Fecal Microbiota Transplantation

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KEYWORDS

• *Clostridium difficile* • Fecal microbiota transplant • Stool transplant • FMT
• Microbiome

KEY POINTS

- Fecal microbiota transplantation (FMT) is effective for treatment of recurrent *Clostridium difficile* infection (CDI) when standard therapy has failed.
- FMT may have a role in some patients with severe and complicated CDI.
- The following factors are important in selecting patients for FMT:
  - Appropriate indications.
  - Appropriate donor selection.
  - Appropriate method of administering FMT.
  - Appropriate follow-up.

INTRODUCTION

Fecal microbiota transplantation (FMT) is the transfer of stool from a "healthy" donor to a recipient believed to harbor an altered colonic microbiome resulting in disease. The goal is to restore eubiosis, or a "healthy" microbiome. Often referred to as stool transplantation, fecal transplantation, fecal flora reconstitution, or fecal bacteriotherapy, FMT has increasingly become a focus in both the public media and peer-reviewed literature. FMT is an effective treatment strategy for recurrent *Clostridium difficile* infection (rCDI) that has not responded to standard therapy. There is interest in using

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FMT for other gastrointestinal (GI) and non-GI diseases, and multiple studies are under way to determine potential alternative indications.

HISTORY

FMT was first described in the fourth century Dong-jin dynasty. A Chinese doctor administered feces by mouth to patients with food poisoning or severe diarrhea with report of life-saving results.[1] There are also descriptions during the sixteenth century Ming dynasty whereby patients were prescribed fresh or fermented fecal suspensions for a range of GI conditions, including diarrhea, vomiting, constipation, and pain. Some reports also indicate the use of infant feces as therapy.[1] Subsequent accounts refer to Fabricius Aquapendente, an Italian seventeenth century anatomist who used FMT in veterinary medicine.[2] It was termed "transfaunation."[3]

More modern descriptions of use in humans were documented by Eiseman and colleagues[4] in 1958; 4 patients improved after they were given fecal enemas for treatment of staphylococcal pseudomembranous enterocolitis.

There has been considerable interest in FMT over the past decade. There have been multiple case reports and series describing differing FMT protocols, methods of stool administration, and variable patient responses. The highest success rates have been for rCDI with less robust findings, but active investigation, in other GI and non-GI diseases.[5]

GOAL AND EFFECTS OF FECAL MICROBIOTA TRANSPLANTATION

The main goal of FMT is to restore the "normal" population of bacteria in a dysbiotic colonic environment. Studies have examined the gut microbiome in patients with CDI before and after FMT. There is clearly a shift in the bacterial populations within the post-FMT gut that mirrors the donor stool. Gene-sequencing studies of stool samples have shown increases in the quantity of Firmicutes and Bacteroidetes and decreases in Proteobacteria and Actinobacteria following FMT, suggesting rapid donor engraftment.[6,7]

SCREENING AND PROCESS OF FECAL MICROBIOTA TRANSPLANTATION

Selection and Screening of Donor

The stool donor may be related or unrelated to the recipient. If related, the donor is typically a spouse or close relative. A systematic review by Gough and colleagues[8] showed resolution of CDI in 93.3% of studies with related donors (n = 19 studies) and 84% of studies with unrelated donors (n = 4 studies). Kassam and colleagues[9] similarly assessed the significance of donor type and found no difference in clinical outcome regardless if the donor was anonymous versus patient-selected. The investigators hypothesize that unrelated/anonymous donors likely harbor a completely different microbiome compared with related donors and thus may be more effective in "resetting" the microbiome of the recipients, although this has not been demonstrated in randomized studies. Furthermore, many patients prefer an anonymous donor to eliminate the sometimes awkward conversation requesting a stool sample from a family member.

With mild variation, donor screening protocols have been established to reduce the risks of transmission of an infection from the donor to recipient. Testing includes both stool and serum analysis as well as an extensive clinical and social risk assessment. A listing of donor assessment recommendations is included in **Box 1**. The inclusion of such a screening protocol is important to prevent transmission of infectious organisms

Box 1
Screening donors for fecal microbiota transplantation: exclusion criteria

History and chart review:

- Active infection
- Exposure to antibiotics in the prior 3 months
- Recent travel with exposure to epidemic diarrheal disease
- Significant gastrointestinal history, including inflammatory bowel disease, irritable bowel syndrome, chronic diarrhea/constipation, gastrointestinal malignancy
- Autoimmune or significant allergy history
- Other considerations: risk factors for Creutzfeldt-Jakob disease, diabetes, metabolic syndrome, chronic pain syndromes, and exposure to medications that may alter the gut microbiome
- Social factor considerations: high-risk sexual behaviors, drug use, incarceration or long-term care facility residence, and body piercing or tattoo in prior 6 months

Stool testing:

Bacteria
- *Clostridium difficile*
- Campylobacter
- *Helicobacter pylori* (if fecal microbiota transplantation administered via oral route)
- Salmonella
- Shiga-toxin producing *Escherichia coli*
- Shigella
- Other considerations: *Aeromonas*, *Plesiomonas*, *Listeria monocytogenes*, *Yersinia*, *Vibrio cholerae*, and *Vibrio parahaemolyticus*

Viruses
- Rotavirus
- Norovirus

Parasites
- *Cryptosporidium*
- *Cyclospora*
- *Giardia*
- *Isospora*

Blood testing:

Bacteria
- Syphilis

Viruses
- Hepatitis A, B, C
- Human immunodeficiency virus

Data from Refs.[54–56]

that may be harbored in donor stool. Additionally, we know little about the transmissibility of autoimmune diseases and other noninfectious conditions that may be influenced by changes in the microbiome. Although there have been instances of homeopathic or home-use of enemas to perform FMT without physician evaluation, this is strongly discouraged for the previously discussed reasons.

Some protocols will provide a laxative to the donor to assist with stool collection. We also recommend the donor avoid any foods (eg, nuts) to which the recipient has a known food allergy.

Regulations and Patient Consent

Currently, FMT is indicated for rCDI, although this application is still considered investigational. Despite Food and Drug Administration (FDA) oversight, physicians may perform FMT outside of a clinical trial (without an investigational new drug [IND] application and approval) for CDI that has not been responsive to standard antibiotic therapies; this has also been referred to as "enforcement discretion."[10] For non-rCDI applications, an IND must be submitted to the FDA.

From a clinical and research standpoint, any non-rCDI use of FMT is considered "off-label" and the evidence base of the benefits and risks should be strongly considered. In many cases, there are no data to justify its use. Following, we discuss the current evidence for CDI, inflammatory bowel disease (IBD), and other diseases in which FMT has been studied.

All patients should provide consent for FMT with the benefits, risks, process, and follow-up clearly explained to the patient. Some risks will be specific to the method of delivery. For example, with colonoscopy, we note the risk of reaction to anesthetic agents, discomfort during the procedure, gastrointestinal bleeding, and perforation. With regard to FMT, we also note the risk of transmission of an infectious agent or diseases/conditions for which the donor was not prescreened.

Screening of Recipient

There are no guidelines on screening requirements for FMT recipients. As noted previously, FMT is recommended for rCDI with less support for other disease indications currently. Although not standardized, we recommend baseline recipient testing for viral hepatitis, human immunodeficiency virus, and syphilis, because if the patient is diagnosed with one of these diseases post-FMT, further assessment can be performed to determine if the stool sample may have played a role.

Additional recipient screening considerations include comorbidities, such as immunocompromised status, which may increase the risk of adverse events.

Fecal Microbiota Transplantation Preparation and Administration

There is often some variation in FMT preparation across institutions where FMT is performed. The general process is the same, however, and involves mixing stool with a bacteriostatic liquid, removing particulate matter, and delivering donor stool to the patient. Patients should stop vancomycin (or any other antibiotic) at least 1 or 2 days before FMT administration.

Stool may be administered via several mechanisms, each with its own benefits and risks, as described in **Table 1**. These include the following:

- Oral (via nasogastric, nasoduodenal, or nasojejunal tube or capsule)
- Colonoscopy (stool deposited into right colon or terminal ileum)
- Enema

The process for performing FMT is described in **Fig. 1**. Currently, there are 3 main methods of obtaining the donor sample:

- Stool sample from unrelated or related local donor
- Stool sample from a stool bank, generally shipped frozen on dry ice overnight
- Frozen, encapsulated stool

Stool is prescreened as described previously, either locally or at a stool bank before shipment. The latter provides a unique identifier that can be tracked back to the donor if necessary. Additionally, stool banks may retain a sample of donor stool for freezer

Table 1
Advantages and disadvantages of various methods of fecal microbiota transplantation administration

Method	Advantages	Disadvantages
Oral/Nasogastric/ Nasoduodenal/ Nasojejunal	• Avoids sedation • Low cost	• Discomfort of tube placement • Risk of vomiting and aspiration • Inability to evaluate mucosa or take biopsies
Colonoscopy	• Ability to evaluate mucosa and take biopsies • Most effective route for treatment of recurrent *Clostridium difficile* infection (rCDI)	• Invasive • Generally requires sedation • Standard risks of colonoscopy (eg, discomfort, perforation, bleeding) • Expensive
Enema	• Less invasive • Can be administered in office setting or at home • No sedation risk • Low cost • Can more easily be repeated	• Donor stool does not reach the entire colon and limited to left-sided colon • Less effective than other routes for rCDI
Capsules	• Less invasive • Can be administered in office setting • No sedation risk	• Expensive, but eliminates cost of endoscopy • Less effective than colonoscopy for rCDI • Large capsule burden • Risks of vomiting and aspiration

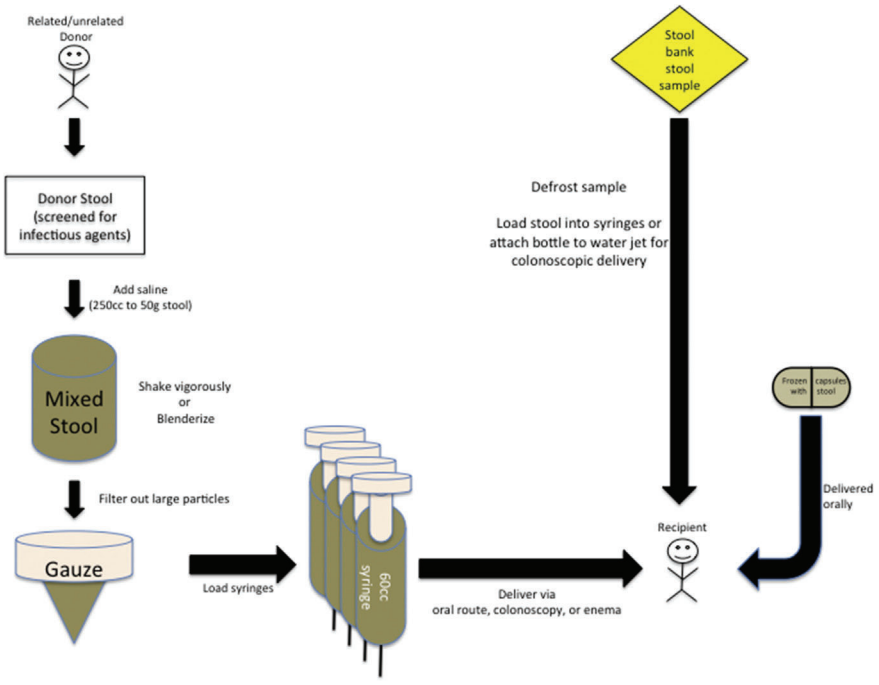


Fig. 1. Process of Fecal Microbiota Transplantation.

storage for future studies or if the recipient develops a rare infection following FMT. For local donors, stool is obtained with the plan to transplant in less than 8 hours. Stool is mixed with normal saline (although mixing with milk has also been described) and vigorously shaken to ensure good mixing. Blenders (either supplied by the health care facility or brought in by the patient) have also been used, but will likely need to be discarded following stool preparation unless there is a method of disinfection. Mixed stool is passed through a filter or gauze to remove large particulate matter that may clog the colonoscope channel. Stool is then drawn up into 60-mL syringes (generally 4–5) and administered to the recipient. There are no guidelines for how much feces to deliver, although many agree that at least 50 g (or 250 mL diluent) should be adequate.[11,12]

More recently, several stool banks have been formed. A stool bank collects stool from a set of prescreened donors, prepares and divides the donated stool, and freezes aliquots of screened stool that can then be shipped overnight to health care facilities. Samples are treated like a drug and frequently go through the institution's pharmacy. This frozen sample is defrosted and drawn up into 60-mL syringes for administration. Alternatively, the stool bottle can be attached to the colonoscope's water jet and sprayed into the colon rather than injecting syringes through the accessory channel. The use of a stool bank sample alleviates the need for mixing and filtering and is quite affordable (approximately $250 plus shipping). It also eliminates the need for the patient to ask a friend or relative to provide a stool sample. As that person would also need to be screened as described previously, a stool bank donor removes this step and associated cost.

Following FMT, we generally administer 1 dose of loperamide in the endoscopy recovery suite, although there are no clear data suggesting this alters outcomes. Some institutions will administer this medication before FMT. Additionally, we place the patient in reverse Trendelenburg for up to an hour with the goal of retaining stool in the colon as long as possible. At the time of discharge, we recommend home disinfection of all surfaces with a water-bleach cleaner (9:1 ratio) or sporicidal agent approved by the Environmental Protection Agency. We follow-up with the patient to assess for efficacy and adverse events.

There also has been the development of frozen, encapsulated stool. Capsules developed by OpenBiome (Medford, MA) use screened donor stool placed inside a size 0 capsule, which is then placed inside a size 00 capsule and frozen.[13] Studies have been performed with trypan blue demonstrating an average of 115 minutes elapsing before the capsule opens; enough time to pass through the acidic environment of the stomach.[14] The capsules are unique in the patented microbial emulsion matrix (MEM) technology using long-chain fatty acids as a carrier matrix to ensure delivery of live microbial communities.[13] FMT capsules must be stored at -20°C or below and must be swallowed by the patient in less than 90 minutes from freezer removal.

INDICATIONS FOR FECAL MICROBIOTA TRANSPLANTATION

The strongest evidence for efficacy of FMT is for the treatment of rCDI.

Recurrent Clostridium difficile Infection

Over the past 2 decades there has been a rise in CDI incidence, particularly among older adults.[15] There has been the emergence of the more virulent BI/NAP1/027 strain, a rise in community-acquired cases of CDI without prior antibiotic exposure, and the emergence of special populations at increased risk of CDI, such as patients with solid organ transplantation, patients with cancer receiving chemotherapy, and patients with

IBD.[16,17] The risk of recurrent CDI is high with at least 10% to 20% of patients developing a first recurrence within 8 weeks of treatment and 40% to 65% of patients with subsequent recurrences.[18] Frequently, these are patients who do not respond to traditional medical therapies with vancomycin or fidaxomicin; therefore, identifying therapies for these patients has been critical.

The greatest evidence for FMT is for treatment of recurrent CDI. These are patients with at least 3 episodes of confirmed CDI that has been unresponsive or refractory to current antibiotic therapies. The hypothesis is that through restoring normal colonic bacterial populations, there is more competition for nutrients and inhibition of *C difficile* growth. There also may be regulation of the immune system (a current area of research) and changes in bile acids that impair the *C. difficile* life cycle.[11]

The effectiveness of FMT for this indication has been impressive, with numerous studies demonstrating cure rates greater than 85% and many greater than 90%. Although many of these have been case reports or case studies with convenience samples, the first randomized controlled trial was performed by van Nood and colleagues[19] with FMT for rCDI through the nasoduodenal route. Given that 81% of patients with rCDI had resolution of C. difficile associated disease (CDAD) after 1 infusion compared with 31% of patients receiving vancomycin only ($P<.001$), the study was terminated early following interim analysis. There have been 2 randomized controlled trials showing efficacy of FMT via colonoscopy.[20,21]

Based on the success of FMT for rCDI, guidelines by the American College of Gastroenterology and the European Society of Clinical Microbiology and Infectious Diseases recommend this treatment option.[22,23]

As described previously, a more recent development has been the use of frozen, oral FMT capsules for treatment of rCDI. In one feasibility study of 20 patients with rCDI who had failed vancomycin therapy, 14 (70%) patients had resolution of diarrhea following capsule administration (15 capsules over 2 consecutive days).[14,24] Of the 6 nonresponders, 4 had resolution of diarrhea after a second administration of FMT capsules. There were no serious adverse events.

Among most studies for CDI, the highest cure rates are seen with colonoscopic administration of donor stool, generally greater than 90%. Oral administration is slightly less effective with resolution rates in the 76% to 79% range.[8] For recurrent CDI, Konijeti and colleagues[25] performed decision analysis to ascertain if FMT was a cost-effective strategy. Comparing various treatment strategies, FMT via colonoscopy was the most cost-effective initial strategy for rCDI with up to $17,000 in cost savings.

It should be noted that although there are case reports of successful treatment of severe and severe and complicated CDI, including in patients in the intensive care unit, this is not currently the recommended standard of care, but can be considered on a case-by-case basis remembering that patients should be treated aggressively with early surgical consultation for consideration of colectomy or loop ileostomy.

Inflammatory Bowel Disease

IBD includes both Crohn's disease (CD) and ulcerative colitis (UC). Similar to CDI, studies have shown dysbiosis with reduction in bacterial diversity (decreased Bacteroidetes and Firmicutes with increased Proteobacteria and Actinobacteria) in these patients.[26,27] There are also decreases in *Faecalibacterium prausnitzii*, which is thought to play a role in both decreasing inflammation and maintaining clinical remission.[28,29]

There are studies dating as far back as 1989 using FMT for treatment of IBD (mostly UC), all using a retention enema as the mode of administration.[30–33] In the first case report, Bennet self-administered an FMT enema following a diagnosis of UC 7 years

prior that had been refractory to both steroid and sulfasalazine therapies.[31] Chronic inflammation remained, but active inflammation and symptoms improved. Follow-up studies by Borody and colleagues[32,33] of patients who had failed conventional IBD therapies (5-aminosalicylic acids [5-ASAs], steroids, azathioprine) documented variable periods of remission ranging from 3 months to 13 years. During this time, there were also numerous murine studies assessing microbiota transfer.[30]

A systematic review by Colman and Rubin[34] described 18 studies (122 patients) of FMT use in patients with IBD with an overall remission rate at only 36.2% among cohort studies; response was 22% when only patients with UC were subanalyzed compared with 60.5% in patients with CD. Among included studies, there was variation in donor stool source, stool preparation (frozen vs fresh) and method of FMT administration. At least 41% of patients received 2 or more FMTs, but there was no correlation with the frequency of FMT and response. There were no serious adverse events.

There are additional systematic reviews suggesting higher rates of efficacy, but with concerns of methodological study flaws and publication bias.[34,35]

A possible explanation for the less robust responses seen with FMT in patients with IBD is that there are other factors contributing to IBD exacerbations beyond the microbiome, such as leaky gut (impaired mucosal barrier function) and inflammation.[36] Multiple risk factors contribute to this dysbiosis, compromised mucosal integrity and inflammation, including genetics and environmental factors (eg, diet, tobacco, infection, stress, surgery, and medications). FMT is a potential treatment focused on microbiome reconstitution, but the effects on the immune system and mucosal integrity are less clear.

In summary, despite the dysbiosis in patients with IBD, FMT studies have been less robust with mixed results. In some cases, there is evidence of remission induction; however, this effect is frequently not seen in all patients, nor is it sustained.

Other Potential Indications

Beyond rCDI and IBD, there is great interest in other applications for FMT. These include both GI and non-GI diseases, such as chronic fatigue syndrome, Parkinson disease, obesity and the metabolic syndrome, and multiple sclerosis.[11]

Among the lay public, there is particular interest in the use of FMT for functional disorders, such as irritable bowel syndrome (IBS). It remains unclear if there is a dysbiotic contribution to IBS, although some studies do show differences in bacterial populations among patients with IBS.[37,38] A single-center experience of 13 patients with IBS nonresponsive to medical therapies who received FMT demonstrated resolution or improvement of symptoms in 70% of patients with most improvement in abdominal pain, dyspepsia, bloating, and flatus.[39] Additional studies in patients with IBS and chronic constipation showed some short-term improvement in symptoms, but fewer than 50% of patients had long-term improvement.[40] Related, there may be a role for postinfectious IBS and small intestinal bacterial overgrowth, but these areas need to be further explored.[38]

One of the greatest areas of research revolves around obesity and the metabolic syndrome, given the growing number of patients who are developing this disease process, particularly in the United States. Studies have suggested a potential intestinal microbiome role in the development of obesity, and microbial analysis demonstrates significant differences in the microbiome of lean versus obese individuals.[41,42] Additionally, in initial murine FMT studies when stool from an obese mouse was transferred to germ-free mice, it led to increased adiposity when compared with lean donor transplants.[43] Follow-up studies have been performed in humans, although on a small

scale. Obese recipients with "lean" donor stool FMTs had improved insulin sensitivity, increased diversity of the gut microbiome and increased *Roseburia intestinalis*, a butyrate-producing bacteria.[44] Although more studies need to be performed to determine if there are long-term benefits, these findings do raise the concern of using obese FMT donors (for any indication, including rCDI), as a lean recipient may develop unintended outcomes: an increase in adiposity.

Other potential FMT applications are less well studied, but there are case reports describing individual successes, particularly with autism, chronic fatigue syndrome, fibromyalgia, idiopathic thrombocytopenic purpura, multiple sclerosis, myoclonus dystonia, and Parkinson disease; none of these have been evaluated in randomized clinical trials.[11,45–48]

ADVERSE EFFECTS OF FECAL MICROBIOTA TRANSPLANTATION

FMT delivers a foreign compound (or a mixture of various microorganisms) into the recipient. Similar to any drug, we must consider possible adverse events that may result from this introduction, particularly as the use of FMT continues to increase. The most common adverse events are described in **Box 2**. Typically, any adverse events are mild and transient, such as abdominal discomfort, nausea, vomiting, bloating, or flatulence. It is often difficult to know if these symptoms are related to the underlying disease that triggered the need for FMT (such as postinfectious IBS), the sedative medications received during endoscopy, the use of air or CO2 during colonoscopy, or a true result of the infused donor stool. More serious complications are rare and often relate to the well-established risks of endoscopy and sedation. Development of a new infection is rare. Most FMT efficacy studies have examined adverse events as a secondary outcome with overall minimal findings.

Box 2
Potential adverse events of fecal microbiota transplantation

Minor (and common):

- Nausea/vomiting (particularly with oral FMT route)
- Abdominal discomfort or pain
- Bloating
- Flatulence
- Diarrhea/constipation
- Low-grade fever

Severe:

- Sedation related (eg, aspiration)
- Endoscopy related (eg, bleeding, perforation)
- Infection ± sepsis (infection may be a long-term sequelae)
- Inflammatory bowel disease flare
- Postinfectious irritable bowel syndrome

Potential:

- Risk of chronic disease development related to changes in gut microbiome
- Other unknown?

There has been ongoing concern that immunocompromised patients may be at greater risk for infection and sepsis following FMT. A multicenter, retrospective study examining post-FMT adverse events in 80 immunocompromised patients showed high CDI cure rates following a single FMT (78%).[49] Two patients died (one from unrelated pneumonia and the other following an aspiration event during sedation for colonoscopy). There were no infections linked to FMT. Among mild adverse events, 3 patients reported abdominal discomfort post-FMT.

Among patients with IBD, also considered to be immunocompromised, there is a subset of patients that will develop an IBD flare. Of the patients with IBD included in the study of immunocompromised patients by Kelly and colleagues,[49] 14% experienced a flare post-FMT. These flares frequently manifest with fever and increases in inflammatory markers along with typical flare symptoms of irregular bowel habits and abdominal pain. We have also witnessed several cases of postinfectious IBS in patients, although it is unclear if these are related to FMT versus prior infection, such as CDI.

Less well known are the long-term risks of FMT, particularly on the development of chronic diseases that may be related to alteration of the gut microbiome or be unknowingly harbored by the donor stool. Although donor screening testing protocols are quite extensive, it is impossible to check for all organisms and there is always a risk of transmitting an untested infectious agent to the recipient.

Based on the evidence, FMT is an overall safe therapy with minimal adverse effects. Despite this, we urge caution in the use of FMT in severely immunocompromised patients, as there are isolated reports of sepsis, possibly related to bacterial translocation in the setting of impaired gut mucosal integrity and inflammation. Nonetheless, for patients with rCDI that have not responded to other therapies, this may be the best option.

SPECIAL POPULATIONS

In addition to immunocompromised patients, there are other groups that warrant special attention when FMT is being considered. These include the following:

- Elderly
- Pediatric populations

Elderly

The increased prevalence of CDI in the elderly population (older than 65) has been well established; mortality is also greatest in this cohort with more cases of severe, severe and complicated, and rCDI. Given this older population often has a number of serious comorbidities, there is increased scrutiny in performing FMT in these patients. Agrawal and colleagues[50] performed a multicenter, retrospective study evaluating the efficacy and safety of FMT in 146 patients aged 65 or older. There was a mix of patients with recurrent, severe, or severe and complicated CDI. Primary cure was established in 82% of patients with recurrent CDI, 91% in patients with severe CDI and 66% in patients with severe and complicated CDI. There were no adverse events, but there were a total of 6 hospital admissions for diarrhea recurrence.

Although FMT appears safe in these populations, there are several concerns to note, including the risks of performing an invasive procedure (although with an overall good safety profile), increased comorbidities making anesthesia of higher risk, greater difficulties performing adequate bowel preparation, current medications that may include blood-thinning or antiplatelet agents, and decreased anal sphincter tone

that may make it more difficult to retain infused stool for an extended period of time.[51] These factors raise the question if donor stool administration via an upper GI route may be safer, although likely slightly less effective. Frozen encapsulated stool also may be an option, although as elderly patients more frequently experience dysphagia, capsules may be administered only in patients with normal swallowing.

Pediatric Population

There is substantially less evidence for the use of FMT in pediatric populations. There are reports of FMT use for both CDI and IBD with varying results.[52] Additionally, there is more concern for adverse events in children. In the short-term, there are the risks of performing any invasive procedure and related anesthesia, but in children who have many years of life ahead of them, there are also the fears of the long-term effects of microbiome manipulation.

FUTURE CONSIDERATIONS/NEXT STEPS

The goal of FMT is to alter the gut microbiome (ideally back to the preinfection state) and we have evidence suggesting clear changes in bacterial populations and an overall increase in the diversity of species following FMT. As described previously, there does not appear to be any significant short-term adverse events following FMT, although we must acknowledge that long-term outcomes related to changes in the microbiome are less clear and will require ongoing, prospective review to assess. An FMT registry to collect long-term data has just been funded and will provide important data on outcomes and complications.

Despite the absence of major adverse events, there remains the potential for infection, the development of donor diseases (such as metabolic syndrome), and dysregulation of the immune system; there are multiple reports of autoimmune diseases post-FMT, although the causality of this is less clear. Therefore, we must consider donor stool a "drug" and subject to regulation by the FDA. There needs to be standardization regarding the screening of donor stool and a clear protocol for the monitoring of adverse events.

Over the past several years, we have learned a lot more about the bacterial populations within our gut; however, we know very little about the function of these bacteria. We know bacteria have the ability to produce and secrete bioactive compounds ranging from antimicrobial agents to neurotransmitters to quorum-sensing molecules that influence and communicate with nearby bacteria. We also know very little about the gut's virome or mycome. Research needs to shift from identifying the bacteria present in the gut to determining the function of these bacteria.

Finally, there is ongoing interest in the broader application of FMT for other diseases beyond rCDI and there are dozens of studies ongoing to determine if there are benefits both for infectious and noninfectious conditions. Additionally, there remains the question if alternatives to donor stool are effective, such as synthetic stool formulations. There is an active clinical trial (NCT01372943) using a purified mixture of donor bacteria for treatment of rCDI with the hypothesis that this probiotic approach would provide a "more controlled, reproducible, cleaner and more aesthetically acceptable method of administration" that is "a safer strategy than using freshly defecated donor fecal matter." Preliminary proof-of-principle data in a very small sample (n = 2) demonstrate effectiveness in treating rCDI, and improvement in patient symptoms.[53] We anticipate ongoing focus on the development of alternatives to stool transplantation, although any competing therapy will need to demonstrate efficacy rates as robust as FMT, which will be challenging.

In conclusion, FMT is clearly a highly effective therapy for management of rCDI with ongoing studies to determine if there is a role in other diseases. The rise in the popularity of FMT and newly found focus on the microbiome and its role in health and diseases make for an exciting future in the field of gastroenterology and infectious disease.

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