diagnosis.[45] Finally, colitis is absent in germ-free, genetically susceptible mice but develops in the presence of intestinal microbiota.[43] Thus, it seems reasonable that restoration of a healthy balance of intestinal flora by FMT could be therapeutic for IBD.

FMT for refractory ulcerative colitis has been described in four publications, comprising nine patients,[6–8,46] all of whom had severe, active longstanding ulcerative colitis (mean, 8.6 years) refractory to treatment with corticosteroids, 5-aminosalicylates and azathiaprine.[5] FMT was administered as retention enemas and resulted in the complete resolution of all symptoms with cessation of ulcerative colitis medications within 6 weeks without relapse.[5] Remission was maintained for up to 13 years and follow-up colonoscopy in eight of the nine patients showed no evidence of ulcerative colitis (n = 6) or only mild chronic inflammation (n = 2).[6–8] Only one case report has been published on FMT for Crohn's disease, a patient who was refractory to prednisone and salazopyrin and responded to FMT within three days allowing discontinuation of medications;[6] disease relapsed within 18 months.[5]

Use of colonoscopic FMT followed by self-administered fecal enemas in a tapered fashion and as maintenance therapy for ulcerative colitis has been described in an additional eight patients (Brandt and Aroniadis, ACG annual meeting, 2012). After FMT, seven of these eight (88%) patients reported improvement in stool frequency and abdominal pain, however, the degree of benefit varied widely and was maximal in those with concomitant CDI (n = 3), or newly diagnosed ulcerative colitis in the setting of antibiotic use (n = 1) and those who were able to effectively retain the enemas.

FMT may be efficacious in managing refractory ulcerative colitis, however, multiple infusions seem to be required to maintain remission. Additionally, FMT may provide greater therapeutic benefit in patients whose onset of ulcerative colitis was associated with an alteration in the fecal microbiota from antibiotic use or concomitant colonic infection. Experience with FMT for ulcerative colitis is just beginning and controlled trials are needed to establish its role, if any.

Treatment of Gastrointestinal Diseases: Irritable Bowel Syndrome and Chronic Constipation

Postinfectious IBS has been reported in up to 30% of patients with acute gastroenteritis, suggesting that the pathogenesis of IBS may be intimately linked to an altered intestinal microbiota.[47–49] The composition of the intestinal microbiota in patients with IBS has not been extensively studied, however, patients with constipation-predominant IBS have been shown to increase population of sulphate-reducing bacteria compared with healthy controls.[50] Probiotics can restore the intestinal microbiota in patients with IBS[49,51] and result in improvement of postinfectious IBS in animal models;[11] FMT, however, may prove more beneficial, as donated feces, in a sense, are the ultimate human probiotic.

In a case series of 55 patients with IBS and IBD treated with FMT, cure was reported in 20 (36%), decreased symptoms in nine (16%) and no response in 26 (47%) patients.[6] In another series, 45 patients with chronic constipation were treated with colonoscopic FMT and subsequent fecal enema infusions, 89% of whom (40 of 45 patients) reported relief in defecation, bloating and abdominal pain immediately after the procedure.[52] Normal defecation, without laxative use, persisted in 18 of 30 patients (60%) contacted 9–19 months later.[52]

Treatment of Nongastrointestinal Diseases

Studies in germ-free animals suggest that intestinal microbiota may contribute to pathogenesis of non-GI diseases. Germ-free animals exhibit dysregulation of their hypothalamic–pituitary–adrenal axis leading to an exaggerated stress response, impaired cardiac output, altered brain derived hormones (e.g., norepinephrine and tryptophan) and increased caloric intake to maintain body weight.[11] Moreover, the microbiota may play a role in pathogenesis of various neurologic disorders and data support the concept of the brain–gut–microbiota axis.[53] Introduction of pathogenic bacteria into the rodent colon results in activation of brain stem nuclei possibly via the afferent vagus nerve, which originates in the brainstem and innervates abdominal viscera.[11]

Treatment of Nongastrointestinal Diseases: Autoimmune and Neurologic Disorders

The beneficial effect of FMT on non-GI disorders was a serendipitous observation. In one patient with ulcerative colitis and idiopathic thrombocytopenic purpura (ITP), FMT not only resulted in remission of ulcerative colitis but also reversal of ITP with platelet counts that increased from a mean of 97 to 195 × 10^9 µl.[54] Normal defecation was achieved in three patients with multiple sclerosis, who underwent FMT for chronic constipation and who also noted improvement of motor symptoms and urinary function, resulting in a regained ability to walk and removal of indwelling catheters.[55] One report described the co-development of myoclonus dystonia and chronic diarrhea in a 6-year old child who had ongoing myoclonus dystonia symptoms for 22 years.[56] FMT resulted in 90% improvement of her myoclonus dystonia symptoms, allowing her to resume employment and execute fine motor tasks, such as drinking from a cup, fastening buttons, and dressing.[56] Neurologic improvement has also been reported in one patient with Parkinson's disease after FMT for chronic constipation.[10]

Treatment of Nongastrointestinal Diseases: Obesity

The intestinal microbiota metabolize ingested nutrients into energy-rich substrates for utilization by the host and commensal flora[11,57] and can adapt their metabolism based on nutrient availability.[11] Obese mice have an increased capacity to harvest energy from luminal nutrients compared with their lean counterparts, which is reflected by a higher *Firmicutes* to *Bacteroidetes* ratio.[11,58] In fact, a 60% increase in body fat and insulin resistance results

when intestinal microbiota from conventionally raised mice are introduced into germ-free mice.[59] Furthermore, the obese (*ob/ob*) phenotype has been shown to be transmissible and is adopted in germ-free mice, infused with intestinal microbiota from conventionally raised, genetically obese mice.[58] Related data are sparse in humans. One double-blinded, controlled trial randomized 18 men with metabolic syndrome to FMT using their own feces or feces donated from lean men.[9] The nine men who received stool from lean donors developed markedly reduced fasting triglyceride levels and peripheral and hepatic insulin sensitivity after FMT compared with those who were transplanted with their own (placebo) stool.[9]

Treatment of Nongastrointestinal Diseases: Chronic Fatigue Syndrome

Thirty-four patients with chronic fatigue syndrome (CFS) were treated with FMT and followed over 11–28 months: 14 (41%) reported persistent relief and 12 (35%) showed little or late relief of related symptoms.[60]

Treatment of Nongastrointestinal Diseases: Autism

A role for microbiota in the pathogenesis of autism is supported by studies which show that the onset of autism is often accompanied by GI complaints and preceded by antibiotic use.[11] Additionally, oral vancomycin has been shown to improve symptoms.[11] In a single case series, the intestinal microbiota of 13 children with autism were analyzed and compared with nine children without the disease.[61] The autistic children were found to have greater numbers and different types of clostridial species when compared with controls.[61] There are published observations of improvement in autistic symptoms in two children after FMT and in five children who received daily cultured *Bacteroidetes* and *Clostridia* for several weeks (T. Borody, personal correspondence).

Conclusion

FMT re-establishes a balanced intestinal microbiota and results in impressive cure rates in patients with recurrent CDI. Standardization of FMT protocols and a randomized controlled trial are ongoing. The complexity of the fecal microbiota is actively being defined and recent studies have shown that the pathogenesis of many diseases, both GI and non-GI, result from microbiota-related dysregulation. FMT is likely to achieve widespread therapeutic benefit for a variety of diseases in the future.

Sidebar

Key Points

- Intestinal microbiota play a role to maintain health and to regulate cellular immunity and energy metabolism.FMT has a cure rate exceeding 90% worldwide for RCDI.
- Case series report promising results for FMT treatment in IBD and IBS, however, randomized controlled trials are needed to validate clinical observations.
- Studies are needed to determine whether FMT is a valid treatment for a wide variety of non-GI diseases including Parkinson's disease, autism, multiple sclerosis, chronic fatigue, and obesity among others.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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