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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 diagnosis of Clostridium difficile (e.g., positive, 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

**Overview**

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

**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 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 (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. Most recurrences occur within one to two weeks after discontinuing antibiotic therapy, although rarely recurrence can occur up to two to three months later. 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 stated, 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 (Kelly and Lamont, 2017; Fischer, et al., 2016; Bagdasarian, et al., 2015; Drekonja, et al., 2015; Broody, et al., 2016; Cammarota, et al., 2014; CDC, 2014; Moore, et al., 2014; Van Nood, et al., 2013; Bakken, et al., 2009; You, et al., 2008).

Treatment for CDI involves discontinuation of the offending antibody 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 CDI an urgent threat with 250,000 people per year requiring hospitalization for treatment. At least 14,000 deaths per year have been reported with an increase in related deaths of 400% between 2000 and 2007. CDI has become more frequent, more severe and more refractory to standard therapy and is more likely to relapse (Infectious Disease Society of America [ISDA], 2018; Drekonja, et al., 2015; Broody, et al., 2016; Cammarota, et al., 2014; CDC, 2013, updated 2018; Moore, et al., 2014; Van Nood, et al., 2013; Bakken, et al., 2009; You, et al., 2008).

In cases of mild-to-moderate CDI metronidazole 500 mg orally three times a day for 10 days is the proposed treatment option. If the patient fails to respond to metronidazole in 5–7 days, vancomycin is recommended. Patients with severe CDI are treated with vancomycin 125 mg four times daily for 7–10 days. Surawicz et al.
(2013) stated that vancomycin orally (125 mg four times per day) plus intravenous metronidazole (500 mg three times a day) is the treatment of choice for patients with severe and complicated CDI who have no significant abdominal distention. Vancomycin orally (500 mg four times per day) and per rectum (500 mg in a volume of 500 ml four times a day) plus intravenous metronidazole (500 mg three times a day) is the treatment of choice for patients with complicated CDI with ileus or toxic colon and/or significant abdominal distention (Kelly and Lamont, 2017; Surawicz et al., 2013; Cohen, et al., 2010)

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 metronidazole and vancomycin. 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 microbial for future use if needed (OpenBiome, 2015). AdvancingBio is another facility that offers donor collection, testing and processing of stool for fecal transplant (AdvancingBio, 2017).

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 (Hayes, Aug 2016; 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. RBC2660 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., 2018; Hayes, 2018; 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, 2018). 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, 2018; Hayes, 2017).
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 reasonably foreseeable 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, 2016). When finalized, the new guidance will supersede the 2013 guidance document.

**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 transfusion was required to resolve the diarrhea (Quraishi, et al., 2017; Hayes, 2016; 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 proceeded 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
Butler et al. (2016) conducted a systematic review for a comparative effectiveness review on the early diagnosis, prevention and treatment of C. difficile. The report was prepared for the Agency of Healthcare Research and Quality (AHRQ). Three randomized controlled trials and 23 case series (n=751) met inclusion criteria. The authors concluded that low strength evidence suggests that FMT may have a significant effect on reducing recurrent CDI and outcomes reported relatively consistent positive evidence for efficacy.

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=≤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.

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 number of patients lost to 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 (mm3), 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: 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 and food allergies (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). Halkjaer et al. (2017) conducted a systematic review of the literature to assess the utility of FMT for the treatment of irritable bowel syndrome (IBS). The search of the literature resulted in six conference abstracts, one case report, one letter to the editor, and one clinical review for a total of 127 patients. In the final analysis, treatment of 48 patients was evaluated and revealed an improvement in 58% of cases. The difference between the studies made it difficult to verify and reproduce results. Data were too limited to draw sufficient conclusions on the use of FMT for the treatment of IBS. Well-designed, randomized controlled trials are needed to investigate the clinical effectiveness of FMT for this condition.

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 millimeters (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.

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 by ACG (2013) stated that metronidazole is the preference for treatment of mild-to-moderate CDI and failure to respond to metronidazole therapy within 5–7 days should prompt consideration for the use of vancomycin at standard dosing. ACG urged caution in the use of fidaxomicin before more definitive evidence of superiority is available. FMT should be considered if there is a third recurrence following a pulsed vancomycin regimen. ACG noted that long-term follow-up is limited and the potential for transmission of infectious agents is a concern. This is a conditional recommendation (uncertainty exists about the risk-benefit ratio) based on moderate-quality evidence.

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 time 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).

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).

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 antibodies (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.

**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:**

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<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>44705</td>
<td>Preparation of fecal microbiota for instillation, including assessment of donor specimen</td>
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<tr>
<th>HCPCS Codes</th>
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<tr>
<td>G0455</td>
<td>Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen</td>
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**References**


