CLINICAL MEDICAL POLICY	
Policy Name:	Fecal Microbiota Transplant
Policy Number:	MP-066-MD-DE
Responsible Department(s):	Medical Management
Provider Notice Date:	10/02/2019; 04/15/2018
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Revision Date:	09/10/2019; 09/11/2018
Products:	Highmark Health Options Medicaid
Application:	All participating hospitals and providers
Page Number(s):	1 of 8

DISCLAIMER

Highmark Health Options medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

POLICY STATEMENT

Highmark Health Options may provide coverage under the medical-surgical benefits of the Company's Medicaid products for medically necessary fecal microbiota transplants in patients with recurrent Clostridium difficile infections.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

The qualifications of the policy will meet the standards of the National Committee for Quality Assurance (NCQA) and the Delaware Department of Health and Social Services (DHSS) and all applicable state and federal regulations.

DEFINITIONS

Clostridium Difficile – A bacterium that causes diarrhea and more serious intestinal conditions. It is a part of the normal balance of bacteria living in the intestines and is also present in the environment (e.g., in soil, in water, and in animal feces).

Fecal Microbiota Transplantation (FMT) – A procedure that involves the instillation of a solution derived from a healthy donor's fecal matter. The instillation occurs via nasogastric tube, retention enema, colonoscope, and oral capsules.

PROCEDURES

1. Fecal microbiota transplant is covered for patients with current or relapsing Clostridium difficile infection(CDI) when the following medical necessity criteria are met:
    A. The patient must have experienced at least 3 episodes of mild to moderate CDI; AND
    B. Documentation confirms Clostridium Difficle infection by a positive stool test; AND
    C. Appropriate donor screening following the FDA guidelines for biologic donors has been completed; AND
    D. The stool samples must be tested for microorganisms; AND
    E. There must be documented failure of a 6- to 8 week taper with vancomycin with or without an alternative antibiotic (e.g., rifaximin, nitrazoxaide); OR
        1) There must be documented failure of a 6- to 8 week taper with vancomycin with or without an alternative antibiotic (e.g., rifaximin, nitrazoxaide); OR
        2) At least two episodes of severe CDI resulting in hospitalization and associated significant morbidity; OR
    F. At least two episodes of severe CDI resulting in hospitalization and associated significant morbidity; OR
    G. Moderate CDI that is not responding to standard therapy for at least one week; OR
    H. Severe fulminant C difficile colitis with no response to standard therapy after 48 hours.

2. Contraindications
    - Exercise caution in patients who have a suppressed immune system;
    - Patients currently receiving chemotherapy;
    - Patients with decompensated liver cirrhosis, advanced HIV/AIDS, recent bone marrow transplants;
    - Toxic megacolon;
    - Pregnancy

3. When the fecal microbiota transplant services are not covered
    Fecal microbiota transplants are not covered and considered not medically necessary for any other condition than those listed above.

4. Post-payment Audit Statement
    The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark Health Options at any time pursuant to the terms of your provider agreement.

5. Place of Service
    The place of service for fecal microbiota transplant is in the outpatient setting.

GOVERNING BODIES APPROVAL

In May 2013, the FDA classified FMT as an Investigational New Drug (IND). Using this classification, the FDA would regulate fecal microbiota, which would require every provider to file an IND application. Physicians must also obtain an adequate informed consent from the patient or legal representative. The legal consent must contain, at a minimum, a statement that the use of FMT products to treat CDI is investigational and a discussion of the therapy's potential risks and alternative options.

In July 2013, the FDA issued guidance stating that it would exercise "enforcement discretion." This would allow physicians to provide FMT (for patients with C. difficile infections not responding to standard therapies) without filing an IND application. Until FMT is formally approved, the use of this procedure is restricted to the treatment of recurring Clostridium difficile. If the provider wishes to utilize FMT for any other indication, an IND application must be filed with the FDA.

In March 2014, the FDA release draft guidance, for public feedback only, concerning two proposed changes to the current approval. The first change is that the donor be "known" to the patient or physician and second, that all donor and stool screening be conducted under the supervision of the physician performing the FMT. Medical professional societies raised concerns regarding the potential to compromise access and safety. In March 2016, the FDA revised draft guidance to propose that enforcement discretion be narrowed so that physicians who obtain material from stool banks to treat CDI that is nonresponsive to standard therapy would need to do an IND application. The FDA requested feedback on how to implement this proposal so that guidance does not create undue burdens for physicians. There has not been any further published guidance by the FDA.

There are no FDA requirements regarding obtaining stool specimens for FMT. There are also no FDA requirements dictating the route of administration (e.g., colonoscopy, nasoenteric delivery, or oral capsule).

There were no CMS National Coverage Determinations or Local Coverage Determinations located during the development of this medical policy.

CODING REQUIREMENTS

Procedure Codes

CPT Codes	Description
44705	Preparation of fecal microbiota for instillation, including assessment of donor specimen
44799	Fecal instillation by oro-nasogastric tube or enema

Diagnosis Codes

ICD-10 Code	Description
A04.71	Enterocolitis due to Clostridium difficile, recurrent
A04.72	Enterocolitis due to Clostridium difficile, not specified as recurrent

REIMBURSEMENT

Participating facilities will be reimbursed per their Highmark Health Options contract.

SUMMARY OF LITERATURE

Clostridium difficile is an anaerobic, spore-forming bacillus that is responsible for a spectrum of gastrointestinal illnesses ranging from asymptomatic carriage to toxic megacolon and death. Clostridium difficile infection (CDI) is a disease defined as the acute onset of diarrhea in a patient with documented toxigenic C. difficile or C. difficile toxin, without any other clear cause of diarrhea. The prevalence of CDI is increasing in both hospitalized and community-based inflammatory bowel disease patients.

The incidence of CDI remained static until the mid- to late-1990s. Since 2000, several reports have been issued on the increased incidence and severity of this disease (Warny, 2005). It has been noted that there is an increase in the community-acquired CDI, but reports suggest that this is likely due to underdiagnosed conditions due to the lack of awareness of CDI outside the hospital setting.

It is not clear what causes the C. difficile overgrowth. It appears that there is a disruption of the normal colonic flora, which occurs most often following the administration of oral, parenteral, or topical antibiotics. CDI is treated with antibiotic therapy, but symptoms recur in up to 35% of patients, and up to 65% of patients with recurrence develop a chronic recurrent pattern of CDI (Gough et al., 2011).

According to the Centers for Disease Control and Prevention, C. difficile was estimated to cause nearly half a million infections in the United States, and 29,000 died within 30 days of the initial diagnosis. Those at more risk for acquiring C. difficile are the elderly, young children, and those who have illnesses or conditions that require prolonged use of antibiotics. CDI infection is a costly bacterial illness in hospitalized patients, involving 1% of hospital stays in the United States. The aggregate cost is $8.2 billion annually (Lucado et al., 2013).

One study from the Mayo Clinic looked at C. difficile infections, specifically in children. Of the estimated 13.7 million children hospitalized from 2005 to 2009, the researchers found 46,176 cases – 0.34 percent – had the infection. Children with the infection were of an average age of 3 years old.

The researchers found children with C. difficile were hospitalized on average for six days compared to two days for children without the bacteria. Children with the infection were five times more likely to need a surgical procedure on their colon, called a colectomy, than other hospitalized children. Children with C. difficile were also more than twice as likely to need to be discharged to a long-term care facility and were more than 2.5 times as likely to die as other hospitalized children.

The FMT is the transfer of a liquid suspension of fecal material containing distal gut microbiota from a healthy donor to a patient with CDI. The instillation of the transplant specimen can be accomplished by several methods including colonoscope, endoscope, nasoduodenal/jejunal tube, nasogastric tube, retention enema, sigmoidoscopy, or a combination approach. The goal of FMT is to treat disease by restoring phylogenetic diversity and microbiota more typical of a healthy person.

The American College of Gastroenterology recommends that FMT should be considered second-line therapy for a third recurrence of CDI (Surawicz et al., 2013). In April 2013, the American College of Gastroenterology published a guideline on diagnosis, treatment, and prevention of CDIs.

The guideline addressed FMT for treatment of three or more CDI recurrences, as follows: If there is a third recurrence after a pulsed vancomycin regimen, FMT should be considered. (Conditional recommendation, moderate-quality evidence).

For treatment of one to two CDI recurrences, the guideline recommended: The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however, vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. (Conditional recommendation, low-quality evidence).

The American Gastroenterology Association (AGA) refers physicians to working group guidelines that also recommend consideration of FMT following three failed rounds of antibiotic (Kelly et al. 2015).

The Infectious Diseases Society of America (IDSA) has stated that FMT has been shown to be a superior therapeutic modality for the treatment of recurrent CDI and recommends the procedure in patients with mild to moderate recurrent CDI (Moore, Rodriguez and Bakken, 2013).

Vinta and colleagues (2017) reported the findings of a clinical trial involving 20 patients with ulcerative colitis who received FMT via colonoscopic delivery of 2-donor concentrate. No serious adverse events were noted. Seven patients achieved the primary outcome of clinical response by week 4. Three patients were in remission at week 1, and two of these patients achieved mucosal healing. There were three patients who required escalation of care. The authors concluded that colonoscopic FMT using a 20-donor fecal microbiota preparation (FMP) is safe and effective in achieving clinical response by week 4 in patients with active ulcerative colitis. It was noted that longer-term follow up and correlation with microbial parameters are needed to provide insight into factors influencing clinical outcomes.

Among adults with Clostridium difficile infection that is recurrent or not responsive to treatment, the use of frozen compared with fresh FMT did not result in a significantly lower rate of resolution of diarrhea, indicating that frozen FMT may be a reasonable treatment option for these patients, according to a study (Malani and Rao, 2016).

Fecal microbiota transplantation is proposed as a treatment for recurrent C. difficile infection (CDI) unresponsive to standard therapy and other conditions that are potentially associated with disruption of normal intestinal flora. Several small randomized controlled trials (RCTs) evaluating FMT for CDI have been published. The findings from these trials that compared FMT with standard treatment suggest that FMT is more effective than currently used treatments of recurrent CDI. There are study limitations including a small sample size and open-label design. Although published evidence is limited and questions remain, e.g., about safety, patient selection criteria, and optimal FMT protocol, FMT should be considered medically necessary for treatment of patients with three or more recurrences of CDI.

Few studies have been reported on the efficacy of fecal transplant among pediatric patients. In 2018, the results of a prospective observational pilot study of 15 children, ages 21 months to 18 years, treated by fecal transplant for recurrent CDI (Fareed et al). The authors reported that fecal transplant successfully treated rCDI in all 15 children. There were three patients that received the transplant that continued to experience GI bleeding, however these patients had been diagnosed with underlying inflammatory bowel disease. While the remaining participants showed significantly increased Bacteroidetes levels, the three with underlying disease showed no difference.

In April 2019, an additional systematic review concluded results that found lower cure rates in randomized trials than in open-label and in observational studies (Tariq, R; et al, 2019). According to the systematic review, colonoscopies and oral route are more effective than enema for stool delivery and the efficacy seems to be higher for recurrent than for refractory CDI.

Currently, FMT is being investigated as a treatment for Type 2 diabetes, obesity, and metabolic syndrome, infections with multidrug-resistant organisms, hepatic encephalopathy, inflammatory bowel disease, autoimmune disorders, and pediatric allergy disorders.

The FDA has shown promise for Crohn's disease and ulcerative coloitis but modifying our intestinal microbiome could help address a broad variety of other conditions (Citroner, 2018).

There is insufficient published evidence on the safety and efficacy of fecal transplant for treating conditions other than CDI. Thus, FMT is considered investigational and not medically necessary for all conditions other than recurrent CDI.

As of June 13, 2019, FDA will now require that all stool samples used in transplants to be tested for drug-resistant microorganisms and all donors will need to be screened for potential drug-resistant infections (Kounang, 2019).

POLICY SOURCE(S)

Centers for Disease Control and Prevention (CDC). Healthcare-associated infections: Clostridium Difficile. September 23, 2015. Accessed on August 1, 2017.

Deshpande A, Pasupuleti V, Thota P, et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother. 2013; 68(9):1951–1961. Accessed on August 1, 2017.

Food and Drug Administration (FDA). Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies. July 2013. Accessed on August 3, 2017.

Gough, Shaikh H, & Manges, AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2011 Nov; 53(10): 994-1002. Accessed on August 1, 2017.

Gupta A, Khanna S. Community-acquired Clostridium difficile infection: an increasing public health threat. Infection and Drug Resistance. Dovepress 17 March 2014; 7: 63-72. Accessed on August 1, 2017.

Kelly CR, Kahn S, Kashyap P, Laine L, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. Gastroenterology. July 2015; 149(1): 223-237. Accessed on August 3, 2017.

Kounang, N. FDA issues safety alert over fecal transplants after patient's death. CNN: Health, June 13, 2019. Accessed on June 19, 2019.

Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005; 353(23):2442–2449. Accessed on August 1, 2017.

Lucado J, Gould C, Elixhauser A. Clostridium difficile infections (CDI) in hospital stays, 2009. Healthcare Cost and Utilization Project website. Accessed on August 1, 2017.

Malani PN, Rao Krishna. Expanded evidence for frozen fecal microbiota transplantation for clostridium difficile infection. JAMA, 2016; 315 (2): 137 DOI: 10.1001/jama.2015.18100. Accessed on August 1, 2017.

Moore T, Rodriguez A, Bakken JS. Fecal microbiota transplantation: a practical update for the infectious disease specialist. Clin Infec Dis. 2014 Feb; 58(4): 541-5. Doi: 10.1093/cid/cit950. Epub 2013 Dec 23. Accessed on August 3, 2017.

Openbiome web site. Accessed on August 3, 2017.

Pennsylvania Department of Human Services. Technology Assessment Group Coverage Decisions. Managed Care Operations Memorandum: OPS # 03/2013-003, Option #3. Accessed on July 28, 2017.

Surawicz CM, Brandt LJ, Binion DJ, et al. Guidelines for diagnosis, treatment and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013; 108:478-498. Accessed on August 1, 2017.

Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Eng J Med. Jan 31 2013; 368(5): 407-415. Accessed on August 7, 2017.

Vinita J, Crawford C, Cohen-Mekelburg S, Viladomiu M, Putzel GG, Schneider Y, et al. Single Delivery of High-Diversity Fecal Microbiota Preparation by Colonoscopy Is Safe and Effective in Increasing Microbial Diversity in Active Ulcerative Colitis. Inflammatory Bowel Disease. February 2017; Clinical Poster Presentations. Accessed on August 1, 2017.

Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. Lancet. 2005; 366(9491):1079–1084. Accessed on August 1, 2017.

Holleran G, Scaldaferri F, Ianiro G, et.al. Fecal microbiota transplantation for the treatment of patients with ulcerative colitis and other gastrointestinal conditions beyond Clostridium difficile infection: an update. Drugs Today. 2018 Feb; 54(2):123-136. Doi: 10.1358/dot.2018.54.2.2760765. Accessed July 11, 2017.

McDonald LC, Gerding DN, Johnson J, Bakken JS et.al. Clinical practice guidelines for Clostridium Difficle infection in Adults and Children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clinical Infectious Diseases, Volume 66, Issue7, 19 March 2018, pages e1-e48. Accessed July 12, 2018.

Fareed S, Sarode N, Stewart FJ, Laghale E, Et.al. Applying fecal microbiota transplantation (FMT) to treat recurrent Clostridium infections (rCDI) in children. PeerJ, 2018 May 20.6e4663.eCollection 2018. Accessed on July 12, 2018.

Tariq R, Pardi DS, Bartlett MG, Khanna S. Low Cure Rates in Controlled Trials of Fecal Microbiota

Transplantation for Recurrent Clostridium difficile Infection: A Systematic Review and Meta-analysis. Clin Infect Dis 2019; 68:1351.

Policy History

Date	Activity
08/04/2017	Initial policy developed
03/13/2018	QI/UM Committee approval
04/20/2018	Revision: Removed the word 'Covered' from the procedure and diagnosis code tables in Attachments B & C
05/15/2018	Provider effective date
09/11/2018	Revision: Reorganized criteria in the Procedure section and added documentation requirement of positive stool test; in the Operational Guidelines added medical necessity language; removed the word 'Covered' from the procedure and diagnosis code tables in Attachments B & C; updated Summary of Literature; under Reference section removed hyperlinks to all references.
09/11/2018	QI/UM Committee Review Approval
11/15/2018	Provider effective date
09/10/2019	Annual Review: Added criteria in 1.D. that specifies the testing of stool samples for microorganisms; Added updated FDA regulations to summary of literature; added clinical findings to summary of literature; added references; format revisions; Removed G0455 from procedure codes due to MA fee schedule.
09/10/2019	QI/UM Committee Review Approval
11/04/2019	Provider Effective Date