Clinical Review Criteria
Fecal GI Infusion for the Treatment of C. Difficile Infection

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Criteria

For Medicare Members

<table>
<thead>
<tr>
<th>Source</th>
<th>Policy</th>
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<tr>
<td>CMS Coverage Manuals</td>
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<tr>
<td>National Coverage Determinations (NCD)</td>
<td>None</td>
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<tr>
<td>Local Coverage Determinations (LCD)</td>
<td>None</td>
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<tr>
<td>GH Medical Policy</td>
<td>In the absence of a NCD or a LCD use KP Medical Policy Fecal GI Infusion for the Treatment of C. Difficile Infection</td>
</tr>
</tbody>
</table>

For Non-Medicare Members

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.

The following information was used in the development of this document and is provided as background only. It 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
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 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...
Oral, capsulezed, 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 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, 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 microorganisms) 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 (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,
movements /24 hours, and remained symptom free for 8 weeks. After a second course of treatment, four of the
symptoms did not improve within 72 hours, they were offered a second course of treatment with fecal material
resolution of diarrhea with no relapse at 8 weeks. The results of the study show that after the first 2 days of
donating. Each patient ingested 15 FMT capsules consecutively each day for two successive days. If their
comprehensively screened for infectious diseases and avoided eating common allergens for several days before
12/21/2015: MTAC REVIEW
Oral, capsulized, frozen fecal microbiota transplantation (FMT capsule, G3 OpenBiome) for the
(IND) application.
Criteria | Codes | Revision History
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
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 bowel
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 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.*

<table>
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<th>Date Created</th>
<th>Date Reviewed</th>
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<td>05/13/2013</td>
<td>05/13/2013</td>
<td>05/02/2017</td>
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**Revision History**

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<tr>
<td>01/06/2016</td>
<td>MTAC review was discussed at MPC and approved to adopt criteria for FMT capsule, G3 OpenBiome</td>
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<tr>
<td>05/02/2017</td>
<td>Revised criteria language so it is specific on how to manage care after two recurrences</td>
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**Codes**

CPT: 44705; G0455