

Medical Coverage Policy



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Fecal Bacteriotherapy

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INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses fecal bacteriotherapy, also referred to as fecal microbiota transplantation (FMT), for the treatment of Clostridium difficile infection (CDI) and other indications.

Coverage Policy

Coverage for donor charges and related services varies across plans. Please refer to the customer's benefit plan document for coverage details.

Fecal bacteriotherapy is considered medically necessary for the treatment of recurrent or refractory Clostridium difficile infection when there is failure, intolerance or contraindication to conventional medical management (e.g., hydration, pharmacotherapy) and ALL of the following criteria are met:

- diagnostic testing confirms active Clostridium difficile infection (e.g., testing performed on, unformed diarrheal stool; colonoscopic or histopathological evidence of pseudomembranous colitis)
- therapy with the inciting antimicrobial agent(s) has been discontinued where possible

- recurrent or persistent episodes of diarrhea following completion of three established antibiotic treatment regimens for a minimum of ten days each (e.g., two courses of oral vancomycin and one course of oral fidaxomicin; two courses of oral fidaxomicin and one course of oral vancomycin)
- treatment to be administered by upper or lower gastrointestinal infusion (e.g., endoscopy, nasogastric tube, retention enema, colonoscopy)

The collection and processing of a bacteriotherapy specimen from the identified donor at a qualified site are considered medically necessary when the recipient of the fecal bacteriotherapy meets all of the above criteria for the procedure.

Fecal bacteriotherapy for EITHER of the following is considered experimental, investigational or unproven:

- oral administration
- any other indication, including first-line therapy for *Clostridium difficile* infection

General Background

Fecal bacteriotherapy, also referred to as fecal microbiota transplantation (FMT), fecal transfusion, or probiotic infusion, is the transfer of a liquid suspension of stool from a healthy donor into the patient's gastrointestinal tract and is proposed for the treatment of *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI). CDI causes diarrhea, intestinal inflammation and cell death. The infection can result in mild diarrhea to life-threatening, fulminant pseudomembranous colitis. The diarrhea can be recurrent or persistent. Recurrent diarrhea is a pattern of diarrhea that occurs repeatedly and consists of watery, loose and/or frequent stools. Persistent diarrhea is generally defined as the passage of loose stools for more than two weeks with progression to chronic diarrhea at the four-week mark. CDI most often occurs in patients who have received recent medical care and treatment with antibiotics and are/or have recently been hospitalized. Other risk factors include anti-neoplastic agents, corticosteroids, increasing age, use of stool softeners and gastrointestinal stimulants, enteral feedings, chronic dialysis, and residency in long-term care facilities (World Society of Emergency Surgery, 2019; DuPont, 2016; Cohen, et al., 2015; Pawloski, et al., 2009).

Recurrent CDI (RCDI) is defined as an episode of *C. difficile* that occurs eight weeks or less after the initial episode that resolved with or without therapy. Recurrences will occur in one in six people within 2–8 weeks. Patients who have at least one episode of recurrent *C. difficile* have a 50 to 65 percent chance of additional episodes. Up to 25% of patients experience recurrence within 30 days of treatment. Recurrent CDI often represents relapse rather than reinfection, regardless of the interval between episodes. The risk of recurrence continues to rise with each subsequent episode, approaching 50–60% after the third episode. The cause of failure of FMT is unknown but a few small studies have suggested potential patient characteristic (e.g., advanced age, severity of CDI, immunocompromised state, in-patient at the time of FMT; a number of CDI-associated hospital admissions) being a contributing factor. Patients with recurrent disease due to *C. difficile* are considered to have refractory CDI. RCDI can become a chronic, recurrent disease that lasts for months or years and leads to repeated hospitalization and even death (Borody and Ramrakha, 2021; Kelly et al., 2021; Centers for Disease Control [CDC], 2020; Fischer, et al., 2016; Bagdasarian, et al., 2015; Drekonja, et al., 2015; Cammarota, et al., 2014; Moore, et al., 2014; Van Nood, et al., 2013; Bakken, et al., 2009; You, et al., 2008).

The Infectious Disease Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) (McDonald, 2018) proposed the following disease severity criteria:

- Nonsevere CDI – White blood cell count $\leq 15,000$ cells/mL and serum creatinine < 1.5 mg/dL
- Severe CDI – White blood cell count $> 15,000$ cells/mL and/or serum creatinine ≥ 1.5 mg/dL
- Fulminant colitis (previously referred to as severe, complicated CDI) – Hypotension or shock, ileus, or megacolon

Treatment for CDI involves discontinuation of the offending antibiotic and oral administration of vancomycin, fidaxomicin or metronidazole. Fifteen to thirty-five percent of patients experience a first recurrence following

pharmacotherapy. After the first recurrence the risk of infection increases to 40%–45% for a second recurrence and 60%–65% of patients have multiple recurrences. In some cases, patients who are nonresponsive to medical management may undergo surgical colectomy which has a mortality rate of 35%-57%. The Centers for Disease Control (CDC) considers *Clostridioides difficile* an urgent threat that causes almost 500,000 illnesses a year in the United States. In 2017, 223,900 people required hospitalization for treatment with an estimated 12,800 deaths. CDI has become more frequent, more severe and more refractory to standard therapy and is more likely to relapse (Borody and Ramrakha, 2021; Guh, et al 2020; CDC, 2019; Infectious Disease Society of America [IDSA], 2018; Drekonja, et al., 2015; Cammarota, et al., 2014; Moore, et al., 2014; Van Nood, et al., 2013; Bakken, et al., 2009; You, et al., 2008).

In cases of nonsevere CDI, the proposed treatment option is a 10 day course of either vancomycin 125 mg orally four times a day or fidaxomicin 200 mg orally twice a day. If oral vancomycin or oral fidaxomicin are not available, then metronidazole 500 mg orally three times a day may be used as an alternative. Patients with severe CDI are treated with vancomycin 125 mg four times daily for 10 days or fidaxomicin 200 mg orally twice a day. Cases of fulminant disease (previously referred to as severe, complicated *C. difficile* infection) are treated with a combination of vancomycin 500 mg orally or via nasogastric tube four times a day and metronidazole 500 mg intravenously every eight hours. If an ileus is present, 500 mg rectal vancomycin can be administered as a retention enema in 100mL normal saline, retained for as long as possible and readministered every six hours. The rectal vancomycin retention enema can be administered in addition to oral vancomycin if the ileus is partial or in place of oral vancomycin if the ileus is complete (Kelly, et al. 2021; CDC, 2020; IDSA, 2018).

FMT has been proposed for the treatment of a subpopulation of patients who have chronic, refractory, recurrent CDI that is unresponsive to standard medical and pharmacotherapy including vancomycin, fidaxomicin and metronidazole. Administration of fecal microbiota from a healthy donor is proposed to restore the healthy gut microbiota of the infected patient. The established route of administration of the processed stool is gastrointestinal infusion by various methods including colonoscopy, endoscopy, nasogastric tube and retention enema. Some institutions have established stool banks that screen, prepare and distribute the donor specimen. Microbiome Health Research Institute Inc. (OpenBiome) is an organization that provides hospitals and private practices with screened, filtered, frozen fecal material in two different preparations for either lower or upper gastrointestinal administration. OpenBiome has also pilot launched PersonalBiome, a biobanking service in which an individual can freeze their own healthy microbiome for future use if needed (OpenBiome, 2020).

In response to a March 2020 FDA alert regarding the risk of serious adverse events likely due to transmission of pathogenic organisms, OpenBiome voluntarily notified clinical and research partners to quarantine all OpenBiome FMT products in their inventory. They suspended all shipments including emergency orders while they implemented new systems for retrospective testing with oversight from the FDA to confirm that FMT material in the past met new safety standards to test for Shiga toxin-producing *E. coli* (STEC) and Enteropathogenic *E. coli* (EPEC) by polymerase chain reaction (PCR). An OpenBiome update on COVID-19 issued on June 30, 2020, stated that the company would temporarily fulfill orders for scheduled patients and clinical trials only, until until SARS-CoV-2 testing is available and has been fully implemented. The company will be compliant with the FDA guidance to only ship material collected and processed prior to December 1, 2019 (OpenBiome, 2020). Effective May 3, 2021, OpenBiome expanded availability of FMT preparations to all scheduled patients. All material collected from donors since December 1, 2019 will be directly tested for the presence of SARS-CoV-2, the virus that causes COVID-19. OpenBiome has taken additional health surveillance measures including regular screening of donors for COVID-19 by temperature taking, evaluation of recent travel status, exposure to and any symptoms associated with COVID-19, and testing donors for COVID-19 at least every 28 days (OpenBiome, 2021).

It has been proposed that FMT is less effective in a patient who is immunocompromised (IC). An IC patient has a weak or impaired immune system, does not have the ability to respond normally to an infection and is considered to be at high risk for CDI. An IC condition can be the result of an HIV infection or AIDS, cancer, solid organ transplantation, inherited or primary immune disorders, stem cell transplantation, sickle cell disease or asplenia, congenital immune deficiencies, chronic inflammatory conditions, or cerebrospinal fluid leaks. Ongoing treatment with anti-neoplastic agents or immunosuppressant medications (e.g., monoclonal antibodies to B and T cells; anti-tumor necrosis factor agents; systemic steroids [e.g., prednisone], antimetabolites [e.g., azathioprine, 6-mercaptopurine, methotrexate], calcineurin inhibitors [e.g., tacrolimus, cyclosporine, mycophenolate mofetil]) can

also result in an IC state. FMT among IC patients with CDI has been limited due to concerns about safety (Cammarota, et al., 2014; Van Nood, et al., 2013; Bakken, et al., 2011). Whether IC is a contraindication to FMT has not been established. A limited number of studies, primarily retrospective in nature, propose that FMT is a safe procedure in some IC patients (Fischer, et al., 2016; Kelly, et al., 2014; Bakken et al., 2011).

Administration of ready-to-use enemas for the treatment of *C. diff* are being investigated. Rebiotix Inc. (Roseville, Minn; acquired by Ferring Pharmaceuticals in 2018) is currently conducting a clinical trial to test RBX2660, a biologic drug containing live human-derived microbes targeted for the treatment of recurrent CDI. The PUNCH CD3 phase III randomized controlled trial of RBX2660 is being conducted at multiple U.S. centers. RBX2660 is derived from fresh stool from multiple donors and packaged in ready-to-use enemas. It has been reported that patients have self-administered the treatment at home. RBX2660 is an FDA-designated investigational new drug (IND) for FMT intended to treat recurrent CDI (Rebiotix Inc., 2020; Hayes, 2020; Kelly, et al., 2015).

Preparations of fecal matter for oral administration for the treatment of CDI are being investigated, but to date there is insufficient evidence to support the safety and effectiveness of this approach. Proposed advantages of oral administration include: less stool is required, the avoidance of a gastrointestinal procedure (e.g., insertion of nasogastric tube, colonoscopy) and allowing wider accessibility to the treatment. However, protocols for capsule preparation (e.g., grams of input material to use), dosage (e.g., number of tablets) and dose-response relationship have not been established (Hirsch, et al., 2015; Youngster, et al., Nov 2014).

A non-frozen, lyophilized oral capsule formulation of RBX2660, known as RBX7455, is being evaluated in a phase I trial (Hayes, 2020; Rebiotix Inc., 2020). SER-262 (Seres Therapeutics, Cambridge, MA) is a synthetic oral microbiome being investigated for patients with primary CDI. The SER-262 Phase 1b study is a 24-week randomized, placebo-controlled, dose escalation study. SER-109 by Seres Therapeutics is also an oral form under investigation for the prevention of recurrent CID in adults with a history of multiple recurrent CDI. SER - 109 is an ecology of bacteria in spore form, enriched from stool donations. The product is prepared according to manufacturing and regulatory standards and is encapsulated for oral delivery. Seres is currently evaluating SER-109 in a Phase 3 clinical study (ECOSPOR III) in patients with multiple recurrent *C. difficile* infection (Seres Therapeutics, 2021; Hayes, 2020).

The donor for FMT is typically a spouse, significant other, family member or friend. As noted above the specimen can also be obtained from a stool bank. One of the risks with fecal bacteriotherapy is the transfer of contagious agents (e.g., viruses, fungi, parasites) from the donor. Therefore, it is imperative that the healthy donor be properly screened for transmissible diseases and pathogens such as hepatitis, human immunodeficiency virus (HIV), and syphilis. Stool testing will be performed for the detection of bacteria (e.g., salmonella), parasites, and CDI. Reported concerns regarding FMT are that the optimal donor-feces processing and infusion protocol have not been defined, and the amount of feces required and the effects of varying potential routes of infusion are unknown. Preferred timing of the procedure relative to preceding antimicrobial use, standardized treatment regimens, mode of administration and donor screening techniques have not been established (Drekonja, et al., 2015; Van Nood, et al., 2013; Bakken, et al., 2009; You, et al., 2008).

Studies evaluating the safety and efficacy of FMT by gastrointestinal infusion for the treatment of CDI are primarily in the form of case reports, case series and retrospective reviews with short-term follow-ups. However, outcomes have reported success rates from 55%–100%. A limited number of systematic reviews and randomized controlled trials support these success rates. Therefore, in patients who are not responding to pharmacotherapy and continue to have relapses of CDI diarrhea, FMT has become an accepted treatment option for a carefully selected subset of patients.

The safety and efficacy of oral administration of fecal microbiota have not been established. There are a limited number of studies with small patient populations and short-term follow-ups. Studies comparing FMT by gastrointestinal infusion to oral preparation are lacking.

U.S. Food and Drug Administration (FDA)

In 2013, the U.S. Food and Drug Administration issued a guidance document for immediate implementation for fecal microbiota transplantation (FMT) for the treatment of *C. difficile* infection not responsive to standard therapies. The FDA determined that human stool should be classified as a biological agent and its use regulated

for patient safety. Because FMT is being used to treat/cure a condition and is considered an unapproved new drug for which an Investigational New Drug (IND) application is required, the FDA is exercising enforcement discretion regarding the IND requirements for this therapy. This is an interim measure until such time that the FDA develops appropriate policies for clinical trials and use of FMT products under the IND. This type of guidance describes the FDA's current thinking on a topic and is only a recommendation, unless specific regulatory or statutory requirements are cited. FDA noted that the safety and efficacy of FMT has not been fully evaluated in controlled clinical trials. The use of FMT and clinical studies to evaluate its safety and effectiveness are subject to regulation by FDA. The FDA pointed out that the complex nature of FMT products presents specific scientific and regulatory challenges (FDA, 2013). Under an FDA enforcement discretion the physician may proceed with using FMT for the treatment of CDI without filing an IND, provided that they have received the appropriate informed consent from the patient and includes, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its potential risks. Use of FMT for any other indication requires submitting an IND to the FDA (FDA, 2013; Infectious Disease Society of America [ISDA], 2016).

March 1, 2016 the FDA released a draft guidance on fecal microbiota transplantation for comment purposes only. The guidance is to inform members of the medical and scientific community and other interested persons that the FDA intends to exercise enforcement discretion under limited conditions, regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat *Clostridium difficile* (*C. difficile*) infection not responding to standard therapies. The guidance states that the FDA intends to continue to exercise enforcement discretion on an interim basis provided that:

- “1. The licensed health care provider treating the patient obtains adequate consent from the patient or his or her legally authorized representative for the use of FMT product. The consent should include, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its reasonably foreseeable risks.
2. The FMT product is not obtained from a stool bank.
3. The stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product to treat his or her patient.”

The enforcement discretion policy does not extend the use of FMT to treat diseases or conditions other than *C. difficile* infection as data are limited. Also, the FDA does not intend to extend enforcement discretion for the IND requirements applicable to stool banks distributing the product (FDA, 2016). Therefore if a physician obtains material from stool banks for the treatment of CDI or wants to treat a patient for a condition other than *C. difficile*, he/she must do so under an IND (OpenBiome, 2020). When finalized, the new guidance will supersede the 2013 guidance document.

On June 18, 2019 the FDA issued a safety alert notifying physicians: “Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*). One of the individuals died.” The FMT used came from the same donor and was not tested for this organism prior to use. Because of this, the FDA has issued additional requirements for screening. “Donor screening must include questions that specifically address risk factors for colonization with MDROs, and individuals at higher risk of colonization with MDROs must be excluded from donation.” Donor testing for FMT must be screened for MDRO and samples in storage must be quarantined until tested.

The FDA issued a safety alert on March 12, 2020, updated on April 7, 2020, to inform of the potential risk of transmission of the pathogenic bacteria enteropathogenic *Escherichia coli* (EPEC) and Shigatoxin-producing *Escherichia coli* (STEC) after using FMT supplied by the stool bank OpenBiome. The FDA added additional protections that apply to any investigational use of FMT (FDA, 2020):

1. “Testing FMT donor stool by nucleic acid amplification tests (NAAT) for EPEC and STEC to exclude use of stool that tests positive for either EPEC or STEC.
 - Testing of stool from each donor before and after multiple stool donations, no more than 60 days apart; and, as applicable, quarantining FMT product lots manufactured from these donations until both pre- and post-donation EPEC and STEC tests are confirmed negative.

2. Testing of all FMT products currently in storage for which the donor has not undergone stool testing for both EPEC and STEC using NAAT as described above.
 - Until this testing is able to be completed, placing those FMT products in quarantine until they have been tested using NAAT and found negative for EPEC and STEC.
 - In the case of FMT products manufactured using pooled donations from a single donor, performing stool testing on individual stool samples (not pooled) within the testing window described above for a given lot of FMT product.”

On April 9, 2020, the FDA issued new safety information regarding additional protections for screening donors for COVID-19 and exposure to SARS-CoV-2 and testing for SARS-CoV-2. The FDA advised that the clinical use of FMT has the potential to transmit SARS-CoV-2. The recommended additional protections included:

“No clinical use of FMT product manufactured from stool donated on or after December 1, 2019, until additional screening and testing procedures and changes to the informed consent process are implemented for such stool donations as described below:

1. Stool donor screening, including an assessment of whether, since December 1, 2019, the donor was diagnosed with laboratory-confirmed SARS-CoV-2 infection, experienced symptoms of COVID-19 (e.g., fever, cough, shortness of breath) not explained by another diagnosis, or was exposed to a suspected or confirmed case of COVID-19 or SARS-CoV-2 infection.
 - In any instances of suspected or confirmed SARS-CoV-2 infection or exposure as described above, exclusion of the donor from further donations and exclusion from clinical use of any FMT product manufactured from stool donated by the affected donor beginning 4 weeks prior to the suspected or confirmed SARS-CoV-2 infection or exposure.
2. Testing of the stool donation or stool donor for SARS-CoV-2 virus or RNA.
 - Testing approaches might include testing upper respiratory specimens (e.g., nasal swabs) or other specimens (e.g., rectal swabs or stool donations).
 - If SARS-CoV-2 is detected, exclusion of the donor from further donations and exclusion from clinical use of any FMT product manufactured from stool donated by the affected donor beginning 4 weeks prior to the first positive test.
3. As part of the informed consent process, conveying to the FMT recipient that healthy, asymptomatic stool donors may potentially be infected with SARS-CoV-2, describing the testing approach and other strategies used to mitigate the risk of SARS-CoV-2 transmission, and advising the FMT recipient of the limitations of testing and risk mitigation strategies.”

Literature Review - Gastrointestinal Infusion

Studies evaluating the safety and efficacy of FMT by gastrointestinal infusion for the treatment of CDI are primarily in the form of case reports, case series and retrospective reviews with small patient populations and short-term follow-ups. However, randomized controlled trials and systematic reviews have reported success rates ranging from 55%–100% and improved quality of life of the patient. Studies have reported that up to 91% of subjects experienced resolution of diarrhea after the first infusion. Some studies reported a second infusion in cases of clinical failure/recurrence and resolution of diarrhea occurred in 60%–100% following the second treatment. In a few cases three or more transfusions were required to resolve the diarrhea (Quraishi, et al., 2017; Cammarota, et al., 2014; Kassam, et al., 2013).

Drekonja et al. (2015) conducted a systematic review to assess the safety, efficacy and comparative effectiveness of FMT for recurrent, refractory, and initial CDI. Two randomized, controlled trials (RCTs), 28 case-series, and five case reports met inclusion criteria. Primary outcomes were resolution of symptoms, recurrence, all-cause mortality and adverse events. A total of 516 subjects with recurrent CDI were included in the two RCTs and 21 case-series. One of the RCTs was a feasibility study comparing two different routes of administration and was not adequately powered to detect clinically significant differences in outcomes. The other RCT compared FMT to standard antimicrobial therapy. Overall success rates were 85% for recurrent disease and 55% for refractory disease. The success rate from the RCTs was 75% compared to 85% for similar patients in case series. Adverse events included diarrhea, cramping, belching, nausea, abdominal pain, bloating and transient fever. No serious adverse events were directly attributed to FMT. Limitations of the studies included: small patient populations; heterogeneity of patient population (i.e. recurrent CDI, refractory CDI, initial therapy); lack of

a comparator; short-term follow-up; heterogeneity of method of administration; variation in the primary outcomes with several studies combining resolution of symptoms with recurrence; and FMT was often administered after standard antimicrobial therapy to asymptomatic patients or patients with reduced symptoms.

Cammarota et al. (2014) conducted a systematic review to evaluate the safety and efficacy of FMT for the treatment of CDI with no limits on subjects' age and study design. A total of 20 cases series, 15 case reports and one randomized controlled trial met inclusion criteria. Most patients were hospitalized, had comorbidities, and developed CDI after receiving antibiotic treatment for various types of infections. Subjects had a pattern of repeat relapses after discontinuation of the antibiotic and treatment with oral metronidazole or vancomycin. Follow-ups ranged from greater than two months to less than one year. A total of 536 patients were treated and 467 (87%) experienced resolution of diarrhea. The effectiveness varied based on the mode of administration: 81% in the stomach; 86% in the duodenum/jejunum; 93% in the cecum/ascending colon; and 84% in the distal colon. No adverse events were reported.

Kassam et al. (2013) conducted a systematic review of the literature to evaluate the safety and efficacy of FMT for the treatment of CDI. Studies with ten or more subjects that used FMT, via any method of administration, for laboratory or endoscopically proven CDI with clinical resolution were included in the analysis. Eleven studies (n=273) met inclusion criteria. No randomized controlled trials were found. The overall efficacy was 93.3% in achieving clinical resolution. The authors noted that the response to FMT might differ based on the delivery mode (lower gastrointestinal vs. upper gastrointestinal delivery). Follow-up ranged from two weeks to eight years. Limitations of the studies included: heterogeneity of the delivery modalities (e.g., colonoscopy, gastrostomy tube, retention enema); heterogeneity of the FMT dose and protocol; variable timing of FMT following stool donation; variable outcomes of resolution after a second FMT (60%–100%); lack of long-term follow-up for adverse events; and the lack of randomized controlled trials.

Van Nood et al. (2013) conducted a randomized controlled trial including (n=43) volunteer subjects to determine the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile*. Patients, age 18 years or older, had a life expectancy of three months or longer and had experienced a relapse of *C. difficile* infection following at least one course of vancomycin or metronidazole. *C. difficile* infection was defined as ≥ 3 loose or watery stools per day for at least two consecutive days or ≥ 8 loose stools in 48 hours and a positive stool test for *C. difficile*. The three study groups were treated with the infusion of donor feces preceded by an abbreviated regimen of vancomycin (4–5 days) and bowel lavage (n=17), or vancomycin only (n=13) or vancomycin and bowel lavage (n=13). One dose of a suspension of donor feces through a nasoduodenal tube was administered to the study group. If *C. difficile* returned after the first donor-feces infusion, a second infusion was given. The study was stopped after an interim analysis. Sixteen infusion patients were cured after the first infusion with two additional patients cured after a second infusion. Four patients in the vancomycin only group and three in the vancomycin/lavage group were cured. Significantly more patients were cured with fecal infusion compared to the control groups ($p < 0.001$, each). Five weeks following the initiation of therapy one patient in the infusion group, eight in the vancomycin group and seven in the vancomycin/lavage group experienced recurrence of *C. difficile*. Eighteen patients in the antibiotic groups where treated with off-protocol infusions and 15 were cured, four after two infusions. Adverse events in the infusion group included diarrhea, cramping and belching within the first three hours following infusion. Limitations of the study include the small patient population; infusion group also received vancomycin and lavage; and early cessation of the study. The authors noted that because most patients had several relapses before study inclusion, typically following vancomycin therapy, the efficacy of vancomycin was “considerably lower than expected”.

Guo et al. (2012) also conducted a systematic review to evaluate the safety and effectiveness of fecal transplantation (FT) compared to standard treatment for *Clostridium difficile*-associated disease (CDAD). No controlled studies were found. Seven case series (n=124) met inclusion criteria. The authors stated that treatment effects of FT for this condition could not be determined in the absence of controlled studies comparing FT to standard therapy (e.g., vancomycin).

Technology Assessments

Based on a systematic review of the literature and meta-analysis of two randomized controlled trials the Ontario Health Technology Assessment on fecal microbiota therapy for CDI (Health Quality Ontario, 2016) concluded that fecal microbiota therapy improved outcomes that are important to patients, including quality of life and ability

to resume daily activities. Sixteen trials met inclusion criteria. The meta-analysis found that fecal transplant significantly improved diarrhea associated with recurrent *C. difficile* infection versus treatment with vancomycin. The authors noted that FMT was not associated with a significant decrease in mortality compared with antibiotic therapy and it was associated with more adverse events such as diarrhea and abdominal cramping.

Literature Review - Oral Administration

The limited number of published studies investigating the safety and efficacy of oral administration of fecal microbiota are primarily in the form of case series and retrospective reviews with small patient populations ($n \leq 20$), short-term follow-ups (90 days–6 months), heterogeneity of dosage and lack of a comparator. Studies reported up to a 68%–90% improvement in symptoms including resolution of diarrhea. Concerns still remain regarding the safety of oral preparations (e.g., vomiting, aspiration), capsule stability and long-term safety (Youngster, et al., 2016; Hirsch, et al., 2015; Youngster, et al., Nov 2014). Studies comparing oral administration to infusion of fecal matter into the lower or upper gastrointestinal track are lacking.

Du et al. (2021) performed a systematic review with meta-analysis to examine the efficacy and safety of oral fecal microbiota transplantation (FMT) capsules for the treatment of recurrent *Clostridioides difficile* infection (rCDI). Fifteen studies ($n=763$) including three randomized control trials (RCT) and 12 case series were included. The patient population was 85% female with age range 41–77. Two studies reported racial demographics. Five studies included patients with inflammatory bowel disease, four included patients who were actively immunosuppressed, and three only included patients who had symptomatic improvement with antibiotics prior to FMT administration. Inclusion criteria were studies that reported cure rates using a delivery method of oral capsules in at least ten patients or more with a minimum follow up period of eight weeks. Studies were excluded if data was presented as a subset of a larger study. The three RCT compared oral FMT capsules to colonoscopy, enema and placebo. Two retrospective and one prospective case series compared to colonoscopy with unmatched controls. Nine studies had no comparator. Two of the studies were of SER-109 and one was of RBX7455, both are investigational commercial products not yet approved by the FDA. Primary outcome was cure rate of CDI. Secondary outcomes evaluated differences between capsule preparation (frozen vs. lyophilized stool) and delivery modality (capsule vs. colonoscopy). Length of follow up varied from 8–26 weeks. Meta-analysis of proportions showed efficacy of oral FMT capsules to be 82.1%. Secondary outcome analyses did not find significant differences in efficacy of capsule preparation ($p=0.37$). In the four studies comparing delivery of oral FMT to colonoscopy, no difference in efficacy was found. Fourteen serious adverse events leading to death or hospitalization were noted, twelve were due to underlying comorbidities and two were hospitalizations for rCDI. Mild adverse events included nausea, diarrhea, and abdominal pain. Author noted limitations included inclusion of retrospective observational studies, significant variability in baseline patient characteristics/selection criteria, donor selection, capsule preparation and FMT protocols. Additional limitations include small patient populations, minimal reporting on racial demographics, and short term follow ups. Further studies in large, diverse populations with long-term follow-up are needed to evaluate efficacy, optimize protocols and outcomes.

Ramai et al. (2020) conducted a systematic review and meta-analysis to assess the safety and efficacy of four different methods of fecal microbiota transplantation (FMT) administration (colonoscopy, capsule, enema, and nasogastric tube [NGT]) in the treatment of recurrent *Clostridioides difficile* infections (CDI). Twenty six studies ($n=1309$ patients) were included: 13 retrospective reviews, eight randomized controlled trials, and five prospective studies. FMT was administered via colonoscopy in 16 studies ($n=483$), NGT in five studies ($n=149$), enema in four studies ($n=360$) and capsules in four studies ($n=301$). Studies were included if the sample size was ≥ 10 and FMT was used to treat recurrent CDI using colonoscopy, capsules, enema, or NGT. Excluded were studies that did not have extractable data, did not meet the study endpoints or were not in English. Case reports, review articles, letters to the editor, abstracts, commentaries, and editorials were not included. The primary outcome was overall cure rate defined as resolution of symptoms after FMT. The secondary outcomes included procedure related adverse effects and a subgroup analyses comparing donor relationship, sample preparation and study design. The random effects of pooled FMT cure rates were as follows: colonoscopy 94.8%, capsule 92.1%, enema 87.2%, and NGT 78.1%. The subgroup analyses had comparable cure rates: sample preparation methods (fresh 94.9% and frozen 94.5%) and donor relationship (mixed 94.5% and unrelated donor 95.7%). Five major adverse events were reported: new-onset ulcerative colitis (capsule), peritonitis (NGT), upper gastrointestinal hemorrhage (NGT), micro perforation from ischemic bowel injury (colonoscopy), and bloody stool (enema). Minor adverse events reported include diarrhea, abdominal pain or discomfort, flatulence, constipation, nausea, fatigue, malaise, anorexia, bloating and vomiting. Limitations were inclusion of retrospective study

designs, small patient populations, short term follow ups and heterogeneity of the studies. Additional long term randomized control trials with large patient populations are needed to validate the outcomes of the study and establish the efficacy of the capsule treatment method.

Iqbal et al. (2018) conducted a systematic review to evaluate the safety and efficacy of freeze-dried encapsulated FMT for the treatment of recurrent CDI. The review included five case series and one randomized controlled trial (Kao, et al., 2017). The total number of patients was 341 and follow ups were primarily eight weeks (range 31–408 days). Inclusion criteria were original studies in which patients of any age were treated with encapsulated FMT and reported on safety and efficacy of outcomes. Excluded were any studies that evaluated any other route of administration, treatments other than FMT or using FMT to treat anything other than CDI. The intervention for each study was the treatment for recurrent CDI with freeze-dried encapsulated FMT up to three times. The comparator in the RCT was colonoscopy. The primary outcome was the clinical resolution of diarrhea without relapse within the follow-up period. First treatment success rate was 83.5% (285/341), second treatment success rate was 66.7% (28/42) and third treatment success rate was 60% (3/5). The overall response to treatment was 92.6% (316/341). Minor adverse events reported were nausea, abdominal discomfort, bloating, and irregular bowel movements. Other adverse events included transient high grade fever (n=1), new diagnosis of ulcerative colitis (n=2) and hospitalization for recurrent CDI (n=1). No deaths or serious infectious disease complications were reported. The overall quality of evidence supporting oral FMT was reported as low-to moderate. Randomized control trials with larger patient populations are needed to establish safety and efficacy of oral FMT.

Jiang et al. (2018) conducted a single center, randomized control trial (n=65) to compare the safety (adverse events) and efficacy of FMT oral administration to administration by enema. Primary outcome was safety during the three months post FMT; secondary outcome was prevention of CDI recurrence during 60 days after FMT. Criteria for participation in the study included: age ≥ 18 years; non-pregnant; ≥ 3 total episodes of CDI; and receipt of at least one course of anti-CDI antibiotics for the most recent bout. Exclusion criteria were: history of total colectomy; history of incontinence; planned receipt of concomitant antibiotics or probiotic; presence of a definable non-CDI diarrhea pathogen; known white blood count $> 15 \times 10^9/L$ or absolute neutrophil count $< 0.5 \times 10^9/L$; presence of toxic megacolon; history of intestinal perforation; or presence of unstable medical conditions. Initially the first eight patients received 100 g orally which produced a cure rate of 63%. The next 23 patients received 100 g orally for two consecutive days which produced a cure rate of 91%. Dosage for enema (n=34) was 100 g administered once with a cure rate of 88%. There was no statistically significant difference in the cure rate between the two groups (p=0.76). Although not significant, a higher number of patients in the oral group experienced nausea or fecal urgency. There was one hospitalization for recurrence of CDI two days after oral FMT. In the enema group, there was more abdominal cramping. There was one hospitalization for IBD flare up seven days after FMT, two for CDI recurrences at day seven and day 14 and one report of diverticulitis at month five. The author-noted limitations of the study were the inability to compare efficacy of multiple oral doses due to the small sample size and the inability to perform spore counts (assumed both procedures preserved spore-forming Clostridia). Additional limitations of the study are the short term follow up and self-reported adverse events. Additional long term randomized control trials with large patient populations are needed to validate the outcomes of the study.

Kao et al. (2017) conducted a randomized controlled trial to compare clinical efficacy of fecal transplant administered by capsule (n=57) vs. colonoscopy (n=52) for the treatment of Clostridium difficile infection (CDI). Subjects, aged 18 to 90 years, had at least three documented episodes of CDI. Each episode was defined as recurrence of diarrhea (>3 unformed bowel movements every 24 hours) within eight weeks of completing a prior course of treatment. Exclusion criteria included: complicated CDI; chronic diarrheal illness; active inflammatory bowel disease (IBD); cancer undergoing therapy; subtotal colectomy, colostomy, or ileostomy; dysphagia; life expectancy of < 3 months; pregnancy; breastfeeding; and conditions requiring antibiotic therapy. Patients randomized to the colonoscopy group received 360 ml of fecal slurry in the cecum. The capsule group swallowed 40 capsules. Capsules were manufactured using approximately 200 cc fecal slurry mixed with 40 cc of 100% glycerol and centrifuged at room temperature for 20 minutes. Then the supernatant was centrifuged and discarded and the final sediment (approximately 12 cc, estimated to contain 10^{13} microbes) was mixed to incorporate residual liquid to allow pipetting into gelatin capsules. Forty capsules were manufactured from one donation. All patients had clinic visits at weeks one, four and 12 after FMT, with a telephone follow-up at week two. The capsules were made by the researchers. The primary outcome was the proportion of patients without

recurrent CDI (RCDI) 12 weeks after FMT. Secondary outcomes included: changes in quality of life and adverse events. The primary outcome was not assessed for 11 patients who were lost to follow-up. At 12 weeks, absence of RCDI was achieved in 96.2% of patients in the capsule group (51/53) and the colonoscopy group (50/52) after a single treatment. There was no significant difference in the success rate of the capsule group (89.5%; 51/57) vs. the colonoscopy group (96.6%; 57/59) ($p=0.048$). Two patients in each group developed RCDI and were successfully treated with a second FMT by the same modality. Quality of life was not assessed in 14 patients. Four weeks following FMT there was significant improvement in the SF-36 questionnaire in both groups with no significant difference between groups. A significantly greater proportion of patients who received the capsules rated their experience as “not at all unpleasant” compared to colonoscopy patients ($p=0.01$). No significant adverse events related to FMT were reported in either group and minor adverse events occurred in 5.4% of the capsule group and 12.5% in the colonoscopy group. Author-noted limitations of the study included: lack of a placebo group which did not allow for measurement of the magnitude of FMT in each group; the generalizability of the findings was limited by the enrollment criteria as patients with severe and complicated CDI were excluded; and lack of blinding. Additional limitations include the small patient population; short-term follow-up and number of patients lost to follow-up.

Youngster et al. (2016) reported on their clinical experience ($n=180$) of patients who received FMT via oral, frozen capsules prepared from unrelated donors. Patients, age ≥ 7 years, with three or more mild-to-moderate episodes of CDI or two episodes requiring hospitalization were offered the oral preparation. Subjects discontinued any anti-CDI treatment for 24–48 hours prior to FMT and were given 15 capsules on each of two consecutive days. The 30 capsules contained sieved, concentrated material derived from a mean of 48 grams of fecal matter. Resolution of diarrhea was defined as three or fewer bowel movements per 24 hours (“cured”). Follow-ups were conducted via telephone using a structured questionnaire recording stool frequency, general and gastrointestinal wellbeing, and mild, moderate, or severe adverse events. At the eight-week follow-up, 147 patients (82%) were “cured” after the first administration of the capsules. Twenty-six patients relapsed within the eight weeks, were retreated and 17 responded. Six patients declined retreatment. Three patients were cured after a third administration. One patient received three treatments, relapsed, and was advised to continue suppressive vancomycin. Related serious adverse events included: one case of fever (>102.4), two cases of ulcerative colitis and six hospitalizations for relapsed CDI/diarrhea. Mild and moderate adverse events included fever ($n=3$), diarrhea ($n=112$), vomiting ($n=5$), nausea/bloating ($n=45$), abdominal pain ($n=40$), fatigue, malaise and headache ($n=54$) and other complaints ($n=12$). Between 2–6 months following treatment five patients relapsed. Limitations of the study include the lack of a comparator, small patient population, short-term follow-up and follow-up via phone calls. Studies comparing the outcome of FMT via oral capsules to infusion FMT are needed to establish the safety and effectiveness of oral FMT.

Literature review - Immunocompromised

Fischer et al. (2016) conducted a retrospective review ($n=462$) to identify risk factors associated with FMT failure and to develop and validate a prediction model for FMT failure. Immunocompromised state was defined as any of the following: HIV infection (any CD4 count), AIDS-defining diagnosis or CD4 <200 cells per cubic millimeter (mm^3), inherited or primary immune disorders, ongoing treatment with anti-neoplastic agents or immunosuppressant medications (including but not limited to monoclonal antibodies to B and T cells, anti-tumor necrosis factor agents, systemic steroids ≥ 20 mg prednisone/day), antimetabolites (azathioprine, 6-mercaptopurine, methotrexate), calcineurin inhibitors (tacrolimus, cyclosporine), and mycophenolate mofetil). A total of 63 patients had inflammatory bowel disease and 77 were immunocompromised. The majority of FMT failures were in the early stage (within one month of FMT). Independent predictors of early FMT failure included: severity of CDI, the need for inpatient FMT, and a number of CDI-associated hospital admission. With each additional hospitalization the odds of failure increased by 43%. Late failure (between 1–3 months) occurred in 13 patients (2.8%) who had IBD on immunosuppressive therapy ($n=6$) or recurrent CDI ($n=12$). The authors noted that the presence of immunosuppression and IBD were not found to be predictors of early FMT failure. Limitations of the study include the retrospective review and possible selection bias. The effect of post-FMT antibiotic exposure on the failure rate could not be examined. Because FMT was administered predominantly by lower endoscopy it was not possible to determine whether the route of delivery had an effect on failure rates. Another limitation is that the weight of donor stool was not examined.

Kelly et al. (2014) conducted a 16-center, retrospective review ($n=80$) of immunocompromised (IC) patients who received FMT for recurrent, refractory or severe CDI to identify the rate of CDI cure after FMT and adverse

events. Cure was defined as the absence of diarrhea, or marked reduction in stooling frequency without the need for further anti-CDI therapy. A 32-item data collection form was developed, which elicited demographic data, CDI characteristics, and pre- and post-FMT data for each patient. Reasons for IC included: HIV/AIDS (n=3), solid organ transplant (n=19), oncologic condition (n=7), immunosuppressive therapy for IBD (n=36), and other IC due to medical condition/medication (n=15). A total of 75 adults and five pediatric patients were treated with FMT for recurrent (54%), refractory (11%), and severe and/or overlap of recurrent/refractory & severe CDI (27%). Twelve of the 16 sites exclusively used an endoscopic lower GI route of administration. Outpatient FMT was performed 79% of the time. The mean follow-up period between FMT and data collection was 11 months (range 3-46 months). At least 12 weeks of post-FMT follow-up data were required in order for the patient's data to be included in the analysis. The CDI cure rate after a single FMT was 78%. A total of 62 patients suffered no recurrence at 12 weeks post-FMT. Eleven patients underwent repeat FMT and eight of those cases were resolved making an overall cure rate of 89%. Twelve patients (15%) had an adverse event within 12 weeks of FMT, of which ten involved hospitalizations. Four patients (11% IBD patients) experienced disease flare post-FMT. Three ulcerative colitis patients underwent colectomy related to a course of ulcerative colitis >100 days after FMT. One patient had a superficial mucosal tear caused by the FMT colonoscopy and three patients reported mild, self-limited abdominal discomfort post-FMT. It was noted that 14% of patients with IBD experienced complications post FMT in the form of a disease exacerbation, one of which required a colectomy within one month post-FMT. There were no infectious complications attributed to FMT. Limitations of the study include: the retrospective review process; data limited to what was available in the medical record, small patient population, short-term follow-ups, and potential selection bias.

Other Indications

FMT has been proposed for the treatment of other diseases associated with alterations in the gut microbiota. Some of these conditions include: cirrhosis of the liver, chronic constipation, inflammatory bowel disease, irritable bowel syndrome, metabolic syndrome, acute graft-versus-host disease (aGVHD), ulcerative colitis, obesity, type 2 diabetes mellitus, fatty liver disease, multidrug-resistant organisms, hepatic encephalopathy, human immunodeficiency virus, pediatric allergies, pancreatitis, pouchitis, food allergies, obesity, metabolic syndrome, rheumatic diseases, and psychiatric illnesses (e.g., depression, anxiety, substance abuse, autism spectrum disorder, eating disorders) (Cohen and Maharshak, 2017; Tian, et al., 2017; Carlucci, et al., 2016; Gupta, et al., 2016; Kakihana, et al., 2016; Kelly, et al., 2015; Canadian Association of Gastroenterology [CAG], 2014). Studies investigating FMT for the treatment of these conditions are few in number and primarily in the form of case reports or small case series. For some conditions, conflicting results have been reported or there was no significant improvement in the treated condition. There is insufficient evidence to support the effectiveness of FMT for any other indication nor is FMT supported by the FDA for these other indications.

Inflammatory Bowel Disease: Inflammatory bowel disease (IBD) represents a heterogeneous group of chronic immune-mediated inflammatory diseases affecting the gastrointestinal tract. There are two primary phenotypes of IBD, ulcerative colitis (UC) and Crohn's disease (CD) (Lane, 2017). FMT has been proposed for the treatment of IBD patients with and without *C. diff*.

Current systematic reviews and meta-analysis continue to support that FMT does not show benefit as a treatment option for IBD. Limitations of the studies included small patient populations and short term follow ups. Studies concluded that FMT was not effective for IBD (Ianiro, 2019; Myneedu, 2019; Xu, 2019). Ianiro et al. (2019) reported that oral placebo capsules performed superior to oral donor stool capsules in two trials evaluating efficacy of FMT for IBD.

Cheng et al. (2021) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of FMT in patients with Crohn's disease (CD). Four case reports, seven cohort studies and one randomized control trial met inclusion criteria. Patient populations ranged from 1-30. Patient demographics were not reported. Inclusion criteria were patients with Crohn's disease with no limits on age or sex, FMT used as a treatment, efficacy and safety were reported and all FMT modalities (i.e. nasogastric tube, colonoscopy, enteric tube, or enemas) were permitted. Excluded were non-human studies, those on CD with clostridium difficile infection (CDI) or other pathogens, data for CD patients not reported separately, studies reporting duplicate data, and those not providing sufficient information. Primary outcome was clinical remission with clinical response being the secondary outcome. Length of follow up ranged from four weeks to 15 months. Eleven studies (n=106) were included in the pooled analysis for a clinical remission rate of 62%. Seven studies reported that the clinical

response and pooled rate was 79%. Remission was achieved in 34/52 patients that received fresh donor stool FMT and in 21/53 that received frozen stool FMT. Adverse events reported were minor and self-resolving with no major FMT-related adverse events being reported. The most common minor adverse events included abdominal pain, bloating, diarrhea, constipation, vomiting, nausea, and fever. Author noted limitations included the small patient populations, lack of control arm in most studies, and short term follow up. Randomized control trials with large patient populations and long term follow up are needed to confirm the findings.

Holvoet et al. (2021) conducted a randomized placebo-controlled trial (RCT) to evaluate the effect of FMT on abdominal bloating in patients with irritable bowel syndrome (IBS). Patients with refractory IBS were randomly assigned 2:1 to single-dose nasojejunal administration of donor stools (n=43) or autologous stools (n=19) (placebo). Patients who received placebo treatment, who did not respond to active treatment or lost response over time were offered an open-label, second microbiota transplant at one year and followed for 12 weeks. Patient characteristics include a median age of 40 years with 31% males in the treatment group and age of 36 years with 59% males in the placebo group. Ethnicity was not reported. Inclusion criteria were patients with refractory IBS with diarrhea predominant or mixed type and 18-75 years of age. IBS was defined according to the ROME III criteria with refractory IBS defined as failure of >3 conventional therapies. The severity of abdominal bloating was assessed by a daily symptom diary (mean abdominal bloating subscore of ≥ 3). Exclusion criteria were a previous diagnosis of celiac disease, predominant constipation, lactose intolerance (unless on a stable diet for longer than three months), prior gastrointestinal surgery, antibiotic use within three months of inclusion, or pregnancy. Also excluded were those with a serious comorbidity and/or severe psychiatric history. Primary endpoints were improvement of IBS symptoms and bloating at 12 weeks (response). This was assessed by using a daily symptom diary to determine general abdominal discomfort, abdominal bloating, abdominal pain, and flatulence on a scale of 1–6. Secondary endpoints were changes in IBS symptom scores and quality of life. Patients completed the IBS-specific quality of life questionnaire. Number of daily bowel movements, consistency of the stools, and abdominal circumference were also recorded. Follow up occurred through one year. At 12 weeks, improvement in both primary endpoints were reported in 56% of the treatment group versus 26% in the placebo group ($p=0.03$). Treatment group reported improvements in level of discomfort (mean reduction 19%), stool frequency (mean reduction 13%), urgency (mean reduction 38%), abdominal pain (mean reduction 26%), flatulence (mean reduction 10%), and quality of life (mean increase 16%). Women in the treatment group had a response rate of 69% versus men at 29% ($p=0.01$). The fecal samples of those with a response had a higher diversity of microbiomes at baseline than the non-responders, but no specific microbiome was identified as being associated with a response. At one year, 21% of the treatment group reported lasting effects versus 5% of the placebo group. At the one year follow-up 67% of patients in the crossover group who responded initially and were given a second FMT dose, experienced a reduction in symptoms. In the original placebo group, re-transplantation with donor stools (n=12) had a 58% response rate with overall improvement of abdominal bloating in 33% of patients, reduction in the IBS symptom score and reduction in number of daily bowel movements. Adverse events were not reported. Author noted study limitations included the fact that patients were selected using the ROME III criteria instead of the fourth edition. Additional limitations include the small sample size and relatively short follow up time. Additional long term randomized control trials with large patient populations are needed to validate the outcomes of the study.

Caldeira et al. (2020) conducted a systematic review and meta-analysis to evaluate the efficacy and safety of fecal microbiota transplantation for the treatment inflammatory bowel disease. Thirty-six studies met the inclusion criteria which was any interventional or observational study that evaluated the efficacy/effectiveness or safety of FMT in patients of any age or gender diagnosed with IBD (ulcerative colitis, Crohn's disease and pouchitis) with or without a treatment comparator and reporting on response, remission or adverse events. Nine randomized control trials (RCT) and 27 quasi-experimental studies (non-randomized interventional studies without a control group) were included. Patient size ranged from 5–174. Studies were excluded if the indication for FMT was not IBD and if they did not address clinical remission, clinical response or adverse events. Type of stool used in the studies varied and was reported as using either capsules, fresh, frozen, or both fresh and frozen. Route of administration was either upper, lower, or oral. Primary outcome measured was clinical remission with secondary outcomes of clinical response and any adverse event. Length of follow up was not reported. Clinical remission was reported in 24 of the quasi-experimental studies and the analysis resulted in 32.3% achieving clinical remission. Analysis of the nine RCT showed a remission rate of 46%. The overall remission rate for both the quasi-experimental studies and the RCT was 37.0%. Subgroup analysis of stool type revealed clinical remission rates of 29.1% for fresh fecal material (21 studies), 44.2% for frozen fecal material (six studies), 57.2% when

both fresh and frozen were used (three studies), and 66.5% for capsules (two studies). In assessment by donor type, seven studies did not report donor type and had a remission rate of 36.4%. Remission rate of relative or acquaintance donor (nine studies) was 24.8% while universal donor (16 studies) achieved remission in 45.1% of patients. Patients with ulcerative colitis presented a remission rate of 35.0% (25 studies), while patients with Crohn's disease showed a remission rate of 47.6% (ten studies). For studies reporting a clinical response, analysis revealed 53.5% of the quasi-experimental studies (26 studies) and 54.4% of the RCT (seven studies) had a clinical response. A clinical response was reported in 52.1% (21 studies) of those patients receiving fresh fecal material, 52.8% (seven studies) of those receiving frozen fecal material, 56.6% (two studies) of those receiving both fresh and frozen and 94.9% (two studies) of those who received capsules. When the fecal material was provide by relatives or acquaintances (eight studies), the pooled clinical response was 37.1% and those who received from universal donors (16 studies) exhibited a response of 59.7%. In the analysis of any adverse event, in sixteen quasi-experimental studies the frequency was 26.9% and 48.2% in four RCTs. In the frequency of adverse events according to fecal material type, analysis revealed 30.2% with fresh fecal material (13 studies), 43.2% with frozen fecal material (three studies), 22.6% with the use of capsules (two studies), and 14.4% when both frozen and fresh were used (one study). The prevalence of adverse events from fecal material from relatives or acquaintances (four studies) was 48.0% while adverse events from universal donors (nine studies) was 26.5%. Five studies did not specify the donor type, resulting in a prevalence of 22.9% for any adverse event. For patients with ulcerative colitis, adverse events occurred in 36.9% (11 studies) while only 5.8% (three studies) of those with Crohn's exhibited an adverse event. Six studies did not specify the IBD subtype with adverse events occurring in 44.3%. Author noted study limitations included heterogeneity of the type of stool used, stool processing methods, route of administration, small patient populations in some studies, and lack of follow up reported. RCTs with large populations and long term follow up are needed to establish the efficacy of this treatment method.

Dang et al. (2019) conducted a systematic review and meta-analysis comparing the safety and effectiveness of basic treatment combined with either fecal microbiota transplantation (FMT) or mixed probiotics therapy in mild to moderate ulcerative colitis (UC). The number of subjects (n=596) in the experimental arms ranged from 14-77 and 14-73 in the control arms. Randomized, placebo controlled studies (n=7) were included if the study participants had active UC with mild to moderate disease, compared the effect of FMT and probiotic mixture VSL#3 and utilized the same or similar clinical remission or response criteria. Excluded were studies on children, evaluation criteria different from other studies and those without a placebo control. Four studies compared FMT to placebo; three studies compared VSL#3 to placebo. Primary outcomes were measured using three different screening tools to determine the degree of severity of activity of UC:

- The Mayo Clinical Scoring (MCS) is a composite activity index for the sum of four items: rectal bleeding, stool frequency, endoscopy results, and a comprehensive assessment by the physician with values between 0-12 points, higher scores correlate with increased severity of disease.
- Ulcerative Colitis Disease Activity Index (UCDAI) assesses four variables (stool frequency, severity of bleeding, colonic mucosal appearance, and the physician's overall assessment of disease activity) with each variable scored from 0-3 with the total index score range 0-12.
- Simple Clinical Colitis Activity Index (SCCAI) scores five clinical criteria: bowel frequency, urgency of defecation, blood in stool, general well-being, and extracolonic features.

Baseline scores were compared to remission criteria. Remission criteria ranged from Mayo subscores ≤ 1 , MCS ≤ 2 with an endoscopic Mayo score of 0 SCCAI ≤ 2 , UCDAI ≤ 2 . Trial periods ranged from 6-12 weeks. The treatment effects of FMT and VSL#3 were not statistically significant in terms of clinical remission. However, in direct comparison for clinical remission, FMT was superior to placebo ($p < 0.001$) with zero heterogeneity between studies. VSL#3 was superior to placebo for clinical remission with low heterogeneity between studies. For clinical response, both FMT ($p < 0.001$) and VSL#3 ($p < 0.001$) were superior to placebo in direct comparison but therapeutic effects were not statistically significant for either. Adverse events of the probiotic group were minor discomfort such as bloating and odor in the mouth. The main adverse event of the FMT group was degenerative enteritis. Study limitations were small sample sizes, short term trials and lack of head to head studies comparing FMT to probiotics. The overall quality of the studies was reported as low-to moderate. Randomized control trials with larger patient populations are needed to establish safety and efficacy of FMT for treatment of UC.

Imdad et al. (2018) conducted a Cochrane systematic review and meta-analysis to assess the efficacy and safety of FMT for the treatment of irritable bowel disease (IBD). Inclusion criteria were randomized control trials (RCT) or non-RCT with a control arm. Patient population was pediatric or adult with either ulcerative colitis (UC)

or Crohn's disease (CD). Four randomized control trials (n=277) on the treatment of UC in adults met inclusion criteria. Results were reported at eight weeks. Primary outcomes of the studies included clinical remission, clinical relapse and serious adverse events. Secondary outcomes were clinical response, endoscopic remission and response, quality of life scores, laboratory measures of inflammation, withdrawals, and microbiome outcomes. FMT was administered rectally or via nasoduodenal route. Rates of resolution of symptoms were 37% (52/140) at eight weeks compared to control group remission of 18% (24/137). A total of 49% (68/140) of FMT patients vs. 28% (38/137) of control patients had a clinical response. Endoscopic remission (n=3 studies) was achieved in 30% (35/117) of FMT patients vs. 10% (11/112) of control patients. Common adverse events (n=4 studies) were abdominal pain, nausea, flatulence, bloating, upper respiratory tract infection, headaches, dizziness, and fever. Serious adverse event rates (n=2 studies) were similar for both groups. These included worsening of UC necessitating intravenous steroids or surgery; infection such as *Clostridium difficile* and cytomegalovirus, small bowel perforation and pneumonia. Due to small patient population and low quality of evidence no conclusions could be drawn about the safety and efficacy of FMT for patients with UC. There were no qualified studies that addressed CD or pediatric population with UC or CD. RCTs with large populations and long term follow up are needed to establish the efficacy of this treatment method.

Chen et al (2018) published their results of a systematic review and meta-analysis of the treatment of CDI in patients with irritable bowel disease (IBD) using FMT. A total of nine cohort studies (prospective and retrospective) (n=346) were included. Inclusion criteria were studies that enrolled CDI patients with IBD (confirmed clinical symptoms and laboratory testing) and received FMT administered by any delivery method. Excluded were case reports, animal studies, general reviews, conference abstracts, letters, and cohort studies with less than ten participants. Follow ups were primarily 2–3 months but ranged from 7 days to >1 year. Some retrospective studies compared IBD patients being treated for CDI to those that did not have IBD. Primary outcomes were CDI cure (initial and overall), recurrence rate and FMT safety (based on reported adverse events). Initial CDI cure rate in patients with IBD was 81%. Overall cure rate (four studies; n=160) was 89%.for those who received more than one FMT treatment. Recurrent rate was 19% (six studies; n=213). Six studies reported no significant difference in cure rate in IBD patients versus non-IBD patients ($p=0.06$). Adverse events (five studies) were gastrointestinal symptoms such as irregular bowel movements, excessive flatulence and IBD flare. Seven patients required a colectomy after FMT due to severity of IBD. Limitations were retrospective study design, small patient populations, short term follow ups and heterogeneity of the studies. The author noted that these limitations restricted the studies power from being conclusive. Additional long term randomized control trials with large patient populations are needed to validate the outcomes of the study.

Fang et al. (2018) conducted a systematic review and meta-analysis to investigate the clinical efficacy and safety of FMT for inflammatory bowel disease (IBD) (i.e., ulcerative colitis [UC] or Crohn's disease [CD]) in pediatric or adult patients. A total of 23 cohort studies and four randomized control trials (RCTs) met the inclusion criteria. Included studies reported on clinical efficacy and safety of FMT for IBD in either adult or pediatric patients. Studies with no clear definition of remission or clinical endpoints or that only included patients who had co-infection with *Clostridium difficile* or other pathogens were excluded. Systematic reviews, meta-analysis, case series and case reports were also excluded. The primary outcome was clinical remission with the secondary outcome being clinical response. FMT was delivered via nasojejunal tube, gastroscopy, enema or colonoscopy. Length of follow up ranged from 1–72 months. Out of 459 patients receiving FMT, 28.8% (132/459) obtained clinical remission. A clinical response was reported in 53% (241/459) of patients. Patient's treated with FMT achieved a statistically significant higher clinical remission rate than placebo for UC ($p=0.0003$). Adverse events included gastrointestinal complaints such as diarrhea, abdominal pain, bloating and fever. No serious adverse events were reported. Limitations of this review include the inclusion of retrospective studies, small patient populations, and short term follow ups of some of the studies. Before conclusions can be drawn about the efficacy of this treatment method, RCTs with large populations and long-term follow-up are needed to validate the efficacy of FMT for IBD.

Scaldaferri et al. (2016) conducted a systematic review and meta-analysis of randomized controlled trials investigating FMT for the treatment of ulcerative colitis (UC). Two studies (n=112) met inclusion criteria. The pooled estimate indicated that FMT therapy could be effective in inducing remission among UC patients; however, the results were not significant.

Sun et al. (2016) conducted a systematic review and meta-analysis to evaluate the safety and efficacy of FMT for the treatment of ulcerative colitis (UC). Eleven studies (n=133) met inclusion criteria. Eight non-control cohort studies and the treatment arms of the two randomized controlled trials (RCTs) were included in the meta-analysis. The pooled proportion of patients who achieved complete remission (CR) was 30.4%. A total of 85 patients in six studies received more than one infusion. The rate of CR in repeat therapy was 28.9%. A subgroup analysis suggested that there was no difference in CR between upper gastrointestinal delivery versus lower gastrointestinal delivery and no difference in CR between single infusion versus multiple infusions (>1) of FMT. All studies reported mild adverse events (e.g., self-limiting fever, abdominal discomfort, abdominal pain, bloating, diarrhea, vomiting). The authors stated that it was worth noting that FMT is not nearly as effective in the treatment of UC as it is in the treatment of *C. difficile* infection. Limitations of the studies included the low quality of the studies, possible publication bias and heterogeneity of treatment regimens (e.g., FMT dosage, pre-FMT therapy). Additional well-designed RCTs are needed to support FMT as a treatment modality for UC.

Colman and Rubin (2015) conducted a systematic review and meta-analysis to evaluate FMT for the treatment of inflammatory bowel disease (IBD). Eighteen studies (n=122) including nine prospective case series, eight retrospective reviews, and one randomized controlled trial met inclusion criteria. Diagnosis included: ulcerative colitis, Crohn's disease and IBD. Although the overall cure rate was 45%, outcomes varied based on diagnosis and type of study (e.g. cohort study). Remission rate was 22% for ulcerative colitis (n=79), 60.5% for Crohn's disease (n=39) and 36.2% for pooled cohort patients (n=70). Follow up ranged from one week to 13 years (median 1.5 months). Limitations of the studies included the small, heterogeneous patient populations, short-term follow-up, lack of a comparator, heterogeneity of route of administration and treatment regimen. No serious adverse events were reported.

Moayyedi et al. (2015) conducted a randomized controlled trial (n=75) to investigate the safety and efficacy of fecal microbiota transplant (FMT) for the treatment of ulcerative colitis (UC). Included patients were age 18 years and older with active ulcerative colitis based on endoscopy score. Patients were allowed to continue concomitant treatments for UC (e.g., mesalamine, glucocorticoids, immunosuppressive therapy or tumor necrosis factor antagonists) if these had been used at a stable dose for at least 12 weeks (4 weeks for glucocorticoids). Patients previously exposed to topical mesalamine or steroids had a 30-day washout period prior to enrollment. Subjects were randomized to 50 milliliters (mL) of FMT (n=36) or 50 mL of water (placebo) (n=34) given via retention enema once a week for six weeks. The primary outcome was remission at week seven defined as a full Mayo score <3 and complete healing of the mucosa on flexible sigmoidoscopy. Secondary outcomes were improvement in symptoms and Inflammatory Bowel Disease Questionnaire, and EuroQol (EQ-5D) scores. Changes in medication, serious adverse events and hospitalization were recorded at 12 months follow-up. The study was stopped early because it was not anticipated that the extent of positive effect would be seen at completion of the study. However, those patients in the study were allowed to continue. Nine FMT patients and two placebo patients were in remission at week seven. Secondary endpoints were not met. There was no statistically significant difference in the effect of FMT over placebo on disease-specific or general quality of life. There was no significant difference in adverse events. Additional limitations of the study include the small patient population and colonoscopy was not performed at study exit. The authors concluded that the effect of FMT in UC remains uncertain.

Obesity: Leong et al. (2020) conducted a randomized control trial to evaluate if fecal microbiome transfer (FMT) would lead to weight loss in adolescents with obesity. Eighty-seven adolescents aged 14–18 years (post pubertal) with a body mass index (BMI) over 30 kg/m² and no pre-diagnosed chronic diseases that could affect weight or metabolism met the inclusion criteria. Patients were randomized 1:1 and stratified by sex. The intervention group (n=42) received a single course of oral encapsulated fecal microbiome from four healthy lean donors of the same sex. The comparator group (n=45) received a saline placebo capsule. Primary outcome was BMI score at six weeks post intervention. Secondary outcomes included body composition, cardiometabolic parameters, well-being, and gut microbiome composition. Follow up was conducted up to 26 weeks. There was no effect of FMT on BMI at six weeks. A reduction in android-to-gynoid-fat ratio (visceral adiposity) was observed at six, 12 and 26 weeks in the FMT group but not the placebo group. There were no noted effects in insulin sensitivity, liver function, lipid profile, inflammatory markers, blood pressure, total body fat percentage, gut health, and health-related quality of life at six, 12 and 26 weeks for either group. Post-hoc exploratory analysis revealed a subgroup of adolescents who had undiagnosed metabolic syndrome at baseline. Of that subgroup, 78% that received FMT treatment had resolution of metabolic syndrome (n=14/18, p=0.0074) at 26 weeks post

intervention. There were no serious adverse events noted. Minor adverse events reported included loose stools (10%), change in frequency of bowel movements (8.7%), nausea/vomiting (4.2%), excessive and/or malodorous burps (3.8%), fever (1.7%), and bloody stools (0.4%). Author noted limitations included no regulation of participants' diet and physical activity. Other study limitations included small patient population and short term follow up. The authors concluded that FMT alone did not reduce BMI.

Multiple Conditions: Rossen et al. (2015) conducted a systematic review to assess the safety and efficacy of fecal microbiota transplant (FMT) for the treatment of various conditions. Forty-five studies met inclusion criteria including: 34 studies for the treatment of *Clostridium difficile* infection (CDI), seven studies on inflammatory bowel disease and one study each on metabolic syndrome, constipation, pouchitis and irritable bowel syndrome. In CDI, 90% resolution of diarrhea was seen in 33 case series (n=867) and 94% resolution of diarrhea was seen after repeated FMT in a randomized controlled trial (n=16). In ulcerative colitis remission rates of 0%–68% were reported (n=106), 70% improvement was seen in IBS (n=13), three patients had reversal of symptoms in constipation, no patients achieved remission in pouchitis (n=8) and no benefit was reported in the treatment of Crohn's disease (n=6). One randomized controlled trial showed significant improvement of insulin sensitivity in ten patients with metabolic syndrome. Overall, reported adverse events were self-limiting and typically occurred within hours after infusion. Serious adverse events were rare. Limitations of the studies included: poor study quality, small patient populations, high risk of bias, variation in length of follow-up and heterogeneity of outcome measures.

Professional Societies/Organizations

American College for Gastroenterology (ACG): Guidelines for the management of *C. difficile* infection (CDI) by ACG (2021) stated that the treatment of choice for an initial episode is a ten day course of either oral vancomycin or oral fidaxomicin. Oral metronidazole may be considered for treatment in low-risk patients. ACG recommends that FMT be considered for patients with severe and fulminant CDI unresponsive to antibiotic therapy. For recurrent CDI, FMT is recommended for patients experiencing a second or further recurrence with delivery through colonoscopy or capsules. Delivery by enema should be used only if other methods are unavailable. Repeat FMT is suggested if the patient experiences a recurrence of CDI within eight weeks of an initial FMT. For patients with inflammatory bowel disease (IBD) and recurrent CDI, FMT should be considered. The panel recommends that immunocompromised patients be tested for CMV and EBV prior to undergoing FMT and if seronegative be advised of the risks, benefits, and alternatives (including patient-selected donor use). They conclude that FMT has emerged as an effective treatment, but questions remain regarding best method of delivery, optimal donor screening, and long-term safety of the procedure (Kelly et al., 2021).

American Gastroenterological Association (AGA): The 2019 AGA guidelines on the management of patients with mild-to-moderate ulcerative colitis (UC) without *Clostridium difficile* infection recommend fecal microbiota transplantation be performed only in the context of a clinical trial. The use of FMT for treatment of UC should be considered experimental at this time. Current evidence was rated as very low because only small, non-comparative cohort studies of heterogeneous patients have been completed. AGA noted that large studies with long-term follow-up are needed.

Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): In 2018, IDSA and SHEA updated the 2010 clinical practice guidelines for the diagnosis and treatment of *clostridium difficile* infection in adults and children. The Societies recommended pharmacotherapy using vancomycin, fidaxomicin, and/or metronidazole depending on the episode and the severity of the *C. difficile*. The strength of the recommendations ranged from strong to weak and the quality of evidence ranged from high to low. The guidelines strongly recommended fecal microbiota transplantation as a treatment option for adults following an initial treatment of CDI and two recurrences (i.e. after three treated CDI episodes) that have been non-responsive to at least two regimens of antibiotics (i.e., various combinations of vancomycin, fidaxomicin, and/or metronidazole). Similar recommendations are made for children but the strength of the recommendations is low and the quality of evidence is low for pharmacotherapy and very low for FMT. The Societies recommendations for the treatment of *C. difficile* included the following:

- Initial episodes, non-severe: oral vancomycin (VAN) 125 mg four times a day for ten days; OR oral fidaxomicin (FDX) 200 mg twice a day for ten days; OR if neither VAN or FDX are available, oral metronidazole 500 mg three times a day for ten days.

- Initial episode, severe: oral VAN 125 mg, four times a day for ten days; OR FDX 200 mg twice a day for ten days
- Initial episode, fulminant; 500 mg VAN oral or via NG tube four times a day. If ileus is present consider rectal instillation of VAN. Intravenous metronidazole, 500 mg every eight hours, with VAN if ileus is present.
- First recurrence: VAN 125 mg four times a day for ten days if metronidazole was used for initial episode; OR prolonged tapered and pulsed VAN regimen if a standard VAN regimen was used initially; OR FDX 200 mg twice a day for ten days if VAN was used for the initial episode.
- Second or subsequent recurrence: VAN in tapered and pulsed regimen; OR oral VAN 125 mg four times a day for ten days followed by rifaximin 400 mg three times a day for 20 days; OR FDX 200mg twice a day for 10 days; OR fecal microbiota transplantation (IDSA, 2018).

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHN): The 2019 NASPGHAN/ESPGHN joint position paper recommends FMT treatment for recurrent *Clostridium difficile* infections (rCDI) in pediatric patients when one of the following conditions is present:

- rCDI (recurrence of symptoms within eight weeks of treatment for CDI) as defined by either:
 - at least three episodes of mild to moderate CDI and failure of a 6–8 week taper with vancomycin with or without an alternative antibiotic (e.g., rifaximin, nitazoxanide)
 - at least two episodes of severe CDI resulting in hospitalization and associated with significant morbidity
- moderate CDI not responding to standard therapy (including vancomycin) for at least one week, but recommends caution and repeat testing for etiologies other than CDI such as irritable bowel disease
- severe CDI or fulminant *C. difficile* colitis with no response to standard therapy after 48 hours

The Societies noted that there are varying degrees of preparation of fecal material ranging from the least manipulated donor sample of fresh stool to the most manipulated, cultured, bacterial cocktail in oral pill form.

Use Outside the United States

As noted by the following professional society statements, FMT is being used in Canada and throughout Europe for a select subpopulation of patients with CDI. Carlucci et al. (2016) noted that in countries that recommend FMT for recurrent CDI (e.g. England, Austria, Australia), FMT is not considered a drug by regulatory bodies. In other countries, Health Canada and the Agence nationale de sécurité du médicament, (ANSM, France) classify FMT as a drug.

Australasian Society of Infectious Diseases: The Australasian Society of Infectious Diseases guideline on the management of *Clostridium difficile* infection in adults and children recommended FMT as a treatment option in adults with recurrent CDI following failure of the standard of care. Depending on the severity of the CDI, oral metronidazole or oral vancomycin were recommended as first-line treatment. Vancomycin is also recommended for second or subsequent recurrence and refractory disease. Oral fidaxomicin is a treatment alternative in recurrent CDI (Trubiano, et al., 2016).

British Society of Gastroenterology (BSG)/Healthcare Infection Society (HIS): The 2018 BSG/HIS guidelines on FMT for the treatment of recurrent and refractory *C. diff* included the following recommendations:

- FMT should be offered to patients with recurrent CDI who have had at least two recurrences, or one recurrence with risk factors for further episodes, including severe and severe complicated CDI (level of evidence: high; strength of recommendation: strong).
- FMT should be considered in cases of refractory CDI (level of evidence: moderate; strength of recommendation: strong).
- FMT for recurrent CDI should only be considered after recurrence of symptoms following resolution of an episode of CDI that was treated with appropriate antimicrobials for at least ten days (level of evidence: low; strength of recommendation: strong).
- Consideration of treatment with extended/pulsed vancomycin and/or fidaxomicin before considering FMT as treatment for recurrent CDI (level of evidence: low; strength of recommendation: strong).
- For severe or complicated CDI, associated with reduced cure rates, recommend that consideration be given to offering patients treatment with medications associated with a reduced risk of recurrence (e.g.,

fidaxomicin and bezlotoxumab), before offering FMT (level of evidence: low; strength of recommendation: strong).

- FMT should be offered after initial FMT failure (level of evidence: high; strength of recommendation: strong).
- FMT should be offered to those with recurrent CDI and inflammatory bowel disease (IBD). Patients should be counselled about a small but recognized risk of exacerbation of IBD (level of evidence: moderate; strength of recommendation: strong).
- FMT is not recommended as treatment for IBD [without CDI]. There is insufficient evidence to recommend FMT for any other GI or non-GI disease than treatment for CDI (level of evidence: moderate; strength of recommendation: strong).

Regarding the route of administration, the Societies recommendations included:

- Upper gastrointestinal (GI) route can be via nasogastric, nasoduodenal, nasojejunal tube, upper GI endoscopy. Administration via a permanent feeding tube is also appropriate (level of evidence: high; strength of recommendation: strong).
- Lower gastrointestinal route via colonoscopy or flexible sigmoidoscopy is preferred. Enema should be used when delivery via colonoscopy or flexible sigmoidoscopy is not possible (level of evidence: high; strength of recommendation: strong).
- Capsulized FMT holds promise as a treatment option for recurrent CDI and should be offered as a potential treatment modality where available. Capsule preparations should follow a standard protocol. Further evidence regarding optimal dosing and formulation is required (level of evidence: high; strength of recommendation: strong).

Canadian Association of Gastroenterology (CAG): The CAG (2014) position statement on FMT stated that metronidazole is recommended as the first line of treatment and vancomycin as second line therapy. Although treatment with fidaxomicin has been suggested, a key focus has been on the emerging evidence of the effectiveness of FMT. Following a systematic review of the literature, CGA concluded that there is sufficient evidence to recommend FMT for the treatment of patients with CDI who have failed or had recurrent infection after two rounds of different antibiotics (usually metronidazole and vancomycin). The evidence consisted of one RCT (n=32) and 16 case series (n=526) involving subjects with antibiotic resistant CDI and reported a response rate of 88% (range 69%–100%). CAG stressed that the physician should be experienced in giving this treatment and donors should be healthy and extensively screened for communicable diseases. The evidence did not support FMT for the treatment of irritable bowel syndrome.

European Society of Clinical Microbiology and Infectious Diseases (ESCMID): The 2014 ESCMID treatment guidance on CID “strongly” recommended FMT for the treatment of multiple recurrent CDIs unresponsive to repeated antibiotic treatment. According to the Society, FMT should be used in combination with oral antibiotic (Debast, et al., 2014)

National Institute for Health and Care Excellence (NICE) (United Kingdom): NICE (2014) issued an interventional procedure guidance for FMT for the treatment of recurrent CDI. The guidance stated that the evidence supported the safety and efficacy for FMT for the treatment of patients with recurrent CDI who have failed to respond to antibiotic and other treatment. First line treatment includes rehydration and antibiotic therapy.

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD		No National Coverage Determination found	
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

- Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible

for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen

HCPCS Codes	Description
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

***Current Procedural Terminology (CPT®) ©2020 American Medical Association: Chicago, IL.**

References

1. Al-Jashaami LS, DuPont HL. Management of Clostridium difficile infection. Gastroenterol Hepatol (N Y). 2016 Oct;12(10):609-616.
2. American College of Gastroenterology (ACG). Prevention, diagnosis, and treatment of Clostridioides difficile infections. May 2021. Accessed Jul 29, 2021. Available at URL address: <https://gi.org/guidelines/>
3. American Gastroenterological Association. Clinical Practice Guidelines. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. 2019. Accessed Jul 30, 2021. Available at URL address: <https://www.gastro.org/guidelines/ibd-and-bowel-disorders>.
4. American Gastroenterological Association. AGA Clinical Practice Update: Expert Review. Management of clostridium difficile infection in inflammatory bowel disease: expert review from the clinical practice updates committee of the AGA institute. 2017. Accessed Jul 30, 2021. Available at URL address: <https://gastro.org/practice-guidance/gi-patient-center/topic/clostridium-difficile-and-inflammatory-bowel-disease/?hilite=%27diff%27>
5. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults: a systematic review. JAMA. 2015 Jan 27;313(4):398-408. doi: 10.1001/jama.2014.17103. PMID: 25626036; PMCID: PMC6561347.
6. Bakken JS. Fecal bacteriotherapy for recurrent Clostridium difficile infection. Anaerobe. 2009 Dec;15(6):285-9.
7. Bakken JS, Borody T, Brandt LJ, Brill JV, Demarco DC, Franzos MA, Kelly C, Khoruts A, Louie T, Martinelli LP, Moore TA, Russell G, Surawicz C; Fecal Microbiota Transplantation Workgroup. Treating Clostridium difficile infection with fecal microbiota transplantation. Clin Gastroenterol Hepatol. 2011 Dec;9(12):1044-9.
8. Borody TJ, Ramrakha S. In UpToDate. Fecal microbiota transplantation in the treatment of recurrent Clostridioides (formerly Clostridium) difficile infection. Lamont T (Ed), UpToDate, Waltham, MA.
9. British Society of Gastroenterology (BSG)/Healthcare Infection Society (HIS). The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. Jul 1, 2018. Accessed Jul 30, 2021. Available at URL address: <https://www.bsg.org.uk/clinical-resource/the-use-of-faecal-microbiota-transplant-as-treatment-for-recurrent-or-refractory-clostridium-difficile-infection-and-other-potential-indications/>

10. Butler M, Olson A, Drekonja D, Shaukat A, Schwehr N, Shippee N, Wilt TJ. Early diagnosis, prevention, and treatment of *Clostridium difficile*: Update. Comparative Effectiveness Review No. 172. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 16-EHC012-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2016, archived. Accessed Jul 30, 2021. Available at URL address: <https://effectivehealthcare.ahrq.gov/topics/c-difficile-update/research>
11. Caldeira LF, Borba HH, Tonin FS, Wiens A, Fernandez-Llimos F, Pontarolo R. Fecal microbiota transplantation in inflammatory bowel disease patients: A systematic review and meta-analysis. *PLoS One*. 2020 Sep 18;15(9):e0238910. doi: 10.1371/journal.pone.0238910. PMID: 32946509; PMCID: PMC7500646.
12. Cammarota G, Ianiro G, Gasbarrini A. Fecal microbiota transplantation for the treatment of *Clostridium difficile* infection. *J Clin Gastroenterol*. 2014;48(8):693-702.
13. Canadian Association of Gastroenterology (CAG). Position statement: fecal microbiota transplant therapy. 2014. Accessed Jul 29, 2021. Available at URL address: https://www.cag-acg.org/images/publications/fecal_microbiota_position_statement_feb2014.pdf
14. Carlucci C, Petrof EO, Allen-Vercoe E. Fecal Microbiota-based Therapeutics for Recurrent *Clostridium difficile* Infection, Ulcerative Colitis and Obesity. *EBioMedicine*. 2016 Nov;13:37-45.
15. Centers for Disease Control and Prevention (CDC). Antibiotic resistance threats in the United States, 2013. Accessed Jul 30, 2021. Available at URL address: <http://www.cdc.gov/drugresistance/threat-report-2013/>
16. Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC. Accessed Jul 30, 2021. Available at URL address: <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf>
17. Centers for Disease Control and Prevention. FAQs for clinicians about *C. diff*. Mar 27, 2020. Accessed Jul 28, 2021. Available at URL address: https://www.cdc.gov/cdiff/clinicians/faq.html#anchor_1529601781962
18. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Jul 30, 2021. Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/lcd-alphabetical-index.aspx?Cntrctr=373&ContrVer=1&CntrctrSelected=373*1&DocType=Active%7cFuture&s=All&bc=AggAAAQAAAA&
19. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Jul 30, 2021. Available at URL address: <https://www.cms.gov/medicare-coverage-database/indexes/ncd-alphabetical-index.aspx>.
20. Chen T, Zhou Q, Zhang D, Jiang F, Wu J, Zhou JY, Zheng X, Chen YG. Effect of faecal microbiota transplantation for treatment of *Clostridium difficile* infection in patients with inflammatory bowel disease: a systematic review and meta-analysis of cohort studies. *J Crohns Colitis*. 2018 May 25;12(6):710-717.
21. Cheng F, Huang Z, Wei W, Li Z. Fecal microbiota transplantation for Crohn's disease: a systematic review and meta-analysis. *Tech Coloproctol*. 2021 May;25(5):495-504. doi: 10.1007/s10151-020-02395-3. Epub 2021 Mar 23. PMID: 33759066.
22. Cohen NA, Ben Ami R, Guzner-Gur H, Santo ME, Halpern Z, Maharshak N. Fecal microbiota transplantation for *Clostridium difficile*-associated diarrhea. *Isr Med Assoc J*. 2015 Aug;17(8):510-4.

23. Cohen N.A. & Maharshak, Novel indications for fecal microbial transplantation: update and review of the literature. *N. Dig Dis Sci* (2017) 62: 1131.
24. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society Of America (IDSA). *Infect Control Hosp Epidemiol*. 2010 May;31(5):431-55.
25. Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. 2014 December 1; 8(12): 1569–1581.
26. Cui B, Feng Q, Wang H, Wang M, Peng Z, Li P, Huang G, Liu Z, Wu P, Fan Z, Ji G, Wang X, Wu K, Fan D, Zhang F. Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. *J Gastroenterol Hepatol*. 2015 Jan;30(1):51-8.
27. Dang X, Xu M, Liu D, Zhou D, Yang W. Assessing the efficacy and safety of fecal microbiota transplantation and probiotic VSL#3 for active ulcerative colitis: A systematic review and meta-analysis. *PLoS One*. 2020 Mar 17;15(3):e0228846. doi: 10.1371/journal.pone.0228846. PMID: 32182248; PMCID: PMC7077802.
28. Debast SB, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect*. 2014 Mar;20 Suppl 2:1-26.
29. Diorio C, Robinson PD, Ammann RA, Castagnola E, Erickson K, Esbenshade A, Fisher BT, Haeusler GM, Kuczynski S, Lehrnbecher T, Phillips R, Cabral S, Dupuis LL, Sung L. Guideline for the management of *Clostridium difficile* infection in children and adolescents with cancer and pediatric hematopoietic stem-cell transplantation recipients. *J Clin Oncol*. 2018 Sep 14;JCO1800407. doi: 10.1200/JCO.18.00407. [Epub ahead of print].
30. Drekonja D, Reich J, Gezahegn S, Greer N, Shaukat A, MacDonald R, Rutks I, Wilt TJ. Fecal microbiota transplantation for *Clostridium difficile* infection: a systematic review. *Ann Intern Med*. 2015 May 5;162(9):630-8. doi: 10.7326/M14-2693.
31. Du C, Luo Y, Walsh S, Grinspan A. Oral Fecal Microbiota Transplant Capsules Are Safe and Effective for Recurrent *Clostridioides difficile* Infection: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol*. 2021 Apr 1;55(4):300-308. doi: 10.1097/MCG.0000000000001495. PMID: 33471490.
32. DuPont HL. Persistent diarrhea: a clinical review. *JAMA*. 2016 Jun 28;315(24):2712-23.
33. Fang H, Fu L, Wang J. Protocol for fecal microbiota transplantation in inflammatory bowel disease: a systematic review and meta-analysis. *Biomed Res Int*. 2018 Sep 13;2018:8941340.
34. Fischer M, Kao D, Mehta SR, Martin T, Dimitry J, Keshteli AH, Cook GK, Phelps E, Sipe BW, Xu H, Kelly CR. Predictors of early failure after fecal microbiota transplantation for the therapy of *Clostridium difficile* infection: a multicenter study. *Am J Gastroenterol*. 2016 Jul;111(7):1024-31.
35. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infect Dis*. 2011 Nov;53(10):994-1002.
36. Guh AY, Mu Y, Winston LG, Johnston H, Olson D, Farley MM, Wilson LE, Holzbauer SM, Phipps EC, Dumyati GK, Beldavs ZG, Kainer MA, Karlsson M, Gerding DN, McDonald LC. Emerging Infections Program *Clostridioides difficile* Infection Working Group. Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. *N Engl J Med*. 2020 Apr 2;382(14):1320-1330. doi: 10.1056/NEJMoa1910215. PMID: 32242357

37. Guo B, Harstall C, Louie T, Veldhuyzen van Zanten S, Dieleman LA. Systematic review: faecal transplantation for the treatment of *Clostridium difficile*-associated disease. *Aliment Pharmacol Ther*. 2012 Apr;35(8):865-75.
38. Gupta S, Allen-Vercoe E, Petrof EO. Fecal microbiota transplantation: in perspective. *Therap Adv Gastroenterol*. 2016 Mar;9(2):229-39. doi: 10.1177/1756283X15607414.
39. Halkjær SI, Boolsen AW, Günther S, Christensen AH, Petersen AM. Can fecal microbiota transplantation cure irritable bowel syndrome? *World J Gastroenterol*. 2017 Jun 14;23(22):4112-4120.
40. Hayes Inc. Emerging technology report. RBX2660 for fecal microbiota transplantation. Lansdale, PA: Hayes, Inc. Jul 2020.
41. Hayes Inc. Emerging technology report. SER-109 for fecal microbiota transplantation. Lansdale, PA: Hayes, Inc. Jul 2020.
42. Health Quality Ontario. Fecal microbiota therapy for *Clostridium difficile* infection: a health technology assessment. *Ont Health Technol Assess Ser* [Internet]. 2016 July;16(17):1-69. Accessed Jul 29, 2021. Available at URL address: <http://www.hqontario.ca/evidence-to-improve-care/journal-ontario-health-technology-assessment-series>
43. Holvoet T, Joossens M, Vázquez-Castellanos JF, Christiaens E, Heyerick L, Boelens J, Verhasselt B, van Vlierberghe H, De Vos M, Raes J, De Looze D. Fecal Microbiota Transplantation Reduces Symptoms in Some Patients With Irritable Bowel Syndrome With Predominant Abdominal Bloating: Short- and Long-term Results From a Placebo-Controlled Randomized Trial. *Gastroenterology*. 2021 Jan;160(1):145-157.e8. doi: 10.1053/j.gastro.2020.07.013. Epub 2020 Jul 15. PMID: 32681922.
44. Hirsch BE, Saraiya N, Poeth K, Schwartz RM, Epstein ME, Honig G. Effectiveness of fecal-derived microbiota transfer using orally administered capsules for recurrent *Clostridium difficile* infection. *BMC Infect Dis*. 2015 Apr 17;15:191.
45. Hvas CL, Dahl Jørgensen SM, Jørgensen SP, Storgaard M, Lemming L, Hansen MM, Erikstrup C, Dahlerup JF. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent *Clostridium difficile* infection. *Gastroenterology*. 2019 Apr;156(5):1324-1332.e3.
46. Ianiro G, Eusebi LH, Black CJ, Gasbarrini A, Cammarota G, Ford AC. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2019 Aug;50(3):240-248. doi: 10.1111/apt.15330. Epub 2019 May 28. PMID: 31136009.
47. Imdad A, Nicholson MR, Tanner-Smith EE, Zackular JP, Gomez-Duarte OG, Beaulieu DB, Acra S. Fecal transplantation for treatment of inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2018, Issue 11. Art. No.: CD012774. DOI:10.1002/14651858.CD012774.pub2.
48. Infectious Disease Society of America (IDSA). Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Feb. 2018. Accessed Jul 28, 2021. Available at URL address: <https://www.idsociety.org/practice-guideline/clostridium-difficile/>
49. Infectious Disease Society of America (IDSA). Fecal microbiota transplantation. Investigational new drug protocol. 2016. Accessed Jul 29, 2021. Available at URL address: <https://www.idsociety.org/public-health/emerging-clinical-issues/emerging-clinical-issues/fecal-microbiota-transplantation/>

50. Iqbal U, Anwar H, Karim MA. Safety and efficacy of encapsulated fecal microbiota transplantation for recurrent *Clostridium difficile* infection: a systematic review. *Eur J Gastroenterol Hepatol*. 2018 Jul;30(7):730-734.
51. Jiang ZD, Jenq RR, Ajami NJ, Petrosino JF, Alexander AA, Ke S, Iqbal T, DuPont AW, Muldrew K, Shi Y, Peterson C, Do KA, DuPont HL. Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent *Clostridium difficile* infection: A randomized clinical trial. *PLoS One*. 2018 Nov 2;13(11):e0205064.
52. Johnsen PH, Hilpüsch F, Cavanagh JP, Leikanger IS, Kolstad C, Valle PC, Goll R. Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *Lancet Gastroenterol Hepatol*. 2018 Jan;3(1):17-24.
53. Kakihana K, Fujioka Y, Suda W, Najima Y, Kuwata G, Sasajima S, Mimura I, Morita H, Sugiyama D, Nishikawa H, Hattori M, Hino Y, Ikegawa S, Yamamoto K, Toya T, Doki N, Koizumi K, Honda K, Ohashi K. Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut. *Blood*. 2016 Oct 20;128(16):2083-2088.
54. Kao D, Roach B, Silva M, Beck P, Rioux K, Kaplan GG, Chang HJ, Coward S, Goodman KJ, Xu H, Madsen K, Mason A, Wong GK, Jovel J, Patterson J, Louie T. Effect of oral capsule- vs colonoscopy-delivered fecal microbiota transplantation on recurrent *Clostridium difficile* infection: a randomized clinical trial. *JAMA*. 2017 Nov 28;318(20):1985-1993.
55. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection. *Am J Gastroenterol*. 2013;108(4):500-508.
56. Kelly CR, Fischer M, Allegretti JR, LaPlante K, Stewart DB, Limketkai BN, Stollman NH. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections. *Am J Gastroenterol*. 2021 Jun 1;116(6):1124-1147. doi: 10.14309/ajg.0000000000001278. PMID: 34003176.
57. Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, Aroniadis O, Barto A, Borody T, Giovanelli A, Gordon S, Gluck M0, Hohmann EL, Kao D, Kao JY, McQuillen DP, Mellow M, Rank KM, Rao K, Ray A, Schwartz MA, Singh N, Stollman N, Suskind DL, Vindigni SM, Youngster I, Brandt L. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol*. 2014 Jul;109(7):1065-71.
58. Kelly CR, Kahn S, Kashyap P, Laine L, Rubin D, Atreja A, Moore T, Wu G. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. *Gastroenterology*. 2015 May 15. pii: S0016-5085(15)00680-0. doi: 10.1053/j.gastro.2015.05.008. [Epub ahead of print]
59. Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, Bakow B, Curran P, McKenney J, Tisch A, Reinert SE, Machan JT, Brandt LJ. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *Clostridium difficile* infection: a randomized trial. *Ann Intern Med*. 2016 Nov 1;165(9):609-616.
60. Kelly CR, Kim AM, Laine L, Wu GD. The AGA's Fecal Microbiota Transplantation National Registry: an important step toward understanding risks and benefits of microbiota therapeutics. *Gastroenterology*. 2017 Mar;152(4):681-684.
61. Kelly CP, Lamont JT, Bakken JS. In UpToDate. *Clostridioides* (formerly *Clostridium*) *difficile* in adults: Treatment and prevention. Feb 24, 2021. Calderwood SB (Ed), UpToDate, Waltham, MA.
62. Lane ER, Zisman TL, Suskind DL. The microbiota in inflammatory bowel disease: current and therapeutic insights. *J Inflamm Res*. 2017 Jun 10;10:63-73. doi: 10.2147/JIR.S116088. eCollection 2017.

63. Leong KSW, Jayasinghe TN, Wilson BC, Derraik JGB, Albert BB, Chiavaroli V, Svirskis DM, Beck KL, Conlon CA, Jiang Y, Schierding W, Vatanen T, Holland DJ, O'Sullivan JM, Cutfield WS. Effects of Fecal Microbiome Transfer in Adolescents With Obesity: The Gut Bugs Randomized Controlled Trial. *JAMA Netw Open*. 2020 Dec 1;3(12):e2030415. doi: 10.1001/jamanetworkopen.2020.30415. PMID: 33346848; PMCID: PMC7753902.
64. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M2, Onischi C, Armstrong D, Marshall JK, Kassam Z, Reinisch W, Lee CH. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology*. 2015 Jul;149(1):102-109.
65. Moore T, Rodriguez A, Bakken JS. Fecal microbiota transplantation: a practical update for the infectious disease specialist. *Clin Infect Dis*. 2014 Feb;58(4):541-5.
66. Myneedu K, Deoker A, Schmulson MJ, Bashashati M. Fecal microbiota transplantation in irritable bowel syndrome: A systematic review and meta-analysis. *United European Gastroenterol J*. 2019 Oct;7(8):1033-1041. doi: 10.1177/2050640619866990. Epub 2019 Jul 30. PMID: 31662860; PMCID: PMC6794695.
67. National Institute for Health and Clinical Excellence (NICE). National interventional procedure guidance (IPG485) Faecal microbiota transplant for recurrent *Clostridium difficile* infection: full guidance Mar 2014. Accessed Jul 30, 2021. Available at URL address: <https://www.nice.org.uk/guidance/ipg485>
68. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)/European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHN). Fecal microbiota transplantation for recurrent *Clostridium difficile* infection and other conditions in children: a joint position paper from the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Jan 2019. Accessed Jul 30, 2021. Available at URL address: <https://naspghan.org/professional-resources/clinical-guidelines/>
69. Ong GK, Reidy TJ, Huk MD, Lane FR. *Clostridium difficile* colitis: A clinical review. *Am J Surg*. 2017 Mar;213(3):565-571.
70. OpenBiome. Fecal microbiota preparation. 2020. Accessed Jul 29, 2021. Available at URL address: <http://www.openbiome.org/>
71. OpenBiome. Forms and guides. FDA regulation of FMT. Jun 2020. Accessed Jul 29, 2021. Available at URL address: <http://www.openbiome.org/forms/>
72. OpenBiome. Regulatory. 2020. Accessed Jul 29, 2021. Available at URL address: <http://www.openbiome.org/regulatory/>
73. OpenBiome. OpenBiome Updates on COVID-19. Feb 23, 2021. Accessed on Jul 29, 2021. Available at URL address: <https://www.openbiome.org/covid19>
74. Pawlowski SW, Warren CA, Guerrant R. Diagnosis and treatment of acute or persistent diarrhea. *Gastroenterology*. 2009 May;136(6):1874-86.
75. Quraishi MN, Widlak M, Bhala N, et al. Systematic review with meta-analysis: The efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. *Aliment Pharmacol Ther*. 2017;46(5):479-493.
76. Ramai D, Zakhia K, Fields PJ, Ofosu A, Patel G, Shahnazarian V, Lai JK, Dhaliwal A, Reddy M, Chang S. Fecal Microbiota Transplantation (FMT) with Colonoscopy Is Superior to Enema and Nasogastric Tube While Comparable to Capsule for the Treatment of Recurrent *Clostridioides difficile* Infection: A

Systematic Review and Meta-Analysis. *Dig Dis Sci*. 2020 Mar 12. doi: 10.1007/s10620-020-06185-7. Epub ahead of print. PMID: 32166622.

77. Rebiotix Inc., About Clostridium difficile infection. 2020. Accessed Jul 29, 2021. Available at URL address: <https://www.rebiotix.com/our-therapy/clostridium-difficile-infection/>
78. Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology*. 2015 Jul;149(1):110-118.e4.
79. Rossen NG, MacDonald JK, de Vries EM, D'Haens GR, de Vos WM, Zoetendal EG, Ponsioen CY. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. *World J Gastroenterol*. 2015 May 7;21(17):5359-71.
80. Saha S, Tariq R, Tosh PK, Pardi DS, Khanna S. Faecal microbiota transplantation for eradicating carriage of multidrug-resistant organisms: a systematic review. *Clin Microbiol Infect*. 2019 Aug;25(8):958-963. doi: 10.1016/j.cmi.2019.04.006. Epub 2019 Apr 12. PMID: 30986562.
81. Scadaferri F, Pecere S, Petito V, Zambrano D, Fiore L, Lopetuso LR, Schiavoni E, Bruno G, Gerardi V, Laterza L, Pizzoferrato M, Ianiro G, Stojanovic J, Poscia A, Papa A, Sterbini FP, Sanguinetti M, Masucci L, Cammarota G, Gasbarrini A. Efficacy and mechanisms of action of fecal microbiota transplantation in ulcerative colitis: pitfalls and promises from a first meta-analysis. *Transplant Proc*. 2016 Mar;48(2):402-7.
82. Seres Therapeutics. Clostridium difficile infection (CDI). 2021. Accessed Jul 29, 2021. Available at URL address: <http://www.serestherapeutics.com/clinical-trials/ecospor-trial>
83. Sokol H, Galperine T, Kapel N, Bourlioux P, Seksik P, Barbut F, Scanzi J, Chast F, Batista R, Joly F, Joly AC, Collignon A, Guery B, Beaugerie L; French Group of Faecal microbiota Transplantation (FGFT). Faecal microbiota transplantation in recurrent Clostridium difficile infection: Recommendations from the French Group of Faecal microbiota Transplantation. *Dig Liver Dis*. 2016 Mar;48(3):242-7.
84. Sun D, Li W, Li S, Cen Y, Xu Q, Li Y, Sun Y, Qi Y, Lin Y, Yang T, Xu P, Lu Q. Fecal microbiota transplantation as a novel therapy for ulcerative colitis: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2016 Jun;95(23):e3765.
85. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol*. 2013 Apr;108(4):478-98; quiz 499. doi: 10.1038/ajg.2013.4. Epub 2013 Feb 26.
86. Suskind DL, Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, Singh N, Damman CJ, Hager KR, Nielson H, Miller SI. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease. *Inflamm Bowel Dis*. 2015 Mar;21(3):556-63.
87. Tian H, Ge X, Nie Y, Yang L, Ding C, McFarland LV, Zhang X, Chen Q, Gong J, Li N. Fecal microbiota transplantation in patients with slow-transit constipation: A randomized, clinical trial. *PLoS One*. 2017 Feb 3;12(2):e0171308.
88. Trubiano JA, Cheng AC, Korman TM, Roder C, Campbell A, May ML, Blyth CC, Ferguson JK, Blackmore TK, Riley TV, Athan E. Australasian Society of Infectious Diseases updated guidelines for the management of Clostridium difficile infection in adults and children in Australia and New Zealand. *Intern Med J*. 2016 Apr;46(4):479-93. Accessed Jul 30, 2021. Available at URL address: <https://www.asid.net.au/resources/clinical-guidelines>
89. U.S. Food and Drug Administration (FDA). Fecal microbiota for transplantation: new safety information - regarding additional protections for screening donors for COVID-19 and exposure to SARS-CoV-2 and

testing for SARS-CoV-2. Apr 9, 2020. Accessed on Jul 29, 2021. Available at URL address: <https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-new-safety-information-regarding-additional-protections-screening>

90. U.S. Food and Drug Administration (FDA). Fecal Microbiota for Transplantation: Safety Alert - Risk of serious adverse events likely due to transmission of pathogenic organisms. Mar 12, 2020. Accessed Jul 29, 2021. Available at URL address: <https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission>
91. U.S. Food and Drug Administration (FDA). Guidance for Industry: Enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat *Clostridium difficile* infection not responsive to standard therapies. Jul 2013. Accessed Jul 29, 2021. Available at URL address: <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf>
92. U.S. Food and Drug Administration (FDA). Guidance document. Enforcement policy regarding investigational new drug requirements for use of fecal microbiota for transplantation to treat *Clostridium difficile* infection not responsive to standard therapies: Draft Guidance for Industry. Mar 1, 2016. Accessed Jul 29, 2021. Available at URL address: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM488223.pdf>
93. U.S. Food and Drug Administration (FDA). Information pertaining to additional safety protections regarding use of fecal microbiota for transplantation—screening and testing of stool donors for multi-drug resistant organisms. Jun 18, 2019. Accessed Jul 29, 2021. Available at URL address: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation>
94. U.S. Food and Drug Administration (FDA). Information pertaining to additional safety protections regarding use of fecal microbiota for transplantation -- testing of stool donors for enteropathogenic *Escherichia coli* and shigatoxin-producing *Escherichia coli*. Apr 6, 2020. Accessed Jul 29, 2021. Available at URL address: <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation-0>
95. Uygun A, Ozturk K, Demirci H, Oger C, Avci IY, Turker T, Gulsen M. Fecal microbiota transplantation is a rescue treatment modality for refractory ulcerative colitis. *Medicine (Baltimore)*. 2017 Apr;96(16):e6479.
96. Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med*. 2013 Jan 31;368(5):407-15.
97. World Society of Emergency Surgery (WSES). 2019 Update of the WSES guidelines for management of *Clostridioides (Clostridium) difficile* infection in surgical patients. 2019. Accessed Jul 28, 2021. Available at URL address: https://www.wses.org.uk/guidelines?cli_action=1563821391.922.
98. Xu D, Chen VL, Steiner CA, Berinstein JA, Eswaran S, Waljee AK, Higgins PDR, Owyang C. Efficacy of Fecal Microbiota Transplantation in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. *Am J Gastroenterol*. 2019 Jul;114(7):1043-1050. doi: 10.14309/ajg.000000000000198. PMID: 30908299; PMCID: PMC7257434.
99. Yoon YK, Suh JW, Kang EJ, Kim JY. Efficacy and safety of fecal microbiota transplantation for decolonization of intestinal multidrug-resistant microorganism carriage: beyond *Clostridioides difficile*

infection. *Ann Med.* 2019 Nov-Dec;51(7-8):379-389. doi: 10.1080/07853890.2019.1662477. Epub 2019 Sep 13. PMID: 31468999.

100. You DM, Franzos MA, Holman RP. Successful treatment of fulminant *Clostridium difficile* infection with fecal bacteriotherapy. *Ann Intern Med.* 2008 Apr 15;148(8):632-3.

101. Youngster I, Mahabamunuge J, Systrom HK, Sauk J, Khalili H, Levin J, Kaplan JL, Hohmann EL. Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent *Clostridium difficile* infection. *BMC Med.* 2016 Sep 9;14(1):134.

102. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA.* 2014 Nov 5;312(17):1772-8.

103. Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, Smith MB, Alm EJ, Gevers D, Russell GH, Hohmann EL. Fecal microbiota transplant for relapsing *Clostridium difficile* infection using a frozen inoculum from unrelated donors: A randomized, open-label, controlled pilot study. *Clin Infect Dis.* 2014 Jun;58(11):1515-22.

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