Corporate Medical Policy

Fecal Microbiota Transplantation

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Origination:	7/2014
Last CAP Review:	11/2019
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Description of Procedure or Service

Fecal microbiota transplantation (FMT) involves the infusion of intestinal microorganisms via transfer of stool from a healthy individual into a diseased individual, with the intent of restoring normal intestinal flora. Fecal transplant is proposed for the treatment of treatment-refractory *Clostridium difficile* infection (CDI), as well as for other conditions including inflammatory bowel disease (IBD).

Background

FMT, also called donor feces infusion, intestinal microbiota transplantation, and fecal bacteriotherapy, involves the infusion of intestinal microorganisms via transfer of stool from a healthy individual into a diseased individual to restore normal intestinal flora. The stool can be infused as a liquid suspension into a patient's upper gastrointestinal tract though a nasogastric tube or gastroscopy, or into the colon through a colonoscope or rectal catheter.

The goal of FMT is to replace damaged and/or disordered native microbiota with a stable community of donor microorganisms. The treatment is based on the premise that an imbalance in the community of microorganisms residing in the gastrointestinal tract (i.e., dysbiosis) is associated with specific disease states, including susceptibility to infection.

The human microbiota, defined as the aggregate of microorganisms (bacteria, fungi, archaea) on and in the human body, is believed to consist of approximately 10-100 trillion cells, approximately 10 times the number of human cells. Most human microbes reside in the intestinal tract and most of these are bacteria. In its healthy state, intestinal microbiota perform a variety of useful functions including aiding in the digestion of carbohydrates, mediating the synthesis of certain vitamins, repressing growth of pathogenic microbes, and stimulating the lymphoid tissue to produce antibodies to pathogens.

To date, the major potential clinical application of fecal microbiota transplantation is treatment of CDI. Infection of the colon with *C difficile* is a major cause of colitis and can cause life-threatening conditions including colonic perforation and toxic megacolon. *C difficile* occurs naturally in intestinal flora. The incidence of CDI in North America has increased substantially. For example, according to hospital discharge diagnosis data, there were more than 300,000 cases of CDI in 2006, compared with fewer than 150,000 cases in 2000. Moreover, CDI causes an estimated 15,000 to 20,000 deaths per year in U.S. hospitals.

It is unclear what causes *C difficile* overgrowth, but disruption of the normal colonic flora in conjunction with colonization by *C difficile* are major components. Disruption of the normal colonic flora occurs most commonly following administration of oral, parenteral or topical antibiotics. Standard treatment for CDI is antibiotic therapy. However, symptoms recur in up to

35% of patients and up to 65% of patients with recurrences develop a chronic recurrent pattern of CDI.

Other potential uses of fecal microbiota transplant include treatment of conditions in which altered colonic flora may play a role. These include IBD, irritable bowel syndrome, idiopathic constipation and non-gastrointestinal disease such as multiple sclerosis, obesity, autism and chronic fatigue syndrome. However, for these conditions, the contribution of alterations in colonic flora to the disorder is uncertain or controversial.

There is interest in alternatives to human feces that might have the same beneficial effects on intestinal microbiota without the risks of disease transmission. A proof of principle study was published in 2013 that evaluated a synthetic stool product in 2 patients with recurrent CDI. The product is made from 33 bacterial isolates that were developed from culturing stool from a healthy donor.

Regulatory Status

In 2016, the U.S. Food and Drug Administration (FDA) issued draft guidance regarding investigational new drug requirements for use of fecal microbiota transplant to treat CDI not responsive to medication therapy. The draft guidance is similar to the 2013 guidance and states that the FDA is continuing to consider how to regulate fecal microbiota transplant and that, during this interim period, the agency will use enforcement discretion regarding use of fecal transplant to treat treatment-resistant CDI infections. FDA requires that physicians obtain adequate informed consent from patients or their legal representative before performing the intervention. The document also states that selective enforcement does not apply to use of fecal transplant for treating conditions other than treatment-resistant CDI.

Related Guideline
Fecal Analysis in the Diagnosis of Intestinal Dysbiosis AHS – G2060

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for fecal microbiota transplantation when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Fecal Microbiota Transplantation is covered

Fecal microbiota transplantation may be considered medically necessary for treatment of patients with recurrent *Clostridium difficile* infection under the following conditions:

- There has been a relapse after at least 3 episodes of mild-to-moderate C. difficile infection (CDI) or at least 2 episodes of severe CDI; AND
- Episodes are refractory to appropriate antibiotic regimens, including at least one regimen of pulsed vancomycin.

When Fecal Microbiota Transplantation is not covered

Fecal microbiota transplantation is considered investigational in all other situations.

Policy Guidelines

The evidence for patients who have recurrent Clostridium difficile infection (CDI) refractory to antibiotic therapy who receive FMT, includes randomized controlled trials (RCTs), multiple systematic reviews, and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Findings of the trial that compared fecal microbiota transplantation (FMT) with standard treatment suggest that FMT is more effective for recurrent CDI. Other RCTs did not find the superiority of any route of administration over another or the superiority of fresh versus frozen feces. Case reports and case series report a high rate of resolution of recurrent CDI following treatment with FMT. Few treatment-related adverse events have been reported. The evidence is sufficient to determine qualitatively that the treatment results in meaningful improvements in the net health outcome.

The evidence for FMT in patients who have inflammatory bowel disease (IBD) includes a large-scale systematic review and meta-analysis, 2 RCTs in patients with ulcerative colitis, as well as observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Two small RCTs on FMT for treatment of ulcerative colitis were discontinued due to futility, and data from already enrolled patients were analyzed. One trial found a statistically significantly higher remission rate after active FMT compared with a control intervention, but this trial had few patients in remission (n=11) and short follow-up (7 weeks). The other trial reported no difference in remission rates. Data on a small number of patients with Crohn disease are available; there are no controlled studies of FMT in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for FMT in patients who have acute CDI, pouchitis, irritable bowel syndrome, constipation, or metabolic syndrome includes a small number of case series and/or case reports. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. Data are available for only small numbers of patients and there is a lack of comparative studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

Among the two published randomized controlled trials evaluating FMT for treatment of Clostridium difficile infection (CDI), the van Nood study (2013) included patients with at least 1 recurrence of CDI and the Youngster study (2014) included patients with a relapse after at least 3 episodes of mild-to-moderate CDI or at least 2 episodes of severe CDI.

There is an RCT studying the efficacy, safety and durability of FMT in individuals with slow transit constipation. That trial is currently on-going.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *44705, G0455*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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. Available online at: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM361393.pdf. Last accessed June, 2014.

American College of Gastroenterology (ACG). Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Available online at: http://gi.org/guideline/diagnosis-and-management-of-c-difficile-associated-diarrhea-and-colitis/. Last accessed June, 2014.

BCBSA Medical Policy Reference Manual [Electronic Version]. 5/22/14

BCBSA Medical Policy Manual [Electronic Version] – 2.01.92, 4/23/15

Specialty Matched Consultant Advisory Panel review 11/2015

Senior Medical Director review 11/2015

BCBSA Medical Policy Manual [Electronic Version] – 2.01.92, 11/12/15

Specialty Matched Consultant Advisory Panel review 11/2016

Medical Director review 11/2016

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van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med. Jan 31 2013;368(5):407-415. PMID 23323867

Youngster I, Sauk J, Pindar C, et al. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clin Infect Dis. Jun 2014;58(11):1515-1522. PMID 24762631

Specialty Matched Consultant Advisory Panel review 11/2017

Medical Director review 11/2017

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Specialty Matched Consultant Advisory Panel review 11/2018

Medical Director review 11/2018

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Specialty Matched Consultant Advisory Panel review 11/2019

Medical Director review 11/2019

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Policy Implementation/Update Information

7/15/14 New policy developed. Fecal Microbiota Transplantation may be considered medically necessary for patients who meet criteria (i.e. at least 3 episodes of recurrent C. difficile infection and episodes are refractory to appropriate antibiotic regimens, including at least one regimen of pulsed Vancomycin. Fecal Microbiota Transplantation is considered investigational for all other situations. Senior Medical Director review. (sk)

12/30/15 References updated. Specialty Matched Consultant Advisory Panel review 11/2015. Senior Medical Director review 11/2015. (td)

1/26/16 Policy Guidelines section revised. References updated. (td)

12/30/16 Policy Statement revised, adding coverage when there has been a relapse after at least 3 episodes of mild-to-moderate C. difficile infection (CDI) or at least 2 episodes of severe CDI. Policy Guidelines updated to reflect the two published RCTs pertinent to the revised policy statement. References updated. Specialty Matched Consultant Advisory Panel review 11/2016. Medical Director review 11/2016. (jd)

12/15/17 References updated. Specialty Matched Consultant Advisory Panel review 11/2017. Medical Director review 11/2017. (jd)

12/14/18 References updated. Specialty Matched Consultant Advisory Panel review 11/2018. Medical Director review 11/2018. (jd)

2/25/20 Minor revisions to description, related policies, and policy guidelines. References updated. Specialty Matched Consultant Advisory Panel review 11/2019. Medical Director review 11/2019. (jd)