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Kaiser Foundation Health Plan of Washington

Clinical Review Criteria

Fecal Microbial Transplant for Treatment of C. Difficile Infection

- Fecal GI Infusion
- Fecal Capsule (G3 OpenBiome)

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	None
Local Coverage Article (LCA)	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Medical Policy Clinical Review Criteria, ***Fecal GI Infusion for the Treatment of C. Difficile Infection,*** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Effective Until August 1st, 2024

Service	Criteria
Fecal GI Infusion	Fecal GI infusion is covered when **ALL of the following** are met: 1) Clostridium difficile infection confirmed by a positive stool test for *C.* difficile toxin 2) Has had at least two recurrences following adequate antibiotic therapy This would be defined as a symptomatic toxin-positive failure after at least one prolonged tapering course of vancomycin (generally over a 4-6-week period).
FMT capsule, G3 OpenBiome	If the above criteria are met, oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the treatment of recurrent or refractory clostridium difficile infection is covered.

Effective August 1st, 2024

Service	Criteria
Fecal GI Infusion	Review no longer required—Policy Retired
FMT capsule, G3 OpenBiome	Review no longer required—Policy Retired

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The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

Clostridium difficile (C difficile) is the leading cause of antibiotic associated diarrhea and its rates continue to rise. During the past several years, the incidence of C difficile infection (CDI) has increased to an epidemic level; it has become more severe, more refractory to standard treatment, and more likely to relapse. According to the CDC, the number of hospitalized patients with any CDI discharge diagnoses more than doubled from approximately 139,000 to 336,600, and the number with a primary CDI diagnosis more than tripled, from 33,000 to 111,000 from 2000 to 2009. This rise in incidence and severity of the disease is possibly associated with the emergence of the hypervirulent strain (NAPI/ribotype 027). CDI is responsible for a spectrum of infections including uncomplicated diarrhea, pseudomembranous colitis, and toxic megacolon, which may lead to sepsis and even death. It often occurs in patients in health-care settings where antibiotics are prescribed, and symptomatic patients are concentrated. The most common risk factor for CDI is the use of broad-spectrum antibiotics or the concomitant use of multiple and prolonged antimicrobials. Other risk factors include advanced age (65 years or older), recent organ transplantation, gastrointestinal surgery, inflammatory bowel disease, immunosuppressive drugs, presence of multiple co-morbidities, and others. Mature colonic bacterial microbiota (community of micro-organisms) in a healthy adult is generally resistant to C difficile colonization. Any factor altering the balance of intestinal microbiota leads to a selective advantage and colonization by C difficile colonization after exposure to the bacteria
The standard treatment for C difficile associated disease includes discontinuation of offending/inducing antibiotic and treatment with metronidazole or vancomycin. Most patients initially respond to this therapy, but 15-30% experience a symptomatic recurrence after discontinuation of the treatment. The risk of recurrence rises to 40% after a first recurrence and to more than 60% after two or more recurrences. The increased incidence and severity of CDI, and the high recurrence rate with conventional treatments have led researchers to explore alternative strategies and therapies with varying degrees of success. These include the use of additional courses of metronidazole and vancomycin, pulsed/tapered antibiotics, the use of new drugs as nitazoxanide and fidaxomicin, immune therapy such as IV immunoglobulin, active immunization, toxin binding, and alternative approaches as the use of probiotics (such as lactobacillus species, which is a low-virulent microorganism that could compete with C difficile for nutrients and sites of mucosal adherence), and fecal transplantation to recreate the colonic environment (Brandt 2012, Guo 2012, Kassam 2011, 2013).

Fecal transplantation (FT), also known as fecal microbiota transplantation (FMT), fecal bacteriotherapy, fecotherapy, fecal microbiota reconstitution, or human probiotics infusion, refers to the process of instilling a liquid suspension of stool from a healthy donor into the gastrointestinal (GI) tract of another person, theoretically to promote normalization of flora and restore the intestinal microbiota. It is of particular utility in recurrent or refractory C difficile infection. The exact mechanism of FMT in treating CDI is not clear but may involve the re-colonization of microbiota with missing components to generate colonization resistance or direct antagonistic activity of the normal microbiota to C difficile. There is also the possibility that the transplantation of donated flora results in an immunological response facilitating the eradication of C difficile. The re-establishment of the normal composition of the intestinal flora by the use of human fecal microbiota was first used by Ben Eiseman in 1958 for the treatment of four patients with pseudomembranous colitis. Lately, FMT has received more attention with the publication of promising results of case series. It is however, not widely accepted as a therapeutic tool due to lack of published trials with long-term outcomes and concerns regarding its safety and acceptability (Guo 2012, Matilla 2012).

There is no clear definition of CDI, its recurrence, relapse or re-infection, and there is no standardized protocol for FMT as regards the choice of donor (family member or volunteer donor), screening of donors, quantity and preparation of stools collected, form of infusion, and measurement of outcomes. There is also no consensus on the most appropriate form of delivery for the fecal microbiota. Until 1989 retention enema was the most common route for FMT; subsequently it was infused via nasogastric tube, colonoscopy and more recently self-administered enemas. The colonoscopic approach seems to be the most common and favored approach as it allows the examination of the disease extent and inoculation of the entire colon and ileum. Regardless of the delivery method, the steps of the procedure are similar and include evaluating the patient eligibility, patient consent, identification and screening of donors, preparation of the sample, and infusion of the suspension prepared. Donor stool is most often used within 8 hours of passage, but frozen samples have been thawed and used 1-8 weeks after passage. Stool is commonly suspended in saline; however, water, milk, and yogurt have also been used as diluents. The suspension is filtered through gauze pads or strainer, and then aspirated into syringes for use. The

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volume of stool suspension used for FMT varied between studies from less than 200 ml to 500 ml or more. Patients undergoing FMT typically remain on their CDI antimicrobials until 2-3 days prior to the procedure. Bowel preparation is performed regardless of the route. If infused via nasogastric tube, the suspension is applied after fitting the tube in place. After the infusion the tube is rinsed with saline solution and removed. If applied via colonoscopy, the colonoscope is inserted and advanced to the terminal ileum, and then working backwards the stool suspension is administered, most in the terminal ileum and ascending colon. The aftercare requires regular clinical checkups and testing the stools for C difficile. The risk of the procedure includes risks associated with application as perforation and hemorrhage, as well as the risk of microbial translocation and sepsis. FMT is relatively contraindicated in patients with severe comorbid conditions or those taking immunosuppressants, though such patients have been successfully treated with the fecal transplant (Brandt 2011, Gough 2011, Postigo 2012, Rohlke 2012, Kleger 2013, Aroniadis 2013).

Fecal transplantation is not regulated by FDA, to date, as fecal matter is organic. According to the FDA the complex nature of FMT products presents specific scientific and regulatory challenges. The Center for Biologics Evaluation and Research (CBER), together with the National Institute of Allergy and Infectious Disease (NIAID) are holding a public workshop in May 2013, to facilitate clinical development of FMT.

Medical Technology Assessment Committee (MTAC)

Fecal GI infusion for the Treatment of C. Difficile infection

04/15/2013: MTAC REVIEW

Evidence Conclusion: There is some evidence from one small RCT that fecal transplantation has a significantly higher success rate than vancomycin in treating patients with recurrent C difficile infection. Meta-analyses of case series with no control groups also show a high cure rate of recurrent CDI with FMT. There is insufficient evidence to determine whether FMT is effective for the treatment of patients with the more virulent strain ribotype 027 C difficile. There is insufficient evidence to determine the most effective and safe modality for delivering the FMT. There is insufficient evidence to determine the long-term efficacy and safety of FMT.

Articles: The literature search for studies on fecal transplantation for the treatment of *C difficile* infection revealed one recent RCT (van Nood 2013), and four systematic reviews (Gough 2011, Guo 2012, Kassam 2013 and Sofi 2013). The latter two pooled the results of the published studies in meta-analyses. Sofi and colleague's analyses combined the results of case series and case reports, while Kassam and colleagues excluded the small case series (<10 subjects) and case reports in an attempt to minimize bias. The search also identified a review comparing nasogastric versus colonoscopic FMT (Postigo 2012), and a protocol for a Cochrane review, which is still being prepared. van Nood 2013 RCT, and the Kassam and colleagues' meta-analysis that had a more valid methodology were selected for critical appraisal: van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile, *N Engl J Med.* 2013; 368:407-415. See Evidence Tables. Kassam Z, Lee CH, Yuan Y et al. Fecal Microbiota Transplantation for Clostridium difficile Infection: Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2013; Mar 19. doi:10.1038/ajg.2013.59 See Evidence Tables.

The use fecal GI infusion for the treatment of C. difficile infection meets the *Kaiser Permanente Medical Technology Assessment Criteria*.

Oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the treatment of recurrent or refractory clostridium difficile infection

BACKGROUND

Clostridium difficile (*C difficile*) infection (CDI) is one of the most prevalent hospital acquired infections in the United States and is the leading cause of antibiotic associated diarrhea. The incidence of *C*DI has increased to an epidemic level; it has become more severe, more refractory to standard treatment, and more likely to relapse. According to the CDC, CDI was estimated to have caused almost half a million infections in the United States in 2011, and 29,000 deaths within 30 days of the initial diagnosis. It is believed that the rise in incidence and severity of the disease may be related to the emergence of the hypervirulent strain of the organism (NAP1/BI/027) that is particularly associated with higher rates of treatment failure and recurrence (Youngster 2014, Hirsch 2015, CDC webpage accessed November 2015). CDI is responsible for a spectrum of infections including uncomplicated diarrhea, pseudomembranous colitis, and toxic megacolon, which may lead to sepsis and even death. It often occurs in patients in health-care settings where antibiotics are prescribed, and symptomatic patients are concentrated. The most common risk factor for CDI is the use of broad-spectrum antibiotics or the concomitant use of multiple and prolonged antimicrobials. Other risk factors include advanced age (65 years or older), recent organ transplantation, gastrointestinal surgery, inflammatory bowel disease, immunosuppressive drugs, presence of multiple co-morbidities, and others. Mature colonic bacterial microbiota (community of micro-organisms) in a healthy adult is generally resistant to colonization and overgrowth of pathogenic bacteria. Any factor altering the balance of intestinal microbiota allows pathogens such as *C difficile* to proliferate and dominate the gut ecosystem

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(Matilla 2012, Rohlke 2012, Sofi 2012, Brandt 2012, Kassam 2013, Hirsch 2015). The standard management of CDI includes discontinuation of offending/inducing antibiotic and treatment with metronidazole or vancomycin. Most patients initially respond to this therapy, but 15-30% experience symptomatic recurrence after discontinuation of the treatment. It is reported that antibiotics targeting CDI may eradicate the active infection, but do not restore the long-lasting dysbiosis of the microbiota, which is the major risk factor for relapse. This risk rises to 40% after a first recurrence and to more than 60% after two or more recurrences. The increased incidence and severity of CDI, and the high recurrence rate with conventional treatments have led researchers to explore alternative strategies and therapies with varying degrees of success. These include the use of additional courses of metronidazole and vancomycin, pulsed/tapered antibiotics, the use of new drugs as nitazoxanide and fidaxomicin, immune therapy such as IV immunoglobulin, active immunization, toxin binding, and alternative approaches such as use of probiotics as lactobacillus species, which is a low-virulent microorganism that could compete with *C difficile* for nutrients and sites of mucosal adherence, and fecal microbiota transplantation (Brandt 2012, Guo 2012, Kassam 2013, Hirsch 2015). Fecal microbiota transplantation (FMT), also known as fecal transplantation (FT), fecal bacteriotherapy, fecotherapy, fecal microbiota reconstitution, or human probiotics infusion, refers to the process of transplantation of stools from a healthy individual into the gastrointestinal (GI) tract of the affected patient, theoretically to promote normalization of flora and restore the intestinal microbiota. It may be particularly useful in recurrent or refractory *C difficile* infection. The exact mechanism of FMT in treating CDI is not clear but may involve the re-colonization of microbiota with missing components to generate colonization resistance or direct antagonistic activity of the normal microbiota to *C difficile.* There is also the possibility that the transplantation of donated flora results in an immunological response facilitating the eradication *of C difficile.* The re-establishment of the normal composition of the intestinal flora by the use of human fecal microbiota was first used by Ben Eiseman in 1958 for the treatment of four patients with pseudomembranous colitis. Lately, FMT has received more attention with the publication of promising results of a small RCT and a number of case series (Guo 2012, Matilla 2012, van Nood 2013). There is no standardized protocol for FMT as regards the choice of donor (family member or volunteer donor), screening of donors, quantity and preparation of stools collected, form of infusion, and measurement of outcomes. There is also no consensus on the most appropriate form of delivery for the fecal microbiota. Traditionally FMT has been performed by transplanting a liquid suspension of feces from a related healthy donor into the gastrointestinal tract of the affected patient through nasogastric tube, endoscopy, enema, or colonoscopy. The traditional methods are time-consuming, may be technically challenging, unaesthetic, and not accepted by many patients (Brandt 2011, Gough 2011, Postigo 2012, Rohlke 2012, Kleger 2013, Aroniadis 2013). More recently, orally administered capsules containing cryopreserved fecal material have been described. The capsules are generally prepared using fecal material harvested from unrelated healthy donors fulfilling strict criteria including screening negative for HIV, hepatitis A, B, and C as well as Treponema pallidum. Fecal matter is collected under sterile conditions, combined with saline, processed, sieved, centrifuged, and mixed again with saline along with glycerol, to protect the biological material from becoming damaged when frozen. The fecal material is then dispensed into double or triple capsules and stored at -80°C (-112°F). The capsules should be kept frozen until the time of administration and ingested as quickly as possible after extraction from the freezer. Capsules may be kept at room temperature for up to 90 minutes for patient comfort and ease of swallowing. Another described method is the immediate freezing and storing of the fecal suspension or slurry in 5- or 10-ml syringes at -80°C then thawing and triple encapsulating it prior to its use. Capsules should never be refrozen and should be disposed of if not used within 90 minutes. OpenBiome (Boston, MA) a stool bank that created a fecal transplant pill (G3) recommends the intake 30 capsules, swallowed consecutively in a single session for the treatment of CDI (OpenBiome website, Youngster 2014, Hirsch 2015). FMT capsule G3 (OpenBiome) are size 00 (approximately the size of a large multivitamin) and are provided with two placebo test capsules. The patient is asked to ingest one test capsule prior to the start of treatment, under direct observation of the physician, to ensure the patient's ability to swallow. Any clinical concerns suggesting an aspiration risk is an absolute contraindication to capsule administration. Other contraindications include severe complicated CDI, dysphagia, history of gastroparesis, allergy to any of the ingredients, adverse events attributable to a previous FMT, and any condition that the treatment my pose a health risk (OpenBiome website). According to OpenBiome, FMT Capsule G3 may be used as a treatment for *C. difficile* infection not responsive to standard therapies in accordance with the FDA's guidance on the use of fecal microbiota for transplantation, and in clinical trials under an Investigational New Drug (IND) application.

12/21/2015: MTAC REVIEW

Oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the treatment of recurrent or refractory *clostridium difficile* infection

Evidence Conclusion: There is a lack of published studies on the use of oral cryopreserved FMT capsules for patients with relapsing or refractory CDI. Currently the literature on oral FMT capsules for patients with relapsing *C difficile* infection (CDI) consists of two small case series and one case report. Youngster and colleagues (2014) (evidence table 1), evaluated the safety and rate of resolution of diarrhea following the administration of cryopreserved FMT capsules in 20 patients (11-89 years of age) with refractory *C. difficile* infection. The oral

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capsulized FMT was prepared from stool samples gathered from healthy adult volunteers who had been comprehensively screened for infectious diseases and avoided eating common allergens for several days before donating. Each patient ingested 15 FMT capsules consecutively each day for two successive days. If their symptoms did not improve within 72 hours, they were offered a second course of treatment with fecal material from the same donor. They were followed-up for 6 months and the primary outcomes were safety and clinical resolution of diarrhea with no relapse at 8 weeks. The results of the study show that after the first 2 days of treatment, 14 of the 20 patients (70%) experienced clinical resolution of diarrhea, defined as less than 3 bowels movements /24 hours, and remained symptom free for 8 weeks. After a second course of treatment, four of the remaining patients became symptom free, resulting in an overall 90% rate of symptom resolution. No serious adverse events were reported. The study was a small observational study with no control or comparison group and relied on patient report on clinical outcomes. Patients with symptomatic improvement were not retested for *C difficile.* The authors indicated that it was a pilot feasibility study that only provides preliminary data on the safety and effectiveness of this the oral capsulized FMT. Hirsch et al, 2015 (Evidence table 2), conducted a chart review of 19 patients treated with orally administered FMT capsules for recurrent CDI. FMT was prepared from stools donated by healthy volunteers unrelated to the recipients. Before receiving the FMT, the patients were required to discontinue any CDI antimicrobial treatment for 24 hours and were given a proton pump inhibitor on the evening and morning prior to the therapy. After a light breakfast, they received 6-22 capsules of FMT under supervision in an outpatient setting and were instructed to sit upright and not eat for an hour after ingesting the capsules. Patients were encouraged to drink 4 oz. of fermented milk product twice daily and to consume pro-biotic nutrients for at least 3 days after the FMT. They were followed-up by phone interviews within 2 days, 3 weeks, and after 90 days to assess the response to the therapy and adverse events. Those with recurrent CDI were retreated with antimicrobial therapy and subsequently offered repeat FMT (approximately 6 weeks after the initial FMT) and followed up for an additional 90 days. The primary outcome was resolution of CDI associated diarrhea without relapse assessed at 90 days after the last FMT. 13 of the 19 patients treated (68%) responded to a single course, and four responded to the second course of therapy with a total response rate of 89%. No serious adverse events were reported. The study was a small retrospective case series with no control or comparison group and relied on patient and family report on clinical outcomes. In addition, the follow-up duration was insufficient to determine the long-term safety and effectiveness of the orally ingested FMT capsules. It is also worth noting that the authors have financial ties to Symbiotic Health Inc. Conclusion: There is insufficient evidence to determine that orally ingested FMT capsules prepared from stools provided by volunteer donors is safe and effective for the treatment of patients with CDI. There is insufficient evidence to determine that orally ingested FMT capsules prepared from stools provided by volunteer donors is safe and effective for the treatment of patients with CDI with the more virulent strain *C difficile* (NAP1/BI/027). There is insufficient evidence to determine the long-term efficacy and safety of orally ingested FMT capsules. Case series may only generate hypothesis and large RCTs with long-term follow up are studies are needed to support the observed findings and determine the optimal donor, optimal dose of FMT, long-term safety, and long-term efficacy of cryopreserved oral capsulized FMT.

Articles: The literature search revealed two small cases series (one prospective and one retrospective) and a case report on the use of oral cryopreserved FMT capsules for patients with relapsing CDI. There are no published meta-analyses or randomized controlled trials, to date, that compared the use of the oral FMT capsules to standard therapy or to other traditional methods of delivering FMT for the treatment of refractory or relapsing CDI.

The following two case series were critically appraised. Youngster I, Russell G, Pindar C, et al. Oral, capsulized, frozen fecal microbiota transplantation for relapsing Clostridium difficile infection. *JAMA*. 2014 Nov 5; 312(17):1772-1778. See Evidence Table 1. Hirsch BE, Saraiya N, Poeth K, et al. Effectiveness of fecal-derived microbiota transfer using orally administered capsules for recurrent Clostridium difficile infection. *BMC Infect Dis*. 2015 Apr 17; 15:191 See Evidence Table 2.

The use of Oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the treatment of recurrent or refractory clostridium difficile infection does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

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

CPT® or HCPC Codes	Description
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen
G0455	Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

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***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Date Created	Date Reviewed	Date Last Revised
05/13/2013	05/13/2013 MDCRPC, 01/07/2014 MPC, 11/04/2014MPC, 09/01/2015MPC, 07/05/2016MPC 05/02/2017MPC, 03/06/2018MPC, 02/05/2019MPC, 02/04/2020MPC, 02/02/2021MPC, 02/01/2022MPC, 02/07/2023MPC , 03/12/2024MPC	03/12/2024

MDCRPC Medical Director Clinical Review and Policy Committee
MPC Medical Policy Committee

Revision History	Description
01/06/2016	MTAC review was discussed at MPC and approved to adopt criteria for FMT capsule, G3 OpenBiome
05/02/2017	Revised criteria language so it is specific on how to manage care after two recurrences
05/02/2017	Adopted Kaiser Permanente policy for Medicare members
03/12/2024	MPC approved to retire clinical criteria as it meets parameters, effective August 1st, 2024. 60-day notice required.

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