Current and Emerging Applications of Fecal Microbiota Transplantation

The role of nurses in the implementation and management of FMT

ABSTRACT

Fecal microbiota transplantation (FMT) is a life-changing treatment for people with recurrent *Clostridioides difficile* infection (rCDI). Frequently acquired in the hospital, CDI can cause serious gastrointestinal symptoms, including persistent watery diarrhea, abdominal pain, and severe dehydration. Antibiotics, the primary treatment, can unfortunately disrupt the gut microbiome and lead to antimicrobial resistance. FMT involves introducing stool from a healthy donor into the affected recipient to strengthen their compromised microbiome. Individuals receiving this treatment have reported remarkable improvement in clinical outcomes and quality of life. In addition to a discussion of rCDI within the context of the gastrointestinal microbiome, this article provides an overview of the FMT procedure, discusses nursing management of individuals undergoing FMT, and highlights emerging applications beyond rCDI. A case scenario is also provided to illustrate a typical trajectory for a patient undergoing FMT.

Keywords: *Clostridioides difficile*, fecal microbiota transplantation, microbiome, nursing care

Daniel Johnson, a 68-year-old man, presents to his primary care provider with complaints of persistent and severe diarrhea and abdominal cramping following a recent extended hospitalization for a severe kidney infection. Because Mr. Johnson has received multiple rounds of antibiotics to clear the infection, his provider suspects antibiotic-associated diarrhea. A stool sample confirms a diagnosis of *Clostridioides difficile* infection (CDI), and Mr. Johnson is started on vancomycin. However, after completing the vancomycin treatment, Mr. Johnson is still experiencing severe diarrhea and is referred to a gastroenterologist for further management. Metronidazole is added to a second round of vancomycin, but his symptoms persist. Owing to Mr. Johnson's clinical course and the negative effect on his quality of life, the gastroenterologist recommends treatment with fecal microbiota transplantation (FMT).

FMT is a treatment in which stool from a healthy donor is transferred into a recipient's gastrointestinal tract to treat an ongoing disease process such as recurrent CDI (rCDI).[1] FMT has been traced back to 300 CE in China, where fresh or fermented fecal water or children's feces was used to treat severe diarrhea, food poisoning, and fever.[2] Today, the procedure is performed to minimize or eliminate the adverse effects of many gastrointestinal-related disorders by introducing healthy bacteria from the stool of a donor into the gut of the recipient (see Figure 1). In the United States, FMT is currently approved only for the treatment of rCDI,[3] but studies with favorable outcomes have been completed in individuals diagnosed with a variety of diseases and disorders including, among others, graft-vs-host disease (GVHD), inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and infections with multidrug-resistant organisms (MDROs).

BACKGROUND

C. difficile, a gram-positive bacteria strain commonly found in soil, water, air, and feces, and on surfaces in

Figure 1. Fecal Microbiota Transplantation

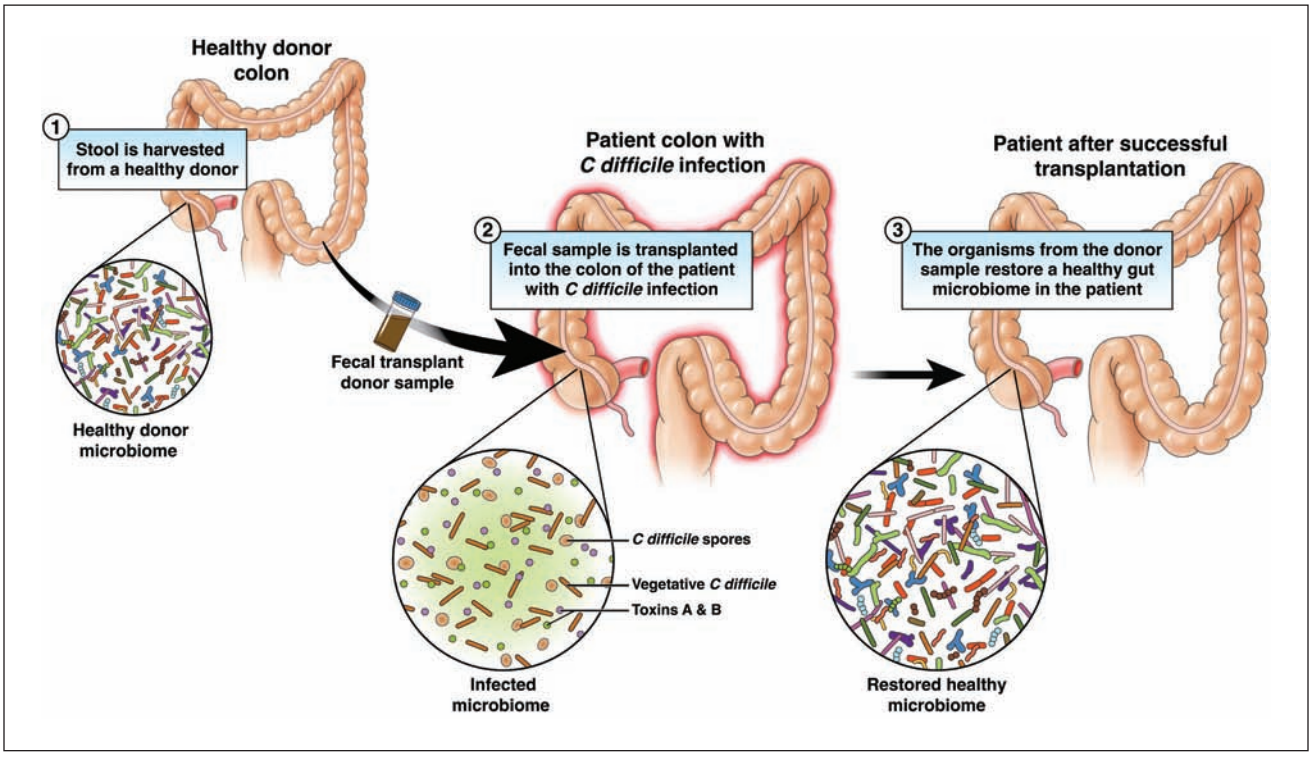

Image courtesy of the American Gastroenterological Association, https://patient.gastro.org/fecal-microbiota-transplantation-fmt.

health care facilities, can cause diarrhea and colitis.[4,5] CDI is responsible for nearly $4.8 billion in excess health care costs for acute care facilities annually.[6] If CDI is left untreated, pseudomembranous colitis, toxic megacolon, or death can occur. Patients' risk of developing CDI is higher with hospitalization. Patients who are frequently admitted to the hospital or are admitted for months at a time have an increased risk of recurrent infections. Other risk factors include being over 65 years of age and having a weakened immune system.[7] CDI is typically treated with antibiotics[7]; however, this can lead to the development of MDROs, that is, to bacteria that have developed a resistance to antibiotics.[8] Resistant bacteria make it difficult to combat infection and treat patients effectively and efficiently.[9]

Approximately 20% to 30% of antibiotic-associated diarrhea is caused by CDI, and among hospitalized patients the rate of recurrence is high, ranging from 20% after the first episode to between 45% and 60% after the second.[10] In addition to health complications, refractory infections lengthen hospital stays and increase costs for the patient. In one study, patients who experienced *C. difficile*–associated diarrhea incurred adjusted hospital costs that were as much as 54% higher than patients who did not.[11] Increased costs during an extended hospital stay are associated with the use of additional health care resources, such as medications, IV therapy, laboratory analyses, diagnostic procedures, inpatient bed occupancy, and medical supplies.[12]

Signs and symptoms of CDI include watery diarrhea (occurring as often as 10 to 15 times a day), abdominal pain, dehydration, colon damage, and increased white blood cell count. The infection is usually treated with antibiotics such as metronidazole, rifaximin, or vancomycin.[6] Unfortunately, rCDI is common. According to the Centers for Disease Control and Prevention (CDC), one in six people will relapse after their original infection or be reinfected from another exposure within two to eight weeks.[13] Recently, use of bezlotoxumab, the first monoclonal antibody approved for the prevention of recurrent bacterial infection such as rCDI, has been shown to lower the rate of recurrent infection.[14] Additionally, FMT has been found to significantly improve quality of life and clinical outcomes in patients diagnosed with rCDI by altering their gut microbiome.[15]

The microbiome consists of all the organisms (microbiota), such as bacteria, viruses, fungi, protozoa, helminths (worms), as well as all their genes, that live in or on a person's body. There are 10 times as many microbes in the gut as there are cells in the body,[16] with the highest microbial density located in the gastrointestinal tract. Most of the gut microbiome is made up of bacteria.[17] The microbiome develops over an individual's lifetime and is so distinctive to each person that it is a more accurate identifier than DNA or a fingerprint.[18, 19]

The Human Microbiome Project, launched by the National Institutes of Health in 2007, has established that the microbiome plays a critical role in various diseases and is, therefore, an essential part of the human ecosystem for maintaining health.[20] In some people who receive antibiotic treatment, such as Mr. Johnson, beneficial protective microbes are unintentionally killed, altering the balance of microbes and allowing *C. difficile* to multiply and release the toxins that cause the classical symptoms of severe diarrhea and abdominal discomfort. FMT is thought to impact the affected gut by introducing healthy donor microbiota, restoring the balance of the microbiome, and enabling beneficial bacteria to keep the *C. difficile* under control.[15] Numerous trials have been conducted to assess FMT efficacy in rCDI. A meta-analysis of 37 studies found that clinical resolution of recurrent and refractory CDI (based on improvement of symptoms or negative *C. difficile* stool culture or toxin) was greater than 90% across all studies.[9] In a study of seriously ill patients who received one or more FMTs for severe and severe–complicated CDI, the cure rate was reported to be 100% and 87%, respectively.[21]

FMT PROCEDURES

There are various ways to administer stool during FMT. Fresh stool administration allows large quantities of stool diluted in saline to be transferred into the colon rectally via colonoscopy or enema or into the stomach nasally through a nasogastric tube (NGT). If gastric administration is not desired for some reason (risk of vomiting, for example), a nasoduodenal tube or nasojejunal tube may be used.[22, 23]

Colonoscopy is a reliable method of delivering stool to affected segments of the bowel.[23] However, there is a rare risk of perforation and patients may react negatively to the medications administered for sedation. Additionally, FMT via colonoscopy is more expensive than other methods, as a gastroenterologist must perform the procedure, whereas FMT via enema or NGT is administered by an RN.

FMT by enema often requires repeat administration, because with this method stool only reaches the distal colon.[23] A single-administration enema was approved by the Food and Drug Administration (FDA) in November 2022, which may increase the popularity of this method of FMT administration.[24]

Patients who cannot undergo FMT via the lower gastrointestinal route can receive FMT via the upper gastrointestinal route through an NGT. However, administration via NGT requires that the patient be upright for a four-hour period to avoid aspiration; therefore, this route is not an option if the patient cannot be maintained in a 45° upright position or upright for this length of time. The effects of gastric or bile acids on donor stool can also minimize the success of FMT engraftment, making upper gastrointestinal routes of administration less desirable.[23]

Nursing support for the patient undergoing FMT includes providing patient education on the FMT procedure, preparation, recovery, and follow-up.

Another option is the use of a frozen capsule of stool that is administered rectally, like a suppository, or swallowed by the patient. Frozen capsule stool is more convenient for health care providers and can reduce patient costs.[23] Capsule delivery offers more protection of the donor material from acid in the stomach than NGT administration.[23] Of note, the first orally administered FMT product was released last April for the prevention of rCDI in adults who have already been treated with antibiotics for rCDI.[25] Early results are promising.

A recent systematic review that included qualitative studies of patient experiences of FMT found that preferences regarding delivery methods varied.[26] For example, Wei and colleagues found that colonoscopy was the preferred treatment, while Zellmer and colleagues noted that enema was preferred to colonoscopy.[27, 28] Five studies reporting on the NGT administration route found that patients did not generally consider this method to be comfortable.[27, 29-32]

Since FMT relies on introducing healthy stool from a donor into an unhealthy microbiome, the selection of the donor is critical. Stool donors can be either autologous, related, close friends, study volunteers, or associated with a stool bank. Research has established that for appropriately screened donors, there is no significant difference between donor types in the

rate of remission of infection or clinical response to FMT.[23, 33] In other words, the donor source does not dictate the efficacy of an FMT. However, the composition of the donor microbiota (namely, greater microbial diversity) was shown to influence efficacy in a study of FMT in refractory ulcerative colitis.[34]

A major concern with FMT is the regulation of the quality and safety of donor stool. The components of donor stool can vary from day to day based on what the donor eats and activities the donor may participate in. Donors typically are screened by interview and laboratory testing. The screening interview serves to rule out the donor's use of any drugs that can alter the gut microbiota or a history of health disorders that may disrupt the gut microbiota (for example, chronic or functional gastrointestinal disorders, systemic autoimmune disorders, and neurological or psychiatric conditions). The donor is also asked about risky behaviors that increase their risk of infectious disease, such as the use of illegal drugs; high-risk sexual behaviors; high-risk travel; recent body tattoos, piercings, or acupuncture; or vaccination with a live attenuated virus in the previous two months. Laboratory testing includes testing blood (complete blood cell count, aminotransferases, bilirubin, creatinine, C-reactive protein, HIV, and hepatitis) and stool (for *C. difficile,* common enteric pathogens, and *Helicobacter pylori* fecal antigen, among others).[35]

Despite screening and testing efforts, the first death from drug-resistant bacteria transmitted via FMT was reported in November 2019.[36] The patient received FMT oral capsules with stool that contained extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli.* The stool had been frozen prior to the release of an FDA regulatory review recommending expanded donor-stool screening to include tests for ESBL-producing organisms. The patient was enrolled in a clinical trial to test the benefit of FMT for patients undergoing allogeneic hematopoietic cell transplantation and had received prophylaxis against GVHD. A total of 21 other patients received FMT capsules generated from the same donor but reported no adverse events, except for one patient with hepatic encephalopathy who developed bacteremia but then recovered.[36] Subsequently, additional though rare cases of infections associated with FMT have been reported.[37, 38]

The FDA issued a safety alert in March 2020 recommending additional safety measures for FMT owing to the risk of transmission of SARS-CoV-2.[39] Donors are screened for both laboratory-confirmed SARS-CoV-2 infection and symptoms of COVID-19 not explained by another diagnosis, as well as for exposure to a suspected or confirmed case. Donor stool collected four weeks prior to the suspected or confirmed infection or exposure is then excluded from FMT eligibility. Another safety alert was released in August 2022 regarding the potential for the monkeypox virus to be transmitted through FMT and recommending donor screening if the stool was donated on or after March 15, 2022.[38]

Finally, it should be noted that insurance may not cover the cost of the procedure for indications other than the FDA-approved *C. difficile* diagnosis.[40] Compassionate use designation can allow for non-FDA-approved FMT administration for disorders other than rCDI, but costs may not be covered by an insurance provider. Financial expenses and lost wages due to time away from work have also been identified as barriers for patients considering FMT.[41]

NURSING MANAGEMENT

In consultation with his gastroenterologist, Mr. Johnson elects to have FMT delivered by colonoscopy. Prior to the procedure, Mr. Johnson has labs drawn, including screening for viral hepatitis, HIV, syphilis, and monkeypox. Diagnosis of any of these diseases will not prohibit Mr. Johnson from receiving FMT but will help to rule out the donated stool as a source of infection.

Choice of donor and stool type is determined by the patient in consultation with the gastroenterology provider. While research has shown there is no difference in outcomes related to type of donor or stool source,[23, 33] some clinicians and researchers suggest that an unrelated donor is preferred as they provide a greater microbial diversity than autologous stool or stool from close relatives or friends.[23]

Nursing support for the patient undergoing FMT includes providing patient education on the FMT procedure, preparation, recovery, and follow-up. In a qualitative investigation involving nine patients undergoing FMT for treatment of ulcerative colitis, patients expressed a lack of understanding about the overall goals of FMT, concerns about the cleanliness and administration of stool products, and fear of the procedure.[41] Patients also had concerns about stigma and how others would perceive this treatment modality. Following FMT, these same patients reported improved quality of life with fewer nighttime stools, more confidence in leaving home for external activities, less concern with fecal soiling, and overall satisfaction with symptom improvements.[41] Study participants were unanimous in endorsing the treatment for others. Educating patients about the procedure and what to expect can reassure them.

A thorough nursing assessment with a focus on gastrointestinal symptomatology is important to establish a preprocedure baseline for postprocedure comparison. Common preprocedure physical complaints for rCDI often include pain related to abdominal cramping and dehydration due to diarrhea. Psychosocial support is particularly important as some individuals may have concerns or even anxiety about receiving a stool donation. Review of the rigorous donor screening as well as stool screening can help to allay patient or family concerns.[40]

Patients undergoing FMT should discontinue any antibiotics for 24 to 48 hours before the procedure and ingest nothing by mouth the day of the procedure. Patients should be advised that the procedure will typically take place in the endoscopy suite. Patients undergoing colonoscopy administration must also use a bowel preparation the night prior to FMT. They should be advised that the goal of this preparation is to empty the bowel of stool, so diarrhea is to be expected. Those undergoing FMT by colonoscopy will most likely be sedated for comfort during the procedure. Patients should also be assured that during the procedure their privacy will be protected.

Some clinicians suggest the patient remain supine in recovery for up to two hours following the procedure to encourage retention of the donor stool. Antimotility drugs such as loperamide are sometimes administered for the same reason.

Because *C. difficile* is highly contagious, it is recommended that patients bring a set of clean, uncontaminated clothes to wear after the procedure to minimize the risk of reinfection.[40] Upon returning home, meticulous cleaning of bedding, clothing, bathroom facilities, and anything touched by hands is also indicated for both the FMT recipient and any caregiver to minimize reinfection. Chlorhexidine or soap and water will remove *C. difficile* spores from the hands; however, alcohol-based hand gels are not effective. Because *C. difficile* is spread via spores, fecal soiling is highly likely. Use of a bleach-to-water dilution of 1:10 is recommended for all surfaces, particularly bathroom and bedroom floors, doorknobs, and countertops.[42, 43]

Patients are typically discharged home on a normal diet. After the procedure, patients should avoid any unnecessary antibiotic therapy to protect the newly established microbiota. If antibiotic use is necessary within the first two months following FMT, the patient or current health care provider should be encouraged to consult with the FMT provider regarding management options (for example, probiotic administration or choice of antibiotic) that minimize injury to the microbiota.[44, 45] Education on symptom monitoring and typical side effects such as mild cramping, bloating, diarrhea, constipation, vomiting, and flatulence should be provided, as well as discussion of psychosocial implications such as the potential for needing additional FMT treatment. A follow-up phone call within several days of the procedure is helpful to assess the patient's response and identify any adverse events or side effects requiring intervention.[40, 46, 47] Follow-up with the gastroenterologist at four to eight weeks following FMT is important to monitor and manage side effects as well as rule out any adverse effects such as excessive pain, nausea, vomiting, or diarrhea that could suggest a failed initial procedure.[45] FMT is considered to have failed if the patient has recurrent diarrhea with a positive *C. difficile* stool test. FMT failure occurs in 10% to 15% of FMT recipients. FMT failure is managed with antibiotics or repeat FMT.[48] Most individuals respond to the initial FMT treatment within four weeks, but a few (17%) require repeat FMT for a successful response.[49]

POTENTIAL APPLICATIONS OF FMT BEYOND rCDI

While FMT is approved in the United States only for the treatment of rCDI, it is being explored for other disease states. For example, FMT appears promising in individuals who develop high-grade GVHD following hematopoietic stem cell transplantation. In a report by Spindelboeck and colleagues, three subjects with acute, refractory GVHD achieved reduced stool volumes that normalized in two of the patients with repeated FMT.[50] A recent systematic review of FMT in improving gastrointestinal GVHD that pooled the results of six studies and five case reports (n = 79 subjects) found that complete remission occurred in 55.9% of patients and partial remission in 25.5%.[51] Adverse effects were reported to be mainly gastrointestinal (abdominal pain, gastric distention, nausea, regurgitation) with most patients reporting no significant events or major complications from FMT.

FMT for treatment of IBD has also been investigated. Although the degree of improvement has not been as high as with rCDI, there have been positive results. Li and colleagues studied 25 patients diagnosed with Crohn disease who were treated with FMT and found that the proportion of patients achieving clinical remission at six, 12, and 18 months after treatment was 48%, 32%, and 22.7%, respectively.[52] Researchers enrolled 30 participants for an observational study of FMT in steroid-dependent ulcerative colitis; after FMT was performed weekly for eight weeks, clinical remission was achieved in 11 (36.7%) participants, clinical response was achieved in 16 (53.3%), and endoscopic remission was seen in three (10%).[53]

FMT has also been investigated in the treatment of IBS, a gastrointestinal disorder affecting 11% of the global population[54] and associated with small intestinal bacterial overgrowth.[55] Twelve patients with both diarrhea-predominant and constipation-predominant IBS were included in a study by Cho and colleagues.[56] Seven (58%) achieved a clinical response, defined as a reduction of 50 points or more on the IBS Symptom Severity Score, after the first FMT and four (33%), who did not respond to the first FMT, responded to a second treatment. Another study by Mizuno and colleagues noted that six of 10 subjects with IBS achieved a clinical response to FMT, and an increase in microbiota diversity was noted four weeks later.[57] A recent meta-analysis of seven randomized controlled trials with a total of 472 subjects with IBS, however, noted that the quality of

evidence in these studies was low and additional rigorous investigation is needed.[58]

FMT has the potential to reduce or treat infections caused by MDROs. Ghani and colleagues found that seven patients (41%) with MDROs experienced decolonization six months after FMT.[59] A systematic review of studies of 151 patients who received FMT for MDRO infections found the decolonization rate ranged from 37.5% to 87.5%, with no serious adverse events reported.[60] Seong and colleagues found that 24 participants (68.6%) with intestinal colonization of MDROs experienced decolonization within one year of FMT.[61]

Studies have also investigated the use of FMT in other gastrointestinal disease processes, such as primary sclerosing cholangitis,[62] nonalcoholic fatty liver disease,[63] cirrhosis,[64] chronic pouchitis,[65] small intestinal bacterial overgrowth,[66] pediatric allergic colitis,[67] slow-transit constipation,[68] and hepatic encephalopathy.[69] FMT is also being used experimentally in critically ill patients with solid organ transplantation,[70] multiple organ dysfunction syndrome,[71] and rescue antibiotic–associated diarrhea.[72] FMT for the treatment of immunocompromised pain has been investigated in disease states such as neutropenia,[73] chronic radiation enteritis,[74] and radiation proctitis.[75] And while studies on the effectiveness of FMT in the treatment of mental health disorders are still primarily in prehuman phases, FMT shows promise in treating major depressive disorder, anxiety, eating disorders, and substance abuse.[76] FMT is also being investigated in patients with autism spectrum disorder,[77] obesity,[78] programmed cell death 1–refractory melanoma,[79] and epilepsy.[80]

EVOLVING DEVELOPMENTS IN FMT

With the broader exploratory application of FMT for disease treatment and management in recent years, future implications for FMT are beginning to be explored. The use of super donors whose microbiomes are highly effective at engrafting in a recipient's gut has been proposed as the future of FMT donor stool, allowing for targeted bacteriotherapy treatment.[81] Active donors who have been monitored over time and whose stool results in high rates of FMT success are considered super donors. The most critical factor is that a super donor must have a gut microbiota with high microbial diversity. Compatibility between the donor and the recipient in terms of genetics (immune response) or environment (diet, xenobiotic exposure, microbial interactions) is also considered to be important to FMT success and requires further investigation in order to develop precise donor–recipient microbiota matches.[81]

Universal stool banks with the capacity to store and distribute stool from these highly screened super donors will contribute to establishing an effective and efficient source of donor stool when FMT is approved for treatment outside of clinical trials and for populations beyond rCDI. These stool banks could be strategically located to minimize the economic costs associated with stool distribution. Currently, stool banks exist globally and are typically located at specific clinical trial centers. OpenBiome in Massachusetts and BiomeBank in Australia are two examples of stool banks that supply stool to multiple clinical trial centers and to patients not enrolled in clinical trials who receive FMT treatment on a compassionate basis (that is, with FDA permission).

FMT involving washed stool prepared by using microfiltration with repeated centrifugation plus suspension has been proposed as providing more precise microbiota dosing by eliminating waste.[82] Exploration is even underway for the development of a synthetic stool substitute known as microbiota ecosystem therapeutics.[16] Initial results show positive outcomes of this substitute for the resolution of rCDI.[16, 83] Cruz and colleagues suggest that in the future therapeutic microbe applications could be used for disease prevention.[84]

While we know that antibiotics can disrupt the balance of gut microbiota, there are also opportunities for these agents to have therapeutic benefits. Further research is needed to help determine the specific effects (both positive and negative) of different classes of antibiotics on gut microbiota.[85] Additionally, early research suggests that FMT improves the gut microbiome of rCDI patients by restoring *Firmicutes* and *Bacteroidetes*, the most prominent bacterial phyla in the microbiota.[86] Restoring these bacteria and maintaining the correct balance between them may help inhibit *C. difficile* spore germination. However, how FMT protects the gut from rCDI is not yet clearly understood. Khoruts and Sadowsky suggest both the direct interaction of donor gut microbiota with *C. difficile* bacteria and the mediated effects of the microbiota between the host physiology and immune defenses can kill or inhibit the *C. difficile* bacteria.[87] Moreover, studies of FMT for treating other gastrointestinal disorders as discussed earlier are needed to determine the efficacy and safety of FMT beyond the rCDI population.[88]

Kubinak and colleagues suggest that donor matching for stool may be important based on their research indicating that specific major histocompatibility complex (MHC) genotypes are associated with antibody responses in the gut.[89] Because they found evidence that the immune system may be selective in determining which bacteria survive in the gut microbiome, the ability to match the FMT recipient's MHC genes with those of their stool donor would then enhance FMT success by allowing for matching with a stool donor who has the same microbial community.

The need to determine optimal FMT treatment intensity has also been identified.[90, 91] Currently, administration of FMT is based on clinical practice

(that is, reported study protocols, presentations at physician conferences, consultation between practitioners), but there are no sanctioned guidelines. Given the lack of established treatment protocols for FMT generally, it is critical that current and ongoing evidence be incorporated into guidelines for FMT delivery. Finally, qualitative exploration of patients' expectations, experiences, and perspectives of FMT and their impact on quality of life is critical in understanding how FMT affects individuals and in identifying how best to support patients considering or undergoing FMT.

CONCLUSIONS

Studies suggest that FMT is an effective treatment for a variety of gastrointestinal diseases, although rCDI is the only disease currently approved for FMT treatment in the United States. Evidence to date involving different disease states indicates that individuals undergoing FMT have experienced minimal adverse effects, abdominal pain and diarrhea being the most frequently reported. Serious adverse events and death involving FMT are rare but have been reported. Future studies to precisely type and match the fecal microbiota of the donor and the recipient will enhance FMT effectiveness.

Nursing support of the person considering FMT requires a thorough understanding of the procedure to prepare them for what to expect before, during, and after treatment. Education on any diet restrictions and bowel preparation prior to the procedure is also important. Assurance of comfort and privacy measures during the procedure as well as stool source and screening supports the patient's psychosocial needs. Postprocedure expectations, including diet, typical responses, and the possible need for additional treatment, are also a critical aspect of nursing support for the patient undergoing FMT. Patients should also be advised on measures to take, including washing their hands with soap and water, to prevent the spread of *C. difficile*.

The future of FMT is promising, but further studies are needed to establish a protocol for this treatment beyond rCDI. As there is no universal protocol, this is a necessary next step for FMT to be used as a common treatment for a wide range of disease processes. Establishment of an evidence-based protocol should also help remove barriers to FMT, such as cost and geographic accessibility. ▼

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