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Clinical Application and Potential of Fecal Microbiota Transplantation

R.E. Ooijevaar,[1] E.M. Terveer,[2] H.W. Verspaget,[3] E.J. Kuijper,[2] and J.J. Keller[3,4]

[1]Department of Gastroenterology and Hepatology, and Department of Medical Microbiology and Infection Control, VU University Medical Center, 1181 HZ, Amsterdam, The Netherlands

[2]Department of Medical Microbiology, Center for Infectious Diseases, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands

[3]Department of Gastroenterology and Hepatology and Centralized Biobanking Facility, Leiden University Medical Center, 2333 ZA, Leiden, The Netherlands

[4]Department of Gastroenterology and Hepatology, Haaglanden Medical Center, 2597 AX, The Hague, The Netherlands; email: j.keller@haaglandenmc.nl

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Abstract

Fecal microbiota transplantation (FMT) is a well-established treatment for recurrent *Clostridioides difficile* infection. FMT has become a more readily available and useful new treatment option as a result of stool banks. The current state of knowledge indicates that dysbiosis of the gut microbiota is implicated in several disorders in addition to *C. difficile* infection. Randomized controlled studies have shown FMT to be somewhat effective in treating ulcerative colitis, irritable bowel syndrome, and hepatic encephalopathy. In addition, FMT has been beneficial in treating several other conditions, such as the eradication of multidrug-resistant organisms and graft-versus-host disease. We expect that FMT will soon be implemented as a treatment strategy for several new indications, although further studies are needed.

INTRODUCTION

Fecal microbiota transplantation (FMT) is now an established treatment for recurrent *Clostridium difficile* infection (reclassified as *Clostridioides difficile*) (rCDI) (1, 2), with cure rates of 80–90% (3). FMT is the transfer of fecal microbial content from a healthy individual into the gastrointestinal (GI) tract of a diseased individual. The mechanism of action is not completely understood, but restoration of a disturbed microbiota (also known as dysbiosis, which is required for CDI pathogenesis) seems to underlie the observed effect (4). Dysbiosis may also be involved in the pathogenesis of many other conditions, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), multiple sclerosis (MS), hepatic encephalopathy (HE), and metabolic syndrome. Targeting the disturbed microbiota, which may be achieved by dietary interventions, probiotics, prebiotics, antibiotics, and FMT, might influence the course of these diseases. FMT seems the most powerful yet uncontrolled strategy to target the microbiota.

Although FMT appears to be safe and easy to perform, it should be used with caution because long-term effects are still unknown or unrecognized. FMT is currently indicated only for the treatment of rCDI (1, 2). However, many clinical trials are investigating the effects of FMT on other conditions, and thus FMT may soon become a treatment approach for a subset of patients with IBD, HE, and other disorders. This review addresses the clinical use of FMT for patients with CDI and summarizes the current knowledge about its potential future indications for other conditions.

THE DYSBIOTIC GUT MICROBIOTA AS A TARGET FOR THERAPY

The human adult microbiota consists of roughly 40×10^{12} bacteria (~0.2 kg) that provide essential metabolic and biological functions such as extracting energy, producing growth factors, stimulating the immune system, and creating colonization resistance (5). The term gut microbiota is defined as the whole population of bacteria, viruses, parasites, and fungi colonizing the intestinal tract (5). The adult gut microbiota consists of more than 2,000 species of bacteria, of which the density and diversity increase from stomach to colon. The healthy gut microbiota is a diverse, stable, resistant, and resilient microbial ecosystem (6). Dysbiosis is a perturbation in function and composition of microbiota that is driven by environmental and host-related factors. The microbiota is predominantly formed by environmental factors (7). Bacteroidetes and Firmicutes are two major phyla, together representing ~90% of the microbiota (8).

The gut microbiota in a dysbiotic state has increasingly been implicated in the pathogenesis and progression of numerous diseases. However, whether dysbiosis reflects changes caused by the disease itself, or should be considered as a driving step in the pathogenesis, is not always understood. Dysbiosis results in the disturbance of several metabolic pathways that influence immunological and mechanical processes both in and outside the intestine, and it impairs colonization resistance. These processes may be reverted by FMT, as shown in **Figure 1**.

Colonization Resistance

Colonization resistance is the protection provided by the healthy microbiota against invading bacterial pathogens and overgrowth of commensal bacteria. This process is poorly understood but seems to occur through direct (host-unrelated) and indirect (host-related) pathways (9). The direct pathways include nutrient competition, production of bacteriocins (peptides with often narrow-spectrum antimicrobial properties produced by bacteria), presence of bacteriophages (viruses that can lyse bacterial cells), and type VI secretion systems (10–12). The indirect pathways include

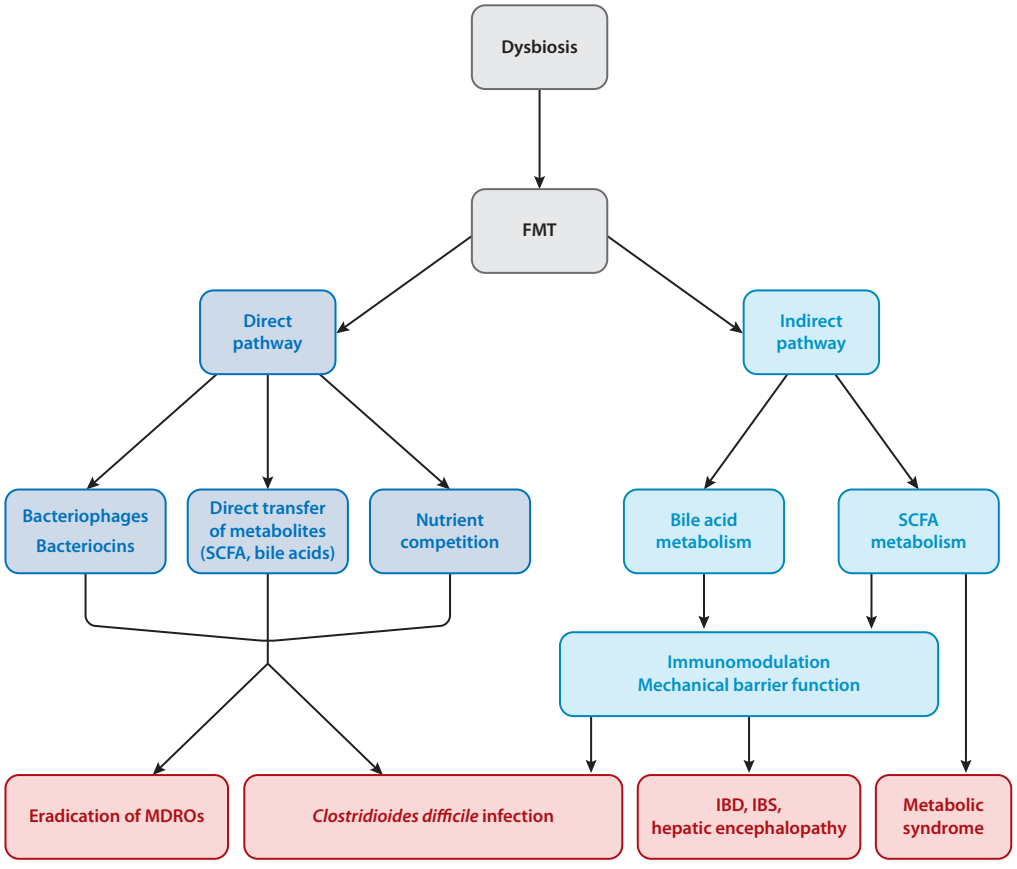

Figure 1

Mechanisms of FMT in a proposed schematic diagram of how FMT exerts its effect by restoring normal microbiota composition. The direct pathway is unrelated to the host and transfers directly with the FMT. Host-related factors are involved in the indirect pathway. Observed clinical effects of FMT have been linked to a perturbation in one or both pathways. An effect of FMT was found for the listed conditions in clinical trials. Abbreviations: FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; MDRO, multidrug-resistant organism; SCFA, short-chain fatty acids.

epithelial barrier maintenance mediated by innate immune receptors and short-chain fatty acid (SCFA) metabolism, as well as bile acid metabolism, which can influence the germination, growth, and sporulation of bacteria (9, 13). In addition, Paneth and intestinal epithelial cells also produce antimicrobial peptides, a process that appears to be driven by the microbiota (14).

Short-Chain Fatty Acids

SCFAs are produced by the gut microbiota through fermentation of indigestible starches and complex sugars (15). The most common SCFAs in the gut are propionate, acetate, and butyrate. Bacteroidetes produce mainly propionate and acetate, whereas Firmicutes produce mostly butyrate (16). Immunomodulatory effects associated with SCFAs include an enhanced barrier function and proliferation of gut epithelial cells, decreased induction of proinflammatory cytokines, and stimulation of the presence of regulatory T cells (17). The increase in these cells promotes mucosal homeostasis and protection from colonic inflammation (18). SCFAs may also

potentiate a proinflammatory state in gut epithelial cells and in leukocytes (19). FMT may affect SCFA metabolism by resolving dysbiosis or directly transferring SCFAs, which may underlie the observed effects of FMT in metabolic syndrome, HE, and IBD (see below).

Bile Acid Metabolism

The primary bile acids cholic acid and chenodeoxycholic acid produced by hepatocytes are secreted in the duodenum, which facilitates the absorption and digestion of fat and fat-soluble vitamins in the small bowel. Ninety-five percent of primary bile acids are reabsorbed in the distal ileum for reprocessing (enterohepatic circulation) (20). The 5% of acids that cannot be reabsorbed by enterohepatic circulation are processed as secondary bile acids by 7α-dehydroxylation, which is mediated by certain bacteria (21). Both primary and secondary bile acids play an important role in protecting against bacterial overgrowth, immunomodulation, and inducing gut epithelial integrity (22). Mice lacking G-protein-coupled bile acid receptor-1 show increased susceptibility to colitis (23). Furthermore, bile acids suppress inflammatory response in human macrophages by inhibiting the production of proinflammatory cytokines (24, 25). In CDI, dysbiosis results in decreased conversion of primary bile acids into secondary bile acids. Primary bile acids may promote germination of *C. difficile*, whereas secondary bile acids prevent germination (26). FMT may restore bile acid metabolism by correcting dysbiosis or directly transferring primary and secondary bile acids.

FECAL MICROBIOTA TRANSPLANTATION IN *CLOSTRIDIOIDES DIFFICILE* INFECTION

The undisputed model of a disorder that is associated with dysbiosis of the gut microbiota is CDI. *C. difficile* is a Gram-positive anaerobic, spore-forming bacteria. Two major events take place during the pathogenesis of CDI: (*a*) dysbiosis characterized by the loss of diversity in and richness of the microbiota, predisposing the individual to spore germination and colonization of *C. difficile*; and (*b*) outgrowth and toxin production of *C. difficile* (4, 27). An infection caused by *C. difficile* can present with symptoms ranging from mild diarrhea up to severe pseudomembranous colitis (4). After antibiotic treatment with vancomycin, metronidazole, or fidaxomicin, recurrence is found in ∼20% of patients with their first CDI episode, and recurrence rates increase with subsequent episodes (1, 2, 28). Recurrence seems related to inadequate recovery of the gut microbiota in a subset of patients, which enables the renewed outgrowth of antibiotic-resistant *C. difficile* spores (29). Several randomized controlled trials (RCTs) have shown that FMT is superior to antibiotics for curing patients with rCDI (30–32). A recent meta-analysis concluded that FMT results in a clinical resolution of CDI symptoms in up to 90% of patients (3). The use of frozen feces suspensions seems to be as effective as that of fresh suspensions, which justifies the storage of feces samples and simplifies the logistics of FMT (33). In general, FMT is advised for patients with rCDI; however, the optimal timing of FMT is unknown. Although it is generally proposed as treatment for patients with a third CDI recurrence, FMT may also be beneficial for patients with a second or even first recurrence, depending on the clinical course and the patient's comorbidities. In general, FMT may be considered at an earlier stage if (*a*) previous episodes were characterized by more severe disease, (*b*) there is a need for prolonged hospitalization or the patient is a resident of a long-term care facility, or (*c*) comorbidities justify prompt treatment.

Whether patients with a first episode of CDI may benefit from FMT is unknown. However, in patients with a first episode of antibiotic-refractory or severe CDI, FMT is successful and may even be lifesaving. A retrospective cohort study described 111 patients with severe CDI, including

66 patients who were treated with FMT and 45 who were treated without FMT. The three-month mortality rate after a diagnosis of severe CDI was 12% (8/66) in FMT-treated patients versus 42% (19/45) with the standard of care, $p < 0.001$ (34).

Fecal Microbiota Transplantation Protocols and Standardization

To date, FMT is not a standardized treatment, and protocols differ according to local procedures. In addition, legislation concerning FMT is not uniform, although FMT for rCDI is an accepted treatment in many countries.

The preferred route of administration for FMT remains a topic of discussion. FMT can be delivered through the upper GI route, via a duodenal tube or capsules taken orally (31, 32), or through the lower GI route, via colonoscopy or enema (30, 35). Efficacy of FMT for the resolution of CDI seems to be more or less equal regardless of the route of administration, although FMT by enema requires repeated attempts (3). To date, no evidence has shown that small intestinal bacterial overgrowth is induced by FMT through the upper GI route. Risk factors for procedure-related adverse events may guide the choice for a particular route of delivery. For example, risk factors for aspiration may favor the use of colonoscopy, whereas the upper GI route may be used to avoid colonoscopy in fragile patients. A recent study showed high cure rates in patients treated with oral capsulized FMT, a method that may decrease patient discomfort (31). However, the method requires swallowing large numbers of capsules, which are not readily available.

In general, patients with recurrent CDI are treated with antibiotics for at least four days prior to the infusion of the donor feces suspension. Antibiotic therapy should be stopped at least 24 h before FMT and should not be continued post-FMT unless severe colitis exists. Antibiotic stewardship following FMT is warranted to prevent the prescription of unnecessary antibiotics, which may cause post-FMT recurrences (36). Bowel lavage is routinely performed prior to FMT by colonoscopy. Whether it is required to promote engraftment of donor microbiota is unknown. We generally advise bowel lavage with reduced volumes of a macrogol solution prior to upper GI FMT, although its contribution to the observed efficacy is questionable because oral capsulized FMT without a prior bowel lavage appears to be effective as well (37). Other medications, including proton pump inhibitors, also affect the microbiota (38); whether they influence FMT outcomes is unknown.

In general, FMT seems safe, although data about long-term patient follow-up are still lacking. Clinical trials rarely report serious adverse events related to FMT in patients with rCDI (30–32). Side effects occur more frequently in patients with active ulcerative colitis (UC) or Crohn's disease (CD) treated with FMT; fever, increased C-reactive protein, and bacteremia have been reported (39–41). These observations may be explained by the exposure of an inflamed (diseased) mucosa to donor microbiota, in contrast with rCDI patients who are pretreated with antibiotics before FMT.

Stool Banking

With the increasing interest in FMT, standardization and easy access to donor feces suspensions are needed to treat patients. To meet these needs, we advocate the use of stool banks. Stool banks can operate at an institutional, national, or international level. Examples of stool banks are OpenBiome and the Netherlands Donor Feces Bank (NDFB). The primary aim of a stool bank is to provide high-quality, ready-to-use donor feces suspensions from a prescreened, well-defined donor pool, enabling easy, safe, and cost-effective FMT treatment (42). The working process of a stool bank is outlined in **Figure 2**. Stool banking enables quality assurance and central registration of adverse events, both of which increase the safety of this unstandardized treatment approach. The NDFB

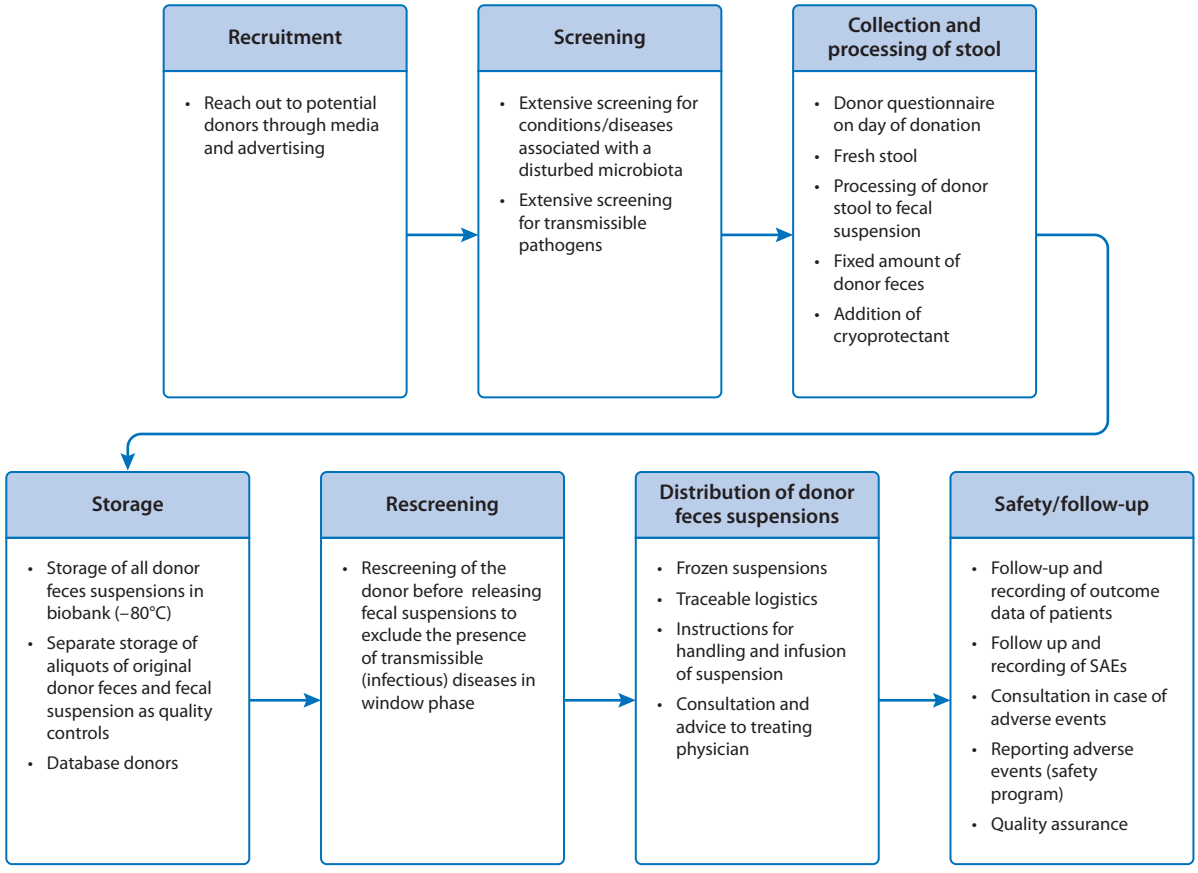

Figure 2

A proposed workflow diagram for the process of running a stool bank. Extensive screening and rescreening of (potential) donors are performed before distribution of frozen, ready-to-use donor feces suspension. Upon donation, stool should be processed as soon as possible (within 6 h) to sustain viability of the donor's microbiota. A cryoprotectant is added to the fecal suspension to allow adequate storage at −80°C. An aliquot of each donation should be stored for potential analysis in case of SAEs. Abbreviations: FMT, fecal microbiota transplantation; SAE, serious adverse event.

discusses each application for FMT in an independent, multidisciplinarily competent body before dispensing donor fecal suspensions. This competent body is also available for consultation in the case of serious adverse events (SAEs) and reports on SAEs. It is important to collect follow-up and safety data on all patients treated.

INFLAMMATORY BOWEL DISEASE

CD and UC are chronic inflammatory disorders that affect parts of the GI tract and can even present with extra intestinal symptoms. Growing evidence supports a role of the gut microbiota in the pathogenesis of IBD (43). CD can be treated by the diversion of the fecal stream, whereas relapse occurs with restoration of the fecal stream and reexposure to luminal contents. In addition, antibiotics can be used as induction therapy in CD and UC, and strict enteral nutrition can induce remission in CD (44, 45). Indeed, dysbiosis of the gut microbiota in patients with IBD exists, as demonstrated by a reduced microbial diversity and loss of anaerobic bacteria (46), which may be a

Table 1 Methods and outcomes of studies investigating FMT as induction therapy in patients with mild or moderate UC activity

Feature of study	Moayyedi et al. (48)	Rossen et al. (50)	Paramsothy et al. (49)	Costello et al. (47)
Study design	Double-blind RCT	Double-blind RCT	RCT	RCT
Number of patients [placebo]	75 [37]	48 [25]	81 [40]	73 [35]
Treatment regimen	6 FMTs	2 FMTs	40 FMTs, 39 enemas, 1 colonoscopy	3 FMTs, 2 enemas, 1 colonoscopy
Comparator (placebo)	Water	Autologous FMT	Water	Autologous FMT
Route of administration	Lower GI, enema	Upper GI, duodenal tube	Lower GI, retention enema, colonoscopy	Lower GI, retention enema, colonoscopy
Stool donor per suspension	Single donor	Single donor	Multiple donors	Multiple donors
Follow-up	6 weeks	12 weeks	8 weeks	8 weeks
Primary endpoint	Endoscopic remission	Endoscopic remission	Endoscopic response	Endoscopic remission
Primary outcome FMT versus comparator	24% (9/38) versus 5% (2/37) $p = 0.03$	30% (7/23) versus 20% (5/25) $p = 0.51$	27% (11/41) versus 8% (3/40) $p = 0.02$	32% (12/38) versus 9% (3/35) $p < 0.01$

Abbreviations: FMT, fecal microbiota transplant; GI, gastrointestinal; RCT, randomized controlled trial; UC, ulcerative colitis.

promising target for new treatment strategies. Initial studies addressing the efficacy of probiotics in IBD treatment showed disappointing results (43). However, four RCTs investigating FMT as induction therapy in patients with mild or moderate UC activity showed promising results for a small subset of patients (**Table 1**) (47–50).

Although two studies were terminated after an interim analysis showing no significant difference between FMT and placebo, the outcomes appeared slightly better with FMT (48, 50). The difference in efficacy among donors in one study was remarkable, and the microbiota profile of patients who achieved remission after FMT resembled that of their donor (48). A recent meta-analysis suggests that the pooled results of the four RCTs show some benefit of FMT over placebo, with the endpoint defined as endoscopic remission (39/140, 28%, versus 13/137, 9%, $p < 0.01$) (51).

In CD, RCTs are lacking; only small uncontrolled cohort studies have been performed, with mixed results. A meta-analysis reports a pooled remission rate of 52% among 71 CD patients treated with FMT (52). However, the remission rate was attributed mainly to one large cohort study (53). Furthermore, the only study reporting endoscopic outcome in CD showed no endoscopic remission at eight weeks post-FMT (54).

Because the observed effects have been very modest, FMT should still be considered an experimental approach in IBD. Future studies may have to implement rational donor selection (use of super donors), selection of patients who are more likely to respond, and anaerobic processing of donor feces. In addition, little is known about the timing of FMT in patients with IBD: Should it be used as induction therapy or applied after initiation of induction therapy? Studies addressing the above questions may pave the way for FMT as a future treatment approach for a subset of patients with UC and CD.

In relation to treating rCDI with FMT in IBD patients, a meta-analysis showed that FMT is equally effective for treating rCDI in patients with IBD (initial cure rate of 81%) when compared

with those without IBD (55). FMT was equally efficacious in treating rCDI for CD and UC patients. A reported adverse event was an IBD flare; whether this flare was the result of FMT or CDI remains a topic of discussion.

IRRITABLE BOWEL SYNDROME

IBS is characterized by abdominal pain and a change in bowel habits. While the pathophysiology of IBS is not completely elucidated, researchers increasingly believe that dysbiosis of the gut microbiota is involved. There appears to be a reduction in SCFA-producing bacteria, which may be responsible for a proinflammatory state of the gut (56). Furthermore, IBS has been associated with a disrupted epithelial barrier function in the gut (57). Germ-free mice that were colonized with fecal bacteria of patients with IBS developed intestinal barrier dysfunction and innate immune activation (58), which suggests a direct role of the microbiota in the pathophysiology of IBS.

Johnsen et al. recently published the first RCT investigating the effect of FMT in IBS patients (59). Patients received one donor FMT infusion with fresh or frozen feces (50–80 g) or an autologous FMT infusion. FMT was delivered in the cecum by colonoscopy. Investigators noted a significant decrease in IBS severity score at three months post-FMT in 65% (36/55) of patients after FMT, compared with 43% (12/28) of patients treated with an autologous FMT (control group), $p = 0.049$. However, at 12 months post-FMT, the difference between groups was less pronounced. Frozen FMT suspensions were not inferior to fresh suspensions (59). A recent review combined data of case reports and studies treating IBS patients with FMT (60). When compiling all small uncontrolled studies, its authors found an overall improvement of symptoms in 58% of patients treated with FMT. Heterogeneity among studies was significant, and publication bias cannot be excluded. In conclusion, a small subset of patients with IBS may benefit from FMT. Future research should elucidate which IBS patients should be selected for FMT and which donor microbiota is effective. In addition, the optimal FMT protocol for IBS needs to be defined. We have not determined yet whether (antibiotic) pretreatment is required and how frequently FMT needs to be repeated.

HEPATIC ENCEPHALOPATHY

HE is a complication of end-stage liver cirrhosis. Patients with cirrhosis have dysbiosis of the gut microbiota. This condition may result in a proinflammatory environment in the gut (61) and a relative abundance of ammonia-producing bacteria such as Enterobacteriaceae and Streptococcaceae (62). Hyperammonemia in this altered gut microbiota can potentiate neuronal dysfunction and HE (63). Commensal taxa such as Lachnospiraceae, Ruminococcaceae, and Clostridiales XIV have been associated with protective properties against neuronal dysfunction and HE. In contrast, taxa of Streptococcaceae, Enterobacteriaceae, Lactobacillaceae, and Peptostreptococcaceae are associated with potentiating HE (64). Current treatment for HE already targets the gut microbiota and consists of lactulose and/or the nonabsorbable antibiotic rifaximin. In one RCT, 10 participants with liver cirrhosis and recurrent HE were treated with a single FMT via a retention enema in combination with standard of care, and 10 participants received solely standard-of-care treatment. FMT was performed with a rationally selected single donor having high relative abundances of Lachnospiraceae and Ruminococcaceae (64). Standard of care consisted of lactulose and/or rifaximin and was continued throughout the study in both groups. After FMT, fewer SAEs (2 versus 8, $p = 0.02$) and new episodes of HE (0 versus 6, $p = 0.03$) were observed; the two SAEs after FMT appeared to be unrelated to the intervention (65), and thus FMT seems safe in those fragile patients. The results of this small study are promising but need confirmation by future studies. In

this regard, it should be noted that the use of a carefully selected single donor in this study may limit the reproducibility of the results. Taken together, the data so far indicate that HE may be an important indication for FMT and may lead to the future development of more sophisticated strategies targeting the microbiota.

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease (GVHD) following allogeneic hematopoietic stem cell transplantation may affect any organ. In particular, lower intestinal localization of GVHD is associated with a high mortality rate (66). Treatment consists of systemic immunosuppressants. However, in a subset of patients, steroid refractory GVHD occurs for which no treatment is available. In a murine model, dysbiosis in intestinal GVHD results in decreased butyrate concentration in intestinal epithelial cells (67), which could add to a proinflammatory state of the gut. FMT with 17 strains of *Clostridia* known to increase butyric acid levels could significantly reverse the GVHD phenotype in these mice. This finding provides a rationale for FMT in GVHD. Two small case series treating GVHD patients with FMT showed hopeful results (68, 69). One group reported that three of four patients with refractory GVHD treated with FMT could be weaned off steroids; one patient initially responded, but symptoms relapsed as steroids were decreased (68). Another case series consisted of three patients that were treated with repeated FMT, which initially resulted in a clinical response (69). However, one patient soon relapsed after the dose of immunosuppressants was lowered. In conclusion, FMT may be a rescue treatment for patients with steroid-refractory GVHD. Future studies may address whether targeting the microbiota could prevent or treat GVHD at an earlier stage.

MULTIDRUG-RESISTANT ORGANISMS

Colonization with multidrug-resistant organisms (MDRO) that may subsequently cause infections in vulnerable patients is an increasing health care threat. Investigators have hypothesized that resistance to MDRO colonization can be increased by FMT, thereby preventing infectious complications. This result was first observed in the feces of patients treated with FMT for rCDI, in which the number and diversity of antimicrobial resistance genes decreased (70). This outcome was achieved primarily by an increase in the normal abundance of Bacteroidetes and Firmicutes and a reduction in the number of Proteobacteria, in which the antibiotic resistance genes are predominantly found (70, 71).

Four small prospective cohort studies used FMT to eradicate MDROs (**Table 2**) (72–75), with mixed results. The eradication of Gram-positive vancomycin-resistant enterococci (VRE) by FMT appears to be more successful when compared with Gram-negative MRDOs. This result may be explained by the transfer and production of bacteriocins during and following FMT, which may be more effective in clearing Gram-positive pathogens (10, 76). Whether rationally selected donors are needed to eradicate MDROs remains undetermined, and further investigation is needed.

METABOLIC SYNDROME

Metabolic syndrome is often described as a collection of symptoms including insulin resistance, dyslipidemia, high blood pressure, and increased abdominal girth. Dysbiosis of the gut microbiota in metabolic syndrome is linked to a proinflammatory state and an impaired mucosal barrier function, often referred to as leaky gut syndrome (77). Two small RCTs showed that FMT of lean donor stool increased glucose clearance in obese Caucasian males with metabolic syndrome

Table 2 Methods and outcomes of studies addressing the efficacy of FMT against colonization with MDROs

Feature of study	Bilinski et al. (72)	Dinh et al. (74)	Singh et al. (75)	Davido et al. (73)
Study design	Prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
Number of patients	20	17 (8 CRE)	15	8 (6 CRE)
Treatment regimen	Single FMT, repeat in case of failure	Single FMT	Single FMT, repeat in case of failure	Single FMT
MDROs	*Klebsiella pneumonia*, *Escherichia coli*, *Pseudomonas aeruginosa*, VRE, CRE, *Acinetobacter ursingii*, *Stenotrophomonas maltophilia*	VRE, CRE	ESBL enterobacteria	VRE, CRE
Route of administration	Upper GI, duodenal tube	Upper GI, duodenal tube	Upper GI, duodenal tube	Upper GI, duodenal tube
Primary endpoint	Complete decolonization at 6 months post FMT	Complete decolonization	Complete decolonization	Complete decolonization
Primary outcome	75% (15/20)	VRE: 33% (3/9) CRE: 38% (3/8)	40% (6/15)	CRE: 38% (2/6) VRE: 50% (1/2)

Abbreviations: CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum beta-lactamases; FMT, fecal microbiota transplant; GI, gastrointestinal; MDRO, multidrug-resistant organism; VRE, vancomycin-resistant enterococci.

(78, 79). Although researchers observed no beneficial effect on clinical parameters, these studies indicate that the microbiota in metabolic syndrome may be a potential target for therapy.

AUTISM SPECTRUM DISORDERS

Autism spectrum disorders (ASD) are characterized by an impairment in social interaction and communication, with restricted, repetitive patterns of behavior. GI symptoms such as constipation or diarrhea often coincide with ASD (80), and patients suffering from neuropsychiatric disorders including ASD were prescribed antibiotics in early childhood more often compared to controls (81, 82). These observations support the hypothesis that gut dysbiosis is involved in the pathophysiology of ASD. In a murine model, gut microbiota shifts resulted in the onset of behavioral changes and an impaired GI barrier function, both associated with neurodevelopmental disorders (83).

In an open-label study investigating the effect of FMT on ASD and GI symptoms, children aged 7–16 years were treated with an intensive FMT regimen through oral or rectal administration (84). A significant decrease in both GI and neuropsychiatric symptoms occurred, and it persisted for eight weeks after treatment. Microbiota analysis revealed that parts of donor microbiota were engrafted into the recipients (84). These results merit further investigation into therapies that modulate gut microbiota in patients with ASD.

OTHER POTENTIAL FUTURE INDICATIONS

A strategy targeting the gut microbiota may influence the course of disorders in which dysbiosis is observed. FMT appears to be suitable if a reset of the microbiota has prolonged effects on the clinical course. However, more targeted approaches could be repeated on a regular basis and may be suitable in chronic diseases as well. To date, case reports have been published about FMT for many disorders, including microscopic colitis, celiac disease, constipation, pouchitis, and multiple

sclerosis (MS) (85–90). In addition, preclinical evidence suggests that targeting the microbiota may be beneficial for many other disorders. In such conditions, FMT is strictly experimental and should not be offered outside a sophisticated setting.

Of interest is the increasing understanding of microbiota changes in MS and Parkinson's disease (PD). MS is a chronic neuroinflammatory disorder of the central nervous system. Studies addressing changes in the gut microbiota in active MS patients generally show dysbiosis, with a reduction in abundance of Prevotella and Parabacteroides compared with healthy controls (91). This dysbiosis results in a proinflammatory state of the gut microbiota (92). Microbiota involvement in the pathogenesis of MS is suggested by two studies showing an increase in disease incidence or severity in an MS murine model when FMT was performed with stool samples acquired from MS patients (93, 94). Finally, case reports have described promising results of FMT in MS patients (85, 88), although these results should be interpreted with caution.

PD is a progressive multifocal neurodegenerative disorder characterized by asymmetrical bradykinesia, rigidity, and tremors. The pathogenesis of PD can be attributed to protein aggregation, changes in calcium homeostasis, and mitochondrial impairment. One study found that the gut microbiota is involved in the process of protein aggregation and neuroinflammation in a murine model, processes that could be influenced by SCFA metabolism (95, 96). In a PD murine model, FMT had neuroprotective effects and increased striatal dopamine concentrations, alleviating motor symptoms (97). A human trial studying the effect of FMT in PD is currently ongoing (NCT03026231).

Another potential indication for microbiota-modulating therapies is the enforcement of the effect of immune checkpoint inhibitors (ICIs). ICIs fight cancer by blocking a checkpoint molecule on T cells, which tumors use to shut down the immune cells, and can hold certain cancers at bay for years. Unfortunately, only ~25% of patients respond to ICIs. One study showed that changing the gut microbiota of mice, either by FMT of different mice or by administration of Bifidobacteria, increases the efficacy of ICI therapy against melanoma (98). Furthermore, an observational study among 249 cancer patients who received antibiotics shortly before or soon after ICI was started showed earlier relapse and death in these patients (99). FMT using stool from cancer patients who responded to ICI (but not from nonresponders) into germ-free mice ameliorated the antitumor effects of ICI (99, 100), and oral supplementation with *Akkermansia muciniphila* post-FMT to nonresponders restored the efficacy of ICI by increasing the recruitment of T lymphocytes into tumor beds of the mice (100). Finally, metagenomic analysis showed clear differences between the microbiota of responders and nonresponders (99, 100). Taken together, preclinical and clinical observations underline the important role of the microbiota in the response to ICIs. These findings point to the potential of clinical intervention studies that aim to increase the effectiveness of ICIs.

CONCLUDING REMARKS

FMT is a rapidly emerging new therapy with a reach far beyond its undisputed indication, rCDI. Accumulating clinical evidence supports its potential as a treatment strategy for a wide range of disorders as shown in **Table 3**.

ClinicalTrials.gov currently lists more than 200 studies about FMT, indicating that FMT has found its way in the scientific community. As yet, FMT is an unstandardized treatment; it should be considered as a powerful attempt to prove the potential of a microbiota-targeting strategy for a particular disorder. Subsequently, more sophisticated and standardized alternatives should replace FMT as a standard treatment approach. In the meantime, FMT protocol should be optimized and standardized for each separate indication, and the long-term safety of FMT needs to be further established. Stool banks are required to facilitate safe FMT and provide opportunities for quality

Table 3 Overview of the outcome of FMT studies performed in patients with various conditions

Disorder	Type of study (references)	Outcome	Comments and important unresolved questions
Recurrent CDI	RCT (30–32) Meta-analysis (3)	Highly effective, cure rate single infusion >80%	Advised in guidelines for recurrent rCDI (1, 2)
Severe CDI	Case series (34)	Effective, probably safe	May be lifesaving
UC	RCT (47–50) Meta-analysis (51, 52)	Pooled response rate of 29% for achieving endoscopic remission	Optimization of protocol required: Is rational selection of donors required? Is it possible to select patients who are more likely to respond? Should FMT be offered as induction or maintenance treatment?
CD	Cohort studies (53, 54) Meta-analysis (52)	Pooled clinical response rate of 53%. No endoscopic remission achieved	RCT needed Rational donor selection needed
IBS	RCT (59)	Improvement of symptoms in 65% of patients after FMT versus 43% in controls No sustained effect after 1 year	Larger RCTs needed Which patients may benefit? Is repeated FMT required? How should patients be pre-treated before FMT?
HE	RCT (65)	Safe, no SAEs related to FMT, no new episodes of HE 150 days post-FMT	Confirmative study needed Rational donor selection needed
MDRO	Cohort studies (72–75)	Suggestive of some effectivity eradicating VRE and ESBL bacteria	Rational donor selection needed RCT needed
Metabolic syndrome/hepatic steatosis	RCT (78, 79)	No effect on clinical endpoints Transient increased insulin sensitivity	Strictly experimental
Autism	Open-label trial (84)	Effect noted on psychiatric and GI symptoms	Further studies are needed
GVHD	Case series (68, 69)	Steroid-refractory GVHD: decreased symptoms	Further studies are needed

Abbreviations: CD, Crohn's disease; CDI, *Clostridioides/Clostridium difficile* infection; ESBL, extended-spectrum beta-lactamases; FMT, fecal microbiota transplant; GI, gastrointestinal; GVHD, graft-versus-host disease; HE, hepatic encephalopathy; IBS, irritable bowel syndrome; MDRO, multidrug-resistant organism; RCT, randomized controlled trial; SAE, serious adverse event; UC, ulcerative colitis; VRE, vancomycin-resistant enterococci.

control and central registration of safety and outcome data to identify possible unknown adverse effects (42). Finally, the many potential future indications also underline the need for centralized coordination and uniform legislation (following the model of the blood banks) to enable further development of this promising FMT treatment strategy.

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Contents

Indexes

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