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REVIEW ARTICLE

Contemporary Applications of Fecal Microbiota Transplantation to Treat Intestinal Diseases in Humans

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The intestinal microbiota comprise an important organ that plays a vital role in host digestion, development, energy maintenance, hemostasis, and immunity. Disruption of the gut microbial community due to diet, lifestyle, or antibiotic exposure increases susceptibility to chronic infection and disease. Fecal microbiota transplantation (FMT) involves the transfer of gut microbiota from a healthy donor to a patient in order to restore normal diversity and function of the microbial community. This method has become a well established alternative therapy for the treatment of recurrent *Clostridium difficile* infection. Recent clinical trials and studies in animal models suggest promise for this method to treat inflammatory bowel diseases, as well as metabolic syndrome. In addition, due to signaling interactions between the gut microbiota and brain, FMT has been suggested as a potential treatment for some psychological disorders, including autism spectrum disorder. Importantly, advances in next-generation sequencing and multi-omics approaches are increasingly improving our understanding of the mechanisms by which FMT results in cure of these various conditions. In this review, we summarize the current applications of FMT and highlight potential future uses and current challenges in understanding and optimizing FMT procedures. © 2017 Published by Elsevier Inc. on behalf of IMSS.

Key Words: Clostridium difficile, Diseases, Dysbiosis, Inflammatory bowel disease, Fecal microbiota transplantation, Metabolic syndrome.

Introduction

Over the last several decades, the gut microbiota has been identified as an organ-like assemblage that plays a critical role in host development, energy production, metabolism, and immunity (1). Recent applications of next-generation sequencing technologies, led by groups such as the Human Microbiome Project (2), have allowed for improved characterization of this community, especially among the bacteria. The intestinal bacteria are primarily comprised of the phyla Firmicutes and Bacteroidetes, but a core group of bacterial species is not shared among all healthy individuals (3). Instead, functionality of the microbial community is conserved, allowing for a variety of healthy assemblages. This is due, in large part, to functional redundancy and guild structure among bacterial species (3). Nevertheless, disruption of the indigenous bacterial community as a result of factors such as diet (4,5) or antibiotic exposure (6,7) can result in dysbiotic assemblages that favor acquisition or propagation of infectious agents and the development of disease (1).

Fecal microbiota transplantation (FMT) involves the transfer of the microbiota from the stool of a healthy individual to the intestinal tract of a recipient patient with a dysbiotic microbiota. This procedure has been shown to reconstitute a normally functioning microbial consortium (8–16). Contemporarily, the procedure was performed in 1958 to treat pseudomembranous colitis and has recently become recognized as a reliable and efficacious treatment for recurrent *Clostridium difficile* infections (R-CDI)

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(15−21). However, literature does point to its use nearly 1,700 years ago by Chinese physicians (22).

Fecal microbiota can be administered to patients via a variety of routes including enemas (23), nasogastric or nasoduodenal tubes (9,24), colonoscopy (16,25), or via oral capsule (26,27). Moreover, the use of frozen or freeze-dried fecal material from anonymous, pre-screened, healthy donors is now common (16,27,28). Unlike traditional antibiotic treatment approaches, FMT does not cause an underlying dysbiosis that leaves the patient susceptible to infection (9,29). The mechanisms by which FMT abrogates infection are only beginning to be characterized (15), and likely involves restoration of gut ecology, the structure and function of gut microbiota, and signal exchange between microbes and the host.

Treatment of R-CDI is the most widely used application of FMT in human patient cohorts (21), although several studies have suggested that FMT may also be efficacious in treating or mitigating symptoms associated with metabolic syndrome (30), autism spectrum disorder (31), or antibiotic resistant bacteria (32). Similarly, FMT is thought to represent a novel treatment for inflammatory bowel disease (IBD) (33), although inconsistent results have been observed when FMT was used to resolve R-CDI with underlying IBD (34,35), or to treat Crohn's disease or ulcerative colitis alone (36−42). There is also currently an on-going clinical trial in the United States investigating the efficacy of FMT to treat primary sclerosing cholangitis (clinicaltrails.gov identifier: NCT02424175). Moreover, animal models have suggested the efficacy of FMT in mitigating metabolic syndrome, as well as other diseases thought to be associated with the gut microbiota (43−46). Results of animal studies must be interpreted carefully, though, due to differences in microbiota between hosts (47), as well as incomplete development of the immune and digestive systems in germ-free models (48). In this review, we discuss the current knowledge regarding the efficacy of FMT to treat R-CDI, inflammatory bowel diseases, obesity and metabolic syndrome, and other disorders. This review also highlights the current challenges in evaluating and optimizing FMT protocols.

Recurrent Clostridium difficile *Infection*

The increased use of FMT has come about primarily as a result of the rapid increase in the severity and frequency of antibiotic resistant *C. difficile* infections (49). The majority of FMT studies done to treat R-CDI have been case series reporting a mean of 85% cure, among all delivery methods, and ≥90% for colonoscopic FMT (20). The first randomized clinical trial (RCT) of FMT to treat R-CDI compared nasogastric FMT against two control groups that were both administered vancomycin and observed 81% resolution of symptoms following FMT but only 23−31% resolution in control groups ($p < 0.001$) (9). A similar result was observed in a subsequent RCT performed by a different group (29). Another RCT evaluated nasogastric versus colonoscopic FMT and found higher, but non-significant ($p = 0.63$), rates of cure using the colonoscopic method (80%), compared to the nasogastric method (60%) (25). The efficacy of using frozen, random donor material was shown to resolve R-CDI symptoms (28) and was recently shown to be non-inferior to fresh donor material in a RCT (50). Furthermore, a dual-center, placebo-controlled RCT found that colonoscopic FMT using donor material resulted in significantly higher rates of resolution (91%) than when autologous FMT was performed (63%, $p = 0.024$) (16). Taken together, FMT has been proven to be an effective treatment for R-CDI and recent guidelines in both the United States and Europe now recommend the use of FMT following a second or third recurrence of *C. difficile* infection (51,52).

Changes in the Microbiota

The microbiota in patients suffering from R-CDI, but not an initial *C. difficile* infection, is significantly less diverse than those of healthy individuals, likely due to repeated exposure to antibiotic treatment regimens (53−55). These dysbiotic communities are generally characterized by a drastic reduction in members of the phylum Bacteroidetes and increases in the Gammaproteobacteria, particularly among members of the genera *Klebsiella*, *Escherichia,* and *Pseudomonas*, among others (11,53−56). Multiple studies have shown that colonoscopic FMT results in normalization of the microbiota within 24 h following treatment (10,11,14), typically characterized by increases in the relative abundance and diversity within the phylum Bacteroidetes (56,57). These changes have been shown to persist for several years following FMT, although some plasticity has been observed in both donor and patient microbial communities over this timespan (14,58). While these general trends are observed across almost all FMT studies done to cure R-CDI, specific species that are indicative of R-CDI, or required for cure following FMT, have not been identified (56,59). Thus, it is likely that restoration of total microbial community function, rather than any specific distribution of species, is the critical result of FMT.

Several studies have reported differences in the extent of fecal microbiota transfer, or engraftment, to patients as a result of the donor community composition (36,54,59,60). In one such study, patient similarity among donor-recipient pairs did not differ significantly ($p = 0.08$), but patients who received material from a donor with greater abundances of *Bacteroides* spp. (*e.g. B. intestinalis*, *B. plebeius*, and *B. uniformis*) showed comparatively higher levels of community similarity to the donor (54). Similarly, taxa or phylotypes that were abundant in donors were more likely to be represented in patient samples following antibiotic treatment and FMT (36,59). However, transfer of