The 5D Framework: A Clinical Primer for Fecal Microbiota Transplantation to Treat *Clostridium difficile infection*

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The 5D Framework: A Clinical Primer for Fecal Microbiota Transplantation to Treat *Clostridium difficile infection*

Clostridium difficile infection (CDI) is the most common health care-associated infection in the United States. Recently, fecal microbiota transplantation (FMT) has emerged as an effective and safe therapy for recurrent CDI; however, despite rapid adoption there is no standardized clinical approach. Given the rapid adoption of FMT, in part due to stool banks, there is a need for a practical primer for clinicians to safely perform FMT. Accordingly, we aim to provide a simple approach entitled the 5D FMT framework to guide physicians. The 5D FMT framework includes: Decision (selecting appropriate patient for FMT), Donor (selection and screening), Discussion (risk, benefits, alternatives), Delivery (selecting appropriate modality for FMT administration) , and Discharge (counseling at discharge and follow-up). We aim to help clinicians take a simple but evidence-based approach to FMT to optimize efficacy and safety. This primer navigates how to decide if a CDI patient is appropriate for FMT, select and screen stool donors, identify the ideal delivery modality and provide follow-up care after FMT.

Introduction

Clostridium difficile infection (CDI) is a significant public health risk and has emerged as the most common cause of health-care associated infection in the United States. [1, 2] The rise of CDI is a reflection, in part, of challenges with antibiotic stewardship and the emergence of more virulent strains. [3] Epidemiologic data suggest CDI-associated hospitalizations nearly doubled from 2000 to 2010 [4-6] and a recent study estimated 29,300 annual CDI-associated deaths in the United States. [2]

Fecal microbiota transplantation (FMT) is now regarded as a safe and effective therapy for the treatment of recurrent CDI. Although the mechanism of action for FMT has not been fully elucidated, there is speculation that it establishes a newly enriched microbiota that directly and indirectly inhibits *C difficile* by production of bactericidal proteins (bacteriocins) as well as competing for nutritional and colonization resources. [7-10] The mechanism of FMT expands beyond the changes in the microbial community structure to include restoration of microbial functionality. [11] Specifically, FMT reestablishes normal microbial communities involved in secondary bile acid metabolism, a process disrupted by antibiotics, and further suppressed in recurrent CDI. [12] Data suggested a number of bacteria with known bile salt hydrolase activity are found to be present at higher levels post-FMT compared to pre-FMT including *Bacteroides ovatus, Bacteroides vulgatus, Blautia obeum, Collinsella aerofaciens, Dorea longicatena, Eubacterium rectale, Faecalibacterium prausnitzii, Parabacteroides distasonis,* and *Ruminococcus torques*rectale [13]. Overall, restoration of secondary bile acid dominance in the colon appears to create an inhibitory milleu for *C difficile* spore germination and vegetative growth. [14, 15]

To date, four randomized controlled trials have measured the efficacy of FMT compared to standard therapies and, more recently, compared to placebo. [16-19] Van Nood and colleagues conducted a three-arm, open-label randomized controlled trial comparing FMT by naso-duodenal tube after an abbreviated course of vancomycin and bowel lavage, standard oral vancomycin and oral vancomycin plus standard bowel lavage. The study was halted early due to the superior effectiveness of the FMT arm. [18] More recently, Kelly and colleagues[17] were the first to conduct a placebo-controlled study and reported an overall 90.9% efficacy rate in the FMT arm compared to 62.5% in the placebo arm (autologous FMT). Several systematic reviews and meta-analyses have shown efficacy rates ranging from 80% to 90% for treating recurrent CDI with a single FMT infusion. [16, 20-22]

From a safety perspective, aside from mild, transient adverse events such as abdominal pain, which may be driven by the delivery modality, FMT is well tolerated with a favorable short-term safety profile. However, recent systematic reviews and meta-analyses, suggested more adverse events with the upper gastrointestinal (GI) delivery route (eg, naso-enteric tube) compared with lower GI administration (eg, colonoscopy, enema). [23] There is a paucity of data regarding the long-term safety of FMT. Although there is no evidence thus far, there are theoretical concerns that microbiota acquired from donor stool could increase the risk of potentially microbiome-mediated diseases. Ongoing studies including the STOOL study (Clinicaltrials.gov NCT02403622) and a national FMT registry recently funded by the National Institutes of Health, which will prospectively monitor 4,000 patients for up to 10 years post-FMT, will help determine the short and long-term safety profile of FMT.

In terms of regulation of FMT, the U.S. Food and Drug Administration (FDA) issued a public announcement in May 2013 stating that it would regulate FMT and fecal material as both a drug and a biologic product. [24] Practically, this would have required clinicians to submit an Investigational New Drug (IND) application before performing FMT to provide oversight, standardization, and increased safety. However, clinicians, patients, and stakeholders voiced concern that the IND requirement would limit access to the procedure and catalyze risky, unscreened "do-it- yourself FMT." Accordingly, the Agency revised its position and announced that it would not enforce the IND requirement for the treatment of *C difficile* infections not responsive to standard therapies. [25]This enforcement discretion does not apply to indications other than CDI, which still require an IND. [26]

Given the rapid adoption of FMT, in part due to stool banks, there is a need for a practical primer for clinicians to safely perform FMT. [27] Accordingly, we aim to provide a simple approach entitled the 5D FMT framework to guide physicians. The 5D FMT framework includes: Decision, Donor, Discussion, Delivery, and Discharge (Table 1).

(1) Decision: Deciding on the appropriate CDI patient to undergo FMT

Indications for FMT

The initial FMT working group, consisting of gastroenterology and infectious disease thought leaders, recommended, the primary indications for FMT are as follows: (1) Recurrent CDI defined as 3 or more episodes of mild to moderate CDI and failure to respond to a 6- to 8-week taper of vancomycin or at least 2 episodes of CDI requiring hospitalization and associated with significant morbidity; (2) Moderate CDI with no response to standard therapy for at least one week and (3) Severe CDI with no response to standard therapy for 48 hours. [28, 29]However many

of the RCTs that came out after these initial recommendations enrolled patients who had failed an initial course of antibiotics. [18] The American College of Gastroenterology and European Society of Clinical Microbiology and Infectious Diseases have both included FMT as an option for recurrent CDI in published treatment guidelines. [7, 30] The recent European FMT guidelines report a strong recommendation with high quality of evidence for the use of FMT for the treatment of recurrent CDI with overall resolution rates ranging between 85% to 89.7%. The recommendation for refractory CDI is also strong although the quality of evidence is low; however, it is noted that patients with refractory CDI likely have more severe disease. The guidelines do not recommend the use of FMT for the first episode CDI, given insufficient evidence. [30]

In terms of severe CDI, there is emerging evidence to suggest that FMT may be a useful tool in the treatment of severe or severe-complicated CDI. Although colectomy remains the standard of care for fulminant cases, it carries significant morbidity with operative mortality rates approaching 50%. [31] There have been several reports on the use of FMT in this population, and the data is promising. [32, 33] Fischer et al presented a series of 57 patients, refractory to maximal medical therapy, who received an FMT in combination with selective use of vancomycin. [34] The sequential FMT protocol consisted of at least one FMT delivered via colonoscopy, with criteria for continued vancomycin based on the presence of pseudomembranes on endoscopic evaluation and criteria to determine the need for repeat FMT based on clinical response. Among the patients treated with this sequential FMT protocol, 91% (52/57) experienced clinical cure at 1 month with a 100% cure rate for severe CDI (n = 19) and an 87% cure rate for severe-complicated CDI (n = 33). [34] This emerging body of literature on the use of FMT in critically ill patients may suggest it may be a viable alternative to colectomy; however, randomized controlled trials are needed.

CDI Stool Testing

Before performing a FMT clinicians should review all available CDI tests, including the type and timing, performed on the patient in order to confirm the diagnosis. Clinicians should carefully review if a nucleic acid amplification test (NAATs also called PCR) for the *C difficile* toxin gene or a toxin A/B enzyme immunoassay (EIA) that directly detects *C difficile* toxin was conducted. If only NAAT/PCR testing is available, eliciting a history of clinical response to anti-CDI antibiotics is important to distinguishing true infection from colonization, as presence of a *C difficile toxin* gene does not mean toxin is being produced. If patients do not respond to anti-CDI antibiotics and have ongoing or intermittent diarrhea, other etiologies should be investigated.

We would recommend clinicians follow the 2016 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for CDI testing, which state that no single commercial test can be used as a stand-alone test for diagnosing CDI, and recommend a 2-step approach (highly sensitive with reflex to highly specific test). [35] These guidelines recommend performing an initial test with a high negative predicative value; therefore, if negative, no further testing needs to be done. Specifically, they suggest glutamate dehydrogenase (GDH) EIA or NAAT/PCR testing. Our recommendation is GDH EIA as it is less expensive and has a slightly superior NPV at higher CDI prevalence compared with NAAT/PCR (98 vs 96 at hypothetical CDI prevalence of 50%), and an NPV of 100% at lower CDI prevalence. [35] The second test should be a test with a high positive predictive value, such as EIA for toxin A/B. Obtaining CDI testing at each suspected CDI recurrence and working with institutional laboratories to use an appropriate testing algorithm is a key component to ensuring appropriate patient selection for FMT. Overall, a clinician's understanding of CDI testing is crucial given the high sensitivity of stool NAAT/PCR

testing and the frequency of colonization, especially in elderly or hospitalized patients, on the background of other conditions (eg, post-infectious irritable bowel syndrome) presenting with diarrheal symptoms, which can result in a misdiagnosis of CDI. This concept is highlighted by evidence suggesting that up to 25% of patients referred to an FMT center for "*C difficile* infection" were found to have an alternative diagnosis, with younger patients being more likely to have a non-CDI diagnosis. [36] Overall, clinicians should consider other possible etiologies for diarrheal symptoms including post-infectious irritable bowel syndrome, inflammatory bowel disease, microscopic colitis, bile salt diarrhea, celiac disease, chronic pancreatitis, other infectious etiologies, or factitious diarrhea.

Special populations

Specific exclusions may be based on the modality of delivery considered and will be discussed further below. Other populations in which FMT should not be offered include patients who are neutropenic. Additionally, there is limited data on pregnant patients, therefore would not recommend FMT given the current body of evidence. [37] The patient who will require long-term chronic antibiotics should be considered carefully, given the disruption of the healthy microbiota instilled, and the increased likelihood of FMT failure, although this is not an absolute contraindication. Finally, FMT may not be ideal in patients with limited life expectancy, such as those with advanced malignancy, in whom it may be more suitable to treat with low dose vancomycin to prevent CDI recurrence rather than subjecting them to an invasive procedure. However, CDI may be debilitating and given the focus of quality of life in this population, the decision to proceed or not with FMT should be made on a case-by-case basis in the context of patient goals of care. Overall, clinicians must be thoughtful in the decision to offer a patient with CDI an FMT.

Patients with inflammatory bowel disease (IBD) and CDI represent a unique and challenging population. Kelly and colleagues demonstrated that FMT is safe in patients who are immunosuppressed and this included patients with IBD on various IBD therapies [38]. Consideration should be given to IBD disease activity in these patients. Colonoscopic administration may be helpful in this population in order to perform a thorough examination of the mucosa and obtain biopsy specimens. The overall efficacy and safety profile of FMT in IBD patients and CDI requires further elucidation and is currently being investigated in an ongoing prospective study (NCT03106844).

(2) Donor: Donor Selection and Screening

Patient Directed vs Universal Stool Donors

There are 2 main stool donor approaches: (1) patient directed donor and (2) universal donor. In the *patient directed* approach a donor is identified by the patient, typically a partner or spouse, friend, or sibling. Donors should be consented for the screening process. Selection and exclusion criteria are based on medical history and appropriate serologic and stool testing. There is heterogeneity in recommended testing protocols between U.S. and European medical societies. [30, 39] An advantage to the patient directed method is that some patients may be more comfortable if they know the source of the fecal material. The patient-directed approach may also be considered in cases where donor diet is important (eg, recipient with a history of anaphylaxis or anaphylactoid reactions to a food source). Drawbacks to the patient-directed approach include delay in treatment while sourcing, screening, and testing a donor as well as

significant costs incurred in screening tests. [40] Additionally, using a donor known to the recipient may also raise ethical concerns around coercion or full-disclosure on screening especially if the recipient is a family member. From a clinical perspective, there are no data to suggest advantages in safety or efficacy in the *patient-directed* approach. [22]

The *universal donor* approach uses healthy volunteers, like a blood bank, who are screened through a centralized process and whose stool is frozen and banked for future use. This approach enables economies of scale, reduced costs, convenience for patients and providers and reduced waiting times for scheduling FMT procedures. [40] The drawback is that an infection transmission or other safety event may impact more than one individual, although safety and traceability protocols may also be enhanced through centralized collection and monitoring. Safety aliquots may be stored and reexamined for enteropathogens should a suspected adverse event arise. Overall, a universal donor approach helps address the screening and logistical barriers that clinicians feel are most challenging in adopting FMT. [41]

Frozen versus Fresh Donor Material

Historically, fresh material was assumed to be superior to frozen fecal material in treating CDI. However, delivering fresh stool for FMT can pose significant operational challenges, a major barrier to the adoption of FMT according to a physician-based survey. [41] Collection and preparation of the fresh fecal material includes dilution, homogenization and filtering to remove particulate material. Donor stool is usually mixed with saline solution and homogenized by either blending or manually stirring. The liquid slurry is then strained if necessary to remove particulate matter that can be easily administered (Figure 1). Fresh stool should be used to perform FMT on the same day it is collected, preferably within 6 hours.

Previously, there was concern that freezing and thawing stool may reduce the number of viable microbiota, although data have emerged to suggest frozen-and-thawed and fresh donor material are equally effective in recurrent CDI. Hamilton and colleagues[42] were among the first to report the efficacy of a standardized, frozen preparation for transplantation of fecal microbiota. More recently, Lee and colleagues[43] performed a large non-inferiority trial assessing the efficacy of fresh versus frozen-and-thawed FMT for the management of recurrent CDI. In this randomized, controlled trial, 108 patients received FMT by enema with material that had been frozen and 111 received FMT with fresh donor material. They demonstrated clinical resolution of CDI, per protocol, in 83.5% of patients in the frozen-and-thawed FMT arm and 85.1% in the fresh FMT arm, concluding that frozen material was not inferior to fresh in achieving clinical resolution of CDI.

Stool Banks

The logistics of stool preparation and delivery has been a barrier to providers offering FMT. [41]Given the operational advantages of the universal donor model and frozen material, stool banks have emerged to enable safe access to FMT at scale. There remains regulatory uncertainty regarding the role of stool banks; however, current draft FDA guidance, released for public comment only, does not affect the existing FDA guidance that enables clinicians to proceed with FMT from stool banks for patients with recurrent CDI. [44]

Providers in the United States (and some countries outside of the United States) may source screened, frozen fecal microbiota preparations from universal stool banks. OpenBiome, a

nonprofit stool bank based in Somerville, MA offers formulations for delivery by the lower GI tract, upper GI tract, and capsules for oral delivery. AdvancingBio, a nonprofit stool bank based in Ranchero, CA offers preparations for delivery to the lower GI tract. In addition to these public stool banks, several academic institutions around the country have set up in-house stool banks within their institutions for local use.

Donor screening, GMP manufacturing, and quality assurance monitoring by universal stool banks:

In addition to the standard practices outlined above, universal donors at one U.S. stool bank (OpenBiome, Somerville, Mass) undergo dual laboratory testing, mandatory material quarantining to address a seroconversion window, standardized continuous health monitoring for changes in health status or risk factors and the preservation of safety aliquots for testing in the case of a suspected adverse event. [45] This robust screening program illustrates a challenge that individual practitioners often face when obtaining healthy stool donors, because the stool bank reports that only 2.8% of donors qualify to provide stool among 1387 candidates in a prospective study. [46] Donor material is processed in a Good Manufacturing Practice (GMP) facility and stored at -80°F until it is shipped to medical facilities overnight on dry ice with temperature verification.

Observational data from this stool bank supports the efficacy and safety data seen in clinical trials in CDI. In a 2,050 patient cohort, the overall clinical cure rate from physician reported outcome data was 84.0% across all FMT delivery modalities including colonoscopy, upper endoscopy, nasogastric tube and enema. [47] Forty-two adverse events were reported, although none were determined to be definitely related to FMT, three were possibly related to the FMT and 39 were not related based on NIH criteria after independent safety review. [47] Screening and safety data from AdvancingBio were unavailable at the time of publication.

Donor Screening

Potential donors should be screened with a complete social history to assess for behaviors, which may confer increased risk for infectious disease transmission, similar to screening methods used for blood donation. Prospective donors should be healthy adults without any gastrointestinal pathology and who have not taken antibiotics within the previous 3 months. Additionally, donors should be excluded if they have a history of diseases that may be associated with alterations in the gut microbiome, including autoimmune or atopic illnesses, chronic pain syndromes (fibromyalgia, chronic fatigue), neurologic or neurodevelopmental disorders, certain neuropsychiatric conditions, metabolic syndrome, obesity (body mass index >30), moderate-to-severe malnutrition, malignant illnesses, or ongoing oncologic therapy. [28]

Those who meet initial eligibility should then undergo serologic and stool testing to screen for infectious pathogens. At a minimum, donors should have serological testing for HIV (EIA), Hepatitis A (HAV IgM), Hepatitis B (HBsAg) and Hepatitis C (anti-HCV Ab), and syphilis (FTA-ABS) and stool testing should include screening for common enteric pathogens, *C difficile* toxin B, and examination for ova and parasites. [42] Some protocols recommend testing donor stool for viruses (adenovirus, norovirus, rotovirus) and antibiotic resistant bacteria such as vancomycin resistant enterococcus (VRE), extended spectrum beta-lactamase (ESBL) producing organisms and carbapenem-resistant enterobacteriaceae (CRE). Practically, it is important to discuss testing with the local microbiology laboratory before screening to ensure formed donor stool won't be discarded in error.

Additional testing should be considered when the recipient is immunocompromised. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) pose a particular dilemma for clinicians. Given the high rates of carriage for both EBV and CMV in a healthy, adult population, excluding EBV or CMV positive donors would make it prohibitively difficult to identify suitable donors to provide access to care. [48]Unless the donor has been screened for CMV and EBV, FMT material should be treated as presumptively CMV and EBV positive and not used in severely immunocompromised patients who are seronegative (IgG) for CMV or EBV. If FMT must be performed in severely immunocompromised patients at risk for CMV or EBV-associated diseases, there are two potential approaches. First, assess the recipient for CMV and EBV, and, if negative, FMT material with unknown donor CMV or EBV status (presumed positive) may be considered after extensive discussion of the risks, benefits, and alternatives including no treatment in the informed consent process. Second, the use of a directed donor with matching serology may be considered.

It should be noted that there have been no reported cases of EBV transmission from a universal donor. There have been two published cases of CMV post-FMT. The first occurred in the context of a randomized controlled trial of FMT for ulcerative colitis with CMV sero-conversion at 7 weeks post-FMT. [49]However, this patient was in the control arm and had received their own fecal material in an autologous FMT. No patient's in the treatment arm receiving donor material acquired CMV. In a second published case, a patient with ulcerative colitis developed CMV colitis after performing FMT at home using donor material from han unscreened infant. [50]It is important to note, that patients with IBD may develop colitis from CMV reactivation; thus, causality remains unclear.

(3) Discussion: Discuss the risks, benefits and alternatives to FMT (informed consent)

Informed Consent
Given the paucity of long-term safety data for FMT, it is critical to conduct and document a thorough informed consent discussion with the patient. This discussion should cover the risks and benefits of FMT material and the delivery modality as well as any alternative treatment options.

Risks
There have been no serious adverse events definitively attributed to FMT material in the peer-reviewed literature. [23, 51] Nevertheless, the patient should be informed of common mild adverse reactions potentially related to FMT including transient diarrhea, abdominal cramps/discomfort and nausea, fever, bloating, belching, vomiting, borborygmus, constipation, and excess flatulence. There have not been any *definitely* related serious adverse events attributable to FMT material. However, the following potential serious adverse events should be communicated to the patient:

(1) *Infection*: Although material should have been screened for common enteric pathogens, there is a risk of transmission of known and unknown infectious organisms contained in the donor stool. Post-FMT bacteremia (eg, *E coli, K pneumoniae*), sepsis and fatal events may occur. Cases reported in the literature include bacteremia, cytomegalovirus colitis, pyrexia of unknown origin, influenza B transmission, and non-CDI diarrhea (eg, norovirus). [38, 52, 53] A multicenter

retrospective study of immunocompromised patients receiving FMT to treat CDI did not report any infectious adverse events in this "high risk" cohort. [38] We strongly recommend that patients who are immunosuppressed and at particularly high risk of CMV or EBV infection should be counseled about the potential for additional risks for opportunistic and viral infections.

***(2) Gastrointestinal**:* Abdominal pain, appendicitis, peritonitis and diverticulitis have been reported as possibly related to FMT in cases reported in the peer reviewed literature. [38, 54-57]There is a theoretical risk of small intestinal bacterial overgrowth when FMT is delivered into the upper GI tract, however there have been no reported cases to date. [58]

(3) *Allergy/Anaphylaxis to antigens in donor stool*: Whilst no cases of allergy or anaphylaxis have been reported in the literature, patients should be screened for food allergies before FMT. If the patient reports a severe food allergy, either the patient should be evaluated by an allergist to confirm the allergy if there is there is any question or if confirmed the stool source should be a directed donor, who has abstained from the offending agent for a period of 7 days.

***(4) Autoimmune**:* Rheumatoid arthritis, Sjogren syndrome, peripheral neuropathy, and idiopathic thrombocytopenic purpura have all been reported in the peer reviewed literature as *possibly* related to FMT. [59]

(5) *Non-infectious disease transmission*: There is a theoretical risk of developing disease that may be related to donor gut microbiota. These include obesity, metabolic syndrome, neurologic disorders, psychiatric conditions and malignancy. Persons with these known conditions should be excluded from donating stool, although a theoretical risk of acquiring these conditions and other unknown microbiome-mediated diseases after FMT remains.

(6) *Inflammatory bowel disease (IBD) flare*: In those with underlying IBD, flares have been reported in up to 15% of cases especially when there is active background disease at the time of FMT [60], although these were uncontrolled studies and potentially driven by oversensitive *C difficile* PCR testing, as the risk appears lower in randomized controlled trials. [49, 61-63]

(7) Treatment failure or improvement but incomplete resolution of symptoms: FMT has been successful in controlled trials, but there is potential for treatment failure or incomplete resolution of patient's symptoms. Patient expectations should be calibrated appropriately during the discussion. Predictors of treatment failure include severe and severe-complicated CDI, inpatient status during FMT, and the number of previous CDI-related hospitalizations [64] as well as underlying IBD. [60]

Procedure-related risks

The chosen delivery modality carries risks independent of FMT material. There have been 2 serious adverse events reported in the peer-reviewed literature determined to be *definitely* related to FMT procedure. These include aspiration after upper delivery of FMT and bowel perforation after colonoscopic delivery of FMT. [65, 66]Importantly, these adverse events were related to the FMT procedure and adverse events associated with the delivery modality. Risks related to the FMT procedure should be clearly discussed with the patient and the choice of delivery modality may depend on the patient or specific clinical situation.

Pre-FMT Patient Education

Patients should be given clear advice on how to clean their home bathroom and high touch surfaces before FMT to prevent ongoing exposure to spores and CDI reinfection.

Specifically, patients should be advised that traditional household cleaning products are not sufficient and they should use an Environmental Protection Agency (EPA)-registered disinfectant with a *C difficile*-sporicidal label claim. [67] These agents can be any chlorine-containing cleaning agents at a concentration of at least 5,000 ppm, eg, household bleach (diluted with one parts bleach to 10 parts water). Patients should take precautions in cleaning high touch surfaces, cleaning surfaces with at least 10 minutes of contact between a surface and disinfectant. If the patient lives in an assisted living residence, they should speak the director of their facility to ensure that the appropriate measures are taken to disinfect their living environment.

Finally, patients should be advised to discontinue antibiotics before FMT. Anecdotal experience suggests discontinuing anti-CDI therapy 2 days before FMT, although the literature reports between 1 and 3 days. [18, 22, 59]

(4) Delivery: Selecting the delivery modality to administer FMT

Routes of administration include the lower GI tract (with instillation into the right side of the colon or TI via colonoscopy or instillation into the distal colon via enema or flexible sigmoidoscopy) or the upper GI tract (via upper endoscopy, nasoenteric tubes, or capsules). Although there is no well-powered head-to-head study on FMT delivery modality, a pilot study [19] (n=20) suggests colonoscopic delivery appears to be a more effective modality then upper GI delivery. A systematic review and meta-analysis conducted by Kassam and colleagues[22] demonstrated that the combined efficacy rates of lower GI delivery, driven by colonoscopy, was consistently higher than combined efficacy rates of upper GI delivery (91.4% versus 82.3% respectively). However, there are advantages and disadvantages to each route of FMT delivery, which should be considered on a case-by-case basis.

Lower GI Tract Administration
Lower GI routes of administration include enema, sigmoidoscopy or colonoscopy. Combined efficacy rates for lower GI administration including enema, sigmoidoscopy, and full colonoscopy has been reported to range from 84% to 93%. [22]

Retention Enema
Retention enema is inexpensive and generally well tolerated. The benefit of this method is it does not require sedation and therefore has little procedural risk. Furthermore, it can be administered by a non-physician. The enema method is often used in pediatrics or patients with colostomies. The study by Zipursky and colleagues,[68] which solicited patients perceptions and willingness to consider FMT treatment, found that patients preferred the enema route of delivery over upper GI delivery. The drawbacks to FMT by enema include that patients may have difficulty retaining the material due to poor rectal sphincter tone. In addition, the efficacy rates with enema administration for the treatment of CDI is the lowest of all FMT modalities. Lee and colleagues[69] demonstrated a 47.9% cure rate after a single enema administration in participants with recurrent CDI. However, the cumulative clinical cure rate improved to 86.2% with repeated enemas, with some participants requiring up to 6 enemas.

Lower endoscopy

These routes of administration, which include both colonoscopy and sigmoidoscopy, are well tolerated. They do carry procedural related risk, but they additionally carry the benefit of examination of the colonic mucosa and biopsy if necessary to ensure there are no competing diagnoses.

Sigmoidoscopy:
Recto-sigmoidoscopy may be the preferred route of delivery based on patient's choice or in patients who are frail or at a high risk of intestinal perforation (severe colitis or significant colonic distention). Several experts have advised less invasive modalities such sigmoidoscopy in high risk patients. [70, 71] To date, there are no studies directly comparing the efficacy of sigmoidoscopy to other delivery modalities, including full colonoscopy, for the treatment of CDI.

Colonoscopy
Colonoscopy remains the most common FMT delivery modality and is supported by a placebo-controlled trail and an abundance of observational data supporting its efficacy in recurrent CDI. [21, 22]It is particularly useful in patients with IBD, as it enables assessment of disease activity at the time of FMT. If may also be appropriate in younger patients, in whom recurrent CDI may herald a new diagnosis of IBD. This route does carry additional costs and requires technical expertise although a cost-effectiveness analysis showed that FMT by colonoscopy was less costly compared with vancomycin for both recurrent CDI and initial CDI. [72, 73]Additionally, administration to the right side of the colon appears to have high overall efficacy with up to a 93% clinical cure rate after a single dose. [16]

Upper GI Tract Administration
Efficacy rates with upper administration have been reported to be 81% to 86%. [22] It is important to note that for pre-pyloric upper GI administration a proton pump inhibitor (PPI) should be administered 48 hours before infusion.

Nasoenteric tube
This delivery method appears to be more routinely used in Europe than the United States, potentially because a Dutch group conducted the first randomized controlled trial using nasoduodenal infusion of FMT [18]. The benefit to this method is that it does not require sedation, however it may be uncomfortable, and studies investigating patients' perceptions regarding nasoenteric administration have demonstrated that patients perceive this route of delivery as the least appealing. [68] Additionally, this route of delivery requires radiological confirmation of tube placement and there is some risk of vomiting and aspiration. [66]A study conducted by van Beurden and colleagues[74] using the duodenal route reported a significant number of participants who experienced regurgitation (13%) and one death due to pneumonia in which a causal relation to the FMT could not be excluded. The inherent risks associated with upper GI delivery should be carefully considered, particularly in patients with severe acute *C difficile* colitis and/or ileus. We caution against delivery of a large stool dose to the upper GI tract to reduce the risk of regurgitation of fecal material.

Upper Endoscopy
This route carries the same risk and has the same efficacy rate as nasoenteric tube administration. [22]However, this method requires sedation and carries additional procedural risks. This option can be considered in patients who have had complicated lower GI surgery and those without intact colons. Some physicians may prefer upper endoscopy because of concerns

around performing a colonoscopy when the colon is severely inflamed. However, it is important to note that patients undergoing FMT for recurrent CDI are typically treated with a course of vancomycin to control the acute infection preprocedure and rarely have inflamed colons at the time of FMT administration.

Capsules
More recently, studies have begun using FMT capsules as a route of delivery, recognizing that there are circumstances when it may be inappropriate, contraindicated, or contrary to patient preferences to deliver material via traditional routes of administration for CDI. In terms of patient perceptions, Zipursky and colleagues[68] report that more aesthetically appealing FMT formulations, such as capsules, would both eliminate potential barriers to treatment and reduce the necessity for healthcare resources and procedure time for clinicians.

Although the optimal dose is still under investigation, there have been several proof-of-concept studies that have shown equivalent efficacy rates. Youngster and colleagues[75] reported their experience with a capsule formulation that averaged 1.6 grams of stool per capsule in which they dosed 15 capsules on 2 consecutive days. They reported a 70% cure rate after an initial dose in a cohort of 140 patients. Those that failed to achieve cure were re-treated, bringing the cumulative cure rate up to 90%. There were several adverse events deemed to be related or possibly related to the FMT including fever, hospitalization due to relapse of CDI and one *de novo* diagnosis of ulcerative colitis. [76] Similarly, Hirsch and colleagues[77] demonstrated a clinical cure rate of 68% in the 19 participants, using capsules containing purified, concentrated, and cryopreserved fecal bacteria and this increased to 89% with retreatment.

Allegretti and colleagues[78] conducted the first dose-finding study for FMT capsules (0.75 grams of stool per capsule with upper GI release) assessing 30 capsules once (low dose) versus 30 capsules on 2 consecutive days (high dose). Efficacy rates between the groups were similar on initial dose (70%) and there were no adverse events reported. Overall, FMT capsules show great promise but may benefit from delayed-release formulations, to mimic the delivery approach of colonoscopic FMT.

Other considerations

Bowel Preparation:
It is unclear if bowel preparation is needed regardless of delivery modality. Previous studies have used bowel lavage when administering the FMT by upper GI route. [18, 74]It has been speculated that bowel prep flushes the bowel of residual *C difficile* spores and antibiotics and prepares the gut for engraftment of donor material. [18]Microbial sequencing studies suggest that the intestinal microbiota rapidly returns to baseline after the administration of varying doses and types of bowel preparation. [79, 80]Certainly, bowel preparation is recommended for lower endoscopy, primarily for visualization. The exception to this is patients with severe complicated disease, in whom an ileus is often present.

Timing of FMT:
FMT is generally performed as an outpatient procedure in stable patients with recurrent CDI. FMT should be performed once patients have responded to anti-CDI antibiotics for a minimum of 4 days [18]. Inpatient FMTs are generally reserved for patients with severe and severe-complicated CDI. Additionally, inpatients are more likely to experience FMT failure as

demonstrated by Fischer et al [64]. In a 462-patient cohort, 52% of the 94 inpatients experienced FMT failure at 1 month compared with 10% of the 368 outpatients who experienced FMT failure at 1 month. This highlights the complexity of the inpatient population.

(5) Discharge: Patient discharge and follow-up after FMT

Immediately after FMT, patients should retain the slurry for 45 minutes to an hour if possible. In cases of endoscopic administration, patients are kept supine in the recovery area of the endoscopy unit and encouraged to retain the material until just before discharge. Loperimide pre-procedure may aid in retention. Vancomycin should not be resumed routinely post-procedure. Patients should be counseled on antibiotic stewardship practices including the avoidance of unnecessary antibiotics, and patients and providers should be very cautious about initiating antibiotics in these patients, specifically if no infection is identified (eg, asymptomatic bacteruria, before dental cleanings in patients with prosthetic joints). Patients should be empowered to advocate for themselves to ensure antibiotics are truly necessary before they are administered.

If patients do require non-CDI antibiotics in the future they should be reassured that the recurrence rates after a successful FMT are low. Fischer and colleagues report that out of 152 patients, the overall long-term CDI recurrence rate was 10.5% after a successful FMT. Of those who experienced a recurrence, 63% had received antibiotics. Prophylactic probiotics or concomitant anti-CDI antibiotics were not found to prevent recurrence. Therefore, we do not recommend the use of prophylactic anti-CDI therapy in the setting of non-CDI antibiotic use post FMT. [81]

Patients should be followed closely to monitor for CDI recurrence for up to 8 weeks after FMT. Although there are variations on this, a possible follow-up plan would include a phone call to the patient between 72 hours and 1 week post FMT and a follow-up visit in the clinic at 8 weeks. Importantly, physicians need to be aware that post-infectious IBS can occur in up to 30% of patients after CDI. [82] Repeat testing, preferably with the two step-testing method previously discussed, should only be conducted in the event of recurrent diarrhea. A pragmatic approach to diarrhea post-FMT is outlined in Figure 2. Stool should not be tested unless patients are experiencing 3 or more unformed stools per day for 2 or more days or there are other systemic symptoms suggestive of severe CDI.

If patients have not experienced a recurrence by 8 weeks after FMT, they can be considered clinically cured. *C difficile* testing for cure after FMT in asymptomatic patients is not recommended. This practice has evolved from existing *C difficile* treatment guidelines that do not recommend testing for cure in asymptomatic patients. The basis for this recommendation is that stool *C difficile* PCR can remain positive for up to 30 days after successful treatment with antibiotics. [10]

In conclusion, the emergence of FMT has transformed the treatment landscape of *C difficile* infection. Given its rapid adoption, the paucity of long-term safety data and ongoing uncertainties in the microbiome space, clinicians must be thoughtful and systematic in treating patients. This 5 D approach is a useful primer for developing an FMT protocol, from patient selection through follow-up.

Table 1: 5D framework for fecal microbiota transplantation to treat *Clostridium difficile infection*

Decision	Donor	Discussion	Delivery	Discharge
Clinicians should *decide* if a CDI patient is appropriate for FMT. Clinicians should review the CDI indication, CDI tests and potential exclusion factors. Clinicians should consider alternative diagnoses, such as post-infectious IBS or IBD, particularly in patients with atypical presentations.	Clinicians should select the *donor* model: patient directed or universal donor from a stool bank Robust donor testing should be completed in keeping with best practices.	Clinicians should have a *discussion* with their patient regarding the risks, benefits and alternatives of FMT (informed consent) including no treatment.	Clinicians should select the ideal FMT delivery modality for the patient depending on the clinical context.	Upon *discharge*, clinicians should council patients on cleaning high-touch surface areas and antibiotic stewardship practices. Clinicians should initiate follow-up to assess for adverse events and recurrence of CDI.

Figure 1: Stool processing for FMT with fresh donor stool.

Figure 2. Post FMT testing algorithm for patients with diarrhea.

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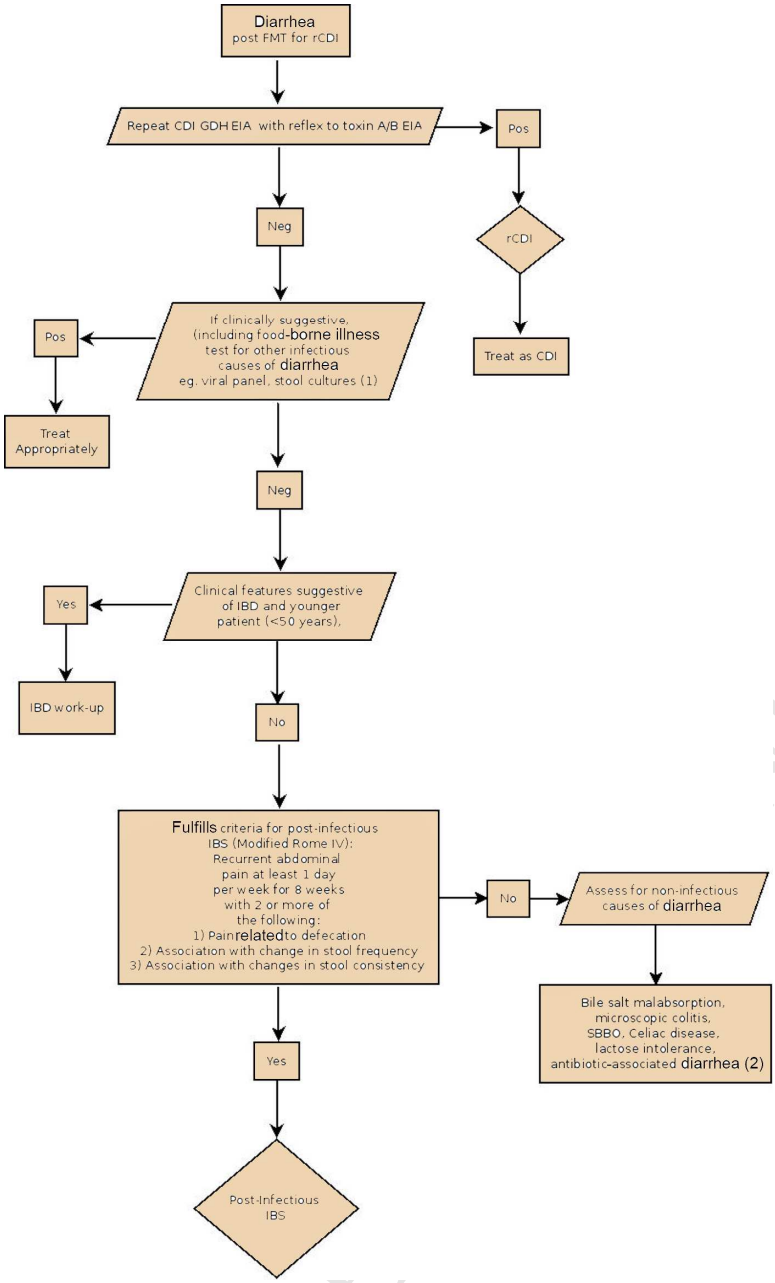
Diarrhea
post FMT for rCDI
Repeat CDI GDH EIA with reflex to toxin A/B EIA
Pos
rCDI
Treat as CDI
Neg
If clinically suggestive,
(including food-borne illness
test for other infectious
causes of diarrhea
eg. viral panel, stool cultures (1)
Pos
Treat
Appropriately
Neg
Clinical features suggestive
of IBD and younger
patient (<50 years),
Yes
IBD work-up
No
Fulfills criteria for post-infectious
IBS (Modified Rome IV):
Recurrent abdominal
pain at least 1 day
per week for 8 weeks
with 2 or more of
the following:
1) Pain related to defecation
2) Association with change in stool frequency
3) Association with changes in stool consistency
No
Assess for non-infectious
causes of diarrhea
Bile salt malabsorption,
microscopic colitis,
SBBO, Celiac disease,
lactose intolerance,
antibiotic-associated diarrhea (2)
Yes
Post-Infectious
IBS

Author Contribution

Jessica Allegretti
Background: Gastroenterologist and Director of Fecal Transplant Program at Brigham and Women's Hospital
Role:
-Conceptualized and designed the idea of a 5D framework.
- Drafted entire manuscript with emphasis on the first D (Decision) and the last D (Discharge).
- Provided critical revision and approved final draft of the manuscript

Zain Kassam
Background: Gastroenterologist, Epidemiologist and Chief Medical Officer at OpenBiome who developed the clinical program and practical physician primer for FMT that has treated >20,000 C. difficile patients.
Role:
- Conceptualized and designed the idea of a 5D framework.
- Designed the content for each of the 5D sections and made significant critical revisions of important intellectual content to each of the 5D sections and introduction.
- Drafted abstract and conclusion.

Majdi Osman
Background: Infectious Disease Specialist that actively oversees largest international FMT donor screening program.
Role:
- Designed the concept of the 3rd D (discussion/informed consent) and drafted section.
- Drafted Donor Screening section.

Shrish Budree
Background: Pediatric Gastroenterologist with background in microbiome analysis at Harvard/Broad Institute
Role:
- Conceptualized and Drafted Figure outlining approach to diarrhea post-FMT
- Drafted 4th D section (delivery modality).
- Revisions and important intellectual edits related to microbiome aspects of FMT.

Monika Fischer
Background: Director of the Fecal Transplant Program at Indiana University with particular expertise in patients with severe complicated infection.
Role: Performed critical revisions of the manuscript with a focus of special populations.

Colleen Kelly
Background: Expert in fecal transplantation and founder of the national FMT registry
Role: Help craft concept, performed critical revisions and provided article final approval

Abbreviations

CDI	Clostridium difficile infection
FMT	Fecal microbiota transplantation
GI	Gastrointestinal
FDA	Food and Drug Administration
IND	Investigational New Drug
NAAT	Nucleic Acid Amplification test
PCR	Polymerase Chain reaction
GDH	Glutamate dehydrogenase
EIA	Enzyme Immunoassay
CMV	Cytomegalovirus
EBV	Ebstein Barr Virus
IBD	Inflammatory bowel disease
IBS	Irritable Bowel Syndrome
EPA	Environmental Protection Agency