Fecal Microbiota Transplantation

Policy # 00441
Original Effective Date: 08/20/2014
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider fecal microbiota transplantation (FMT) for treatment of patients with recurrent Clostridium difficile infection (CDI) to be eligible for coverage. (See Background/Overview)

Patient Selection Criteria
Coverage eligibility may be considered for fecal microbiota transplantation (FMT) for treatment of patients with recurrent Clostridium difficile infection (CDI) when all of the following criteria are met:
- Episodes are refractory to appropriate antibiotic regimens, including at least 1 regimen of pulsed vancomycin.
- There have been at least 2 episodes of recurrent infection; and
- Episodes are refractory to appropriate antibiotic regimens, including at least 1 regimen of pulsed vancomycin.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers fecal microbiota transplantation (FMT) in all other situations to be investigational.*

The use of fecal microbiota transplantation (FMT) for treatment of patients with recurrent Clostridium difficile infection (CDI) when patient selection criteria are not met is considered to be investigational.*

Background/Overview
Fecal microbiota transplantation involves the infusion of intestinal microorganisms via transfer of stool from a healthy person into a diseased patient, with the intent of restoring normal intestinal flora. Fecal transplant is proposed for the treatment of treatment-refractory CDI, as well as for other conditions including inflammatory bowel disease (IBD).

Fecal microbiota transplantation, 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
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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 (ie, 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 to 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 FMT 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 in the past decade. 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 nongastrointestinal 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.

Among the 2 published randomized controlled trials (RCTs) evaluating FMT for treatment of CDI, the van Nood study included patients with at least 1 recurrence of CDI, and the Youngster study included patients with a relapse after at least 3 episodes of mild-to-moderate CDI or at least 2 episodes of severe CDI. (Both studies are described in the Rationale section).
The American College of Gastroenterology recommends that FMT should be considered second-line therapy for a third recurrence of CDI.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

In July 2013, the FDA issued guidance regarding investigational new drug requirements for use of FMT to treat CDI not responsive to medication therapy. The document states that FDA is continuing to consider how to regulate FMT and that, during this interim period, the agency will use enforcement discretion regarding use of fecal transplant to treat treatment-resistant CDI infections. The 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.

Centers for Medicare and Medicaid Services (CMS)

There is no national coverage determination (NCD).

**Rationale/Source**

**Recurrent Clostridium Difficile Infection**

The available literature consists of 2 RCTs and numerous case series or case reports. Other than a few case reports of patients with acute CDI, studies treated patients with recurrent infection.

**Randomized Controlled Trials**

The first RCT that evaluated FMT was published in 2013. This nonblinded study, by van Nood et al in the Netherlands, included 43 patients 18 years and older with at least 1 recurrence of CDI. Exclusion criteria included prolonged compromised immunity, admission to an intensive care unit, and need for vasopressor medication.

Patients were randomized to 1 of 3 treatment groups: (1) fecal microbiota transplantation (FMT, here called donor feces infusion) (n=17); (2) antibiotic therapy (n=13); or (3) antibiotics and bowel lavage (n=13). The FMT intervention involved collecting feces from healthy screened donors on the day of infusion, diluting the feces with 500 mL of sterile saline and infusing the solution (mean, 141 g) through a nasoduodenal tube. Patients assigned to the FMT group also received a modified course of vancomycin (500 mg orally 4 times a day for 4-5 days) and bowel lavage before infusion. A second infusion was given to patients in the FMT group who had a relapse after the first treatment. Potential donors underwent an evaluation process that included completing a questionnaire on potential risk factors for transmissible diseases, screening feces for parasites, and screening blood for antibodies for viruses. The study was initially designed to include 120 patients (40 per group), but, because of the high relapse rate in the control groups, the data and safety monitoring group recommended early termination of the trial.

The primary efficacy outcome was cure without relapse within 10 weeks of initiating treatment. Cure was defined as absence of diarrhea that could not be explained by other causes and 3 consecutive negative tests for CDI toxin. Relapse was defined as diarrhea with a positive stool test for CDI toxin during this 10-
week period. For the 3 patients who received a second infusion, follow-up was extended to 10 weeks after the second treatment. Patients were questioned about symptoms of diarrhea, and stool tests were performed on days 14, 21, 35, and 70 and when diarrhea was reported. One patient in the FMT group was excluded from analysis.

A total of 15 of 16 patients (94%) of analyzed patients in the FMT group were cured: 13 after a single infusion and another 2 after a second infusion from a different donor. In contrast, only 4 of 13 patients (31%) in the antibiotics-only group and 3 of 13 patients (23%) in the antibiotics and bowel lavage group were cured. The overall cure rate was significantly higher in the FMT group compared with the other 2 groups (p<0.001). Most patients in the FMT group experienced short-term adverse events (ie, diarrhea in 94%, cramping in 31%, belching in 19%) that resolved within 3 hours.

Data on the diversity of fecal microbiota were available for 9 patients in the FMT group. Diversity was measured on a scale ranging from 1 to 250, with higher values indicating more diversity. Before infusion, mean microbiota diversity was low (mean, 57, SD=26). Within 2 weeks of infusion, diversity increased to a mean of 179 (SD=42), a level similar to the diversity levels in the donors (mean=172, SD=54).

A second RCT, published by Youngster et al in 2014, compared infusion of donor stools by colonoscopy or nasogastric tube. A total of 20 patients with relapsing and recurrent CDI were included. Patients needed to have a relapse of CDI following at least 3 episodes of mild-to-moderate CDI and failure of a course of vancomycin or at least 2 episodes of severe CDI that resulted in hospitalization and was associated with significant morbidity. All patients underwent FMT and were randomized to 1 of 2 infusion routes, colonoscopy or a nasogastric tube. Both groups had 90 mL thawed inoculum. Stool donors were healthy nonrelatives who successfully completed an extensive screening process. Stool was frozen up to 156 days before use. Patients could receive a second FMT if symptoms did not resolve following the initial transplant. The primary efficacy outcome was clinical cure, defined as resolution of diarrhea (ie, <3 bowel movements per 24 hours) while off antibiotics for CDI, without relapse for 8 weeks. Fourteen patients were cured after the first FMT, 8 in the colonoscopy group and 6 in the nasogastric tube group; the difference between groups was not statistically significant (p=0.628). Of the remaining 6 patients, 1 refused additional treatment and the other 5 underwent a second transplant. According to the study protocol, patients could choose the route of administration for the second procedure, and all of them chose the nasogastric tube. Four additional patients were cured after the second transplant, for an overall cure rate of 18 of 20 (90%). This study did not find that either route of administration of donor feces was superior to the other, but patients preferred use of a nasogastric tube.

Uncontrolled Studies
Several systematic reviews of uncontrolled studies on FMT for treating CDI have been published. Of these, only Sofi et al conducted a pooled data analysis. The investigators searched the literature through April 2012. The authors did not identify any RCTs that evaluated FMT (their literature search was conducted before publication of a 2013 RCT, discussed next). A total of 25 observational studies (10 case reports, 15 case series) provided data on 239 adult patients treated with fecal microbiota transplants for CDI. All of the case series were retrospective, and sample sizes ranged from 4 to 70 patients; only 4 studies included...
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more than 25 patients. Most studies included recurrent CDI, but several case reports treated patients who were severely ill due to acute CDI. Fecal transplants were performed by the gastroduodenal route in 91 patients (32%) and by the colonic route in 198 (68%) patients. Treatment success was defined as resolution of CDI symptoms at follow-up. Mean follow-up posttransplant ranged from 10 days to 65 months. In a pooled analysis of individual patient data, the overall treatment success rate was 91.2%. Subanalyses revealed a significantly higher treatment failure rate in patients treated by the colonic versus the duodenal route and patients with symptoms for at least 60 days versus less than 60 days.

A 2014 retrospective case series included 94 patients with refractory or recurrent CDI who underwent 1 or more FMT via retention enema. Cure was defined as no recurrence of diarrhea in the 6 months after treatment. A total of 45 of 94 patients (48%) were cured following a single FMT. When 4 or more FMTs were administered, the cure rate was 86.2%, and this increased further to 91.5% when antibiotics were administered between FMTs.

Section Summary
One small RCT, which enrolled patients who had failed at least 1 course of antibiotic treatment, reported a large increase in resolution of *C difficile* with FMT plus antibiotics compared with antibiotics alone with or without bowel lavage. A second RCT compared different modes of administration and did not find a significant difference in fecal transplantation via colonoscopy or nasogastric tube. This study also reported a high overall CDI cure rate, but did not have a medical treatment control group. Case reports and case series report a high rate of resolution of CDI following treatment with FMT. Further studies are needed to determine the optimal patient selection criteria and treatment protocol for this therapy.

Inflammatory Bowel Disease
In 2012, Anderson et al published a systematic review of the available literature on fecal microbiota transplant for treatment of IBD. The investigators searched for published studies and conference abstracts in any language reporting on patients with IBD treated with fecal transplants for IBD symptoms or infectious diarrhea. A total of 17 studies with 41 patients met the review's inclusion criteria. None of the studies were controlled; all were case reports or case series. Nine articles reported on 26 patients (18 with ulcerative colitis, 6 with Crohn disease, 2 with undefined IBD) who received fecal microbiota transplants because their IBD was resistant to standard management. The other 8 articles included 15 patients (9 with ulcerative colitis, 6 with Crohn disease) whose primary indication for fecal transplant was recurrent CDI.

Outcome data were reported for 17 of the 26 patients being treated for IBD. Thirteen of 17 (76%) patients stopped IBD medications within 6 weeks. Data on IBD symptoms before and after the procedure were available for 16 patients. All of these reported a reduction or resolution of IBD symptoms within 4 months of receiving fecal transplants, and 15 reported complete resolution of symptoms within a year. Three of 13 patients reported no disease recurrence at long-term follow-up (which was 3-6 months in 15 patients and 1-13 years in 12 patients).
Section Summary
Data are available on only a small number of patients with IBD treated with fecal microbiota transplant and there is a lack of controlled studies. Improvements in IBD symptoms have been reported, but further controlled studies in larger numbers of patients are needed to establish efficacy.

Ongoing Clinical Trials
A search of online clinicaltrials.gov database in March 2014 found a number of ongoing RCTS evaluating fecal microbiota transplant. These trials can be grouped into several categories, as follows:

Evaluating fecal microbiota transplant as a treatment for recurrent CDI:

- **Stool Transplant in Pediatric Patients With Recurring C Difficile Infection (NCT01972334):** Double-blind RCT comparing fecal transplant to a placebo procedure in children (age 8-18 years) with recurrent CDI. Estimated enrollment is 46 patients.

- **Oral Vancomycin Followed by Fecal Transplant Versus Tapering Oral Vancomycin (NCT01226992):** Nonblinded RCT to compare 2 weeks of oral vancomycin treatment followed by single-dose fecal transplant via rectal enema with 2 weeks of oral vancomycin treatment followed by tapering of vancomycin. Estimated enrollment is 146 patients.

Evaluating fecal microbiota transplant as a treatment for other conditions:

- **Fecal Biotherapy for the Induction of Remission in Active Ulcerative Colitis (NCT01545908):** Double-blind RCT to compare 6 weekly fecal transplant enemas with placebo enemas in patients with ulcerative colitis. Estimated enrollment is 130 patients.

- **Standardized Fecal Microbiota Transplantation for Crohn Diseases (NCT01793831):** Nonblinded RCT to compare a single fecal transplant procedure with standard medical care in patients with ulcerative colitis or Crohn disease. Estimated enrollment is 30 patients.

Evaluating technical aspects of the transplant procedure:

- **Multi-Centre Trial of Fresh vs. Frozen-and-Thawed HB T(Fecal Transplant)for Recurrent CDI (NCT01398969):** Double-blind RCT to compare an enema of fresh human fecal bacteriotherapy and frozen-and-thawed fecal bacteriotherapy. The study includes patients with recurrent CDI. Estimated enrollment is 136 patients.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers
In response to requests, input was received through 5 clinicians at 2 academic medical centers and 5 clinicians associated with 3 physician specialty societies when this policy was under review in 2014. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. There was near-consensus agreement that fecal transplantation may be considered medically necessary for treating at least some patients with CDI. In addition, there was
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near-consensus that FMT is considered investigational for IBDs and consensus that it is considered investigational for conditions other than those previously mentioned. Input was mixed on criteria to use for selecting patients with CDI for fecal transplantation; in general, number of recurrences was considered an important criterion. There was near consensus among reviewers that there are potential safety concerns associated with FMT and that these should be studied further before the procedure is offered routinely in clinical practice.

Summary
Fecal microbiota transplantation is proposed as a treatment of recurrent CDI unresponsive to standard therapy and other conditions that are potentially associated with disruption of normal intestinal flora. Two small RCTs evaluating FMT for CDI has been published. Findings of the trial that compared FMT with standard treatment suggest that FMT is more effective than currently used treatments of recurrent CDI. However, the study had limitations including a small sample size and open-label design. The other RCT did not find a significant difference in efficacy when donor feces was administered via colonoscopy or nasogastric tube. Although published evidence is limited and questions remain eg, about safety, patient selection criteria optimal FMT protocol, due to support from the available evidence and clinical reviewers, FMT may be considered medically necessary for treatment of patients with 3 or more recurrences of CDI.

There is insufficient published evidence on the safety and efficacy of fecal transplant for treating conditions other than CDI, such as IBD. Thus, FMT is considered investigational for all conditions other than recurrent CDI.

References
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**Policy History**

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08/07/2014 Medical Policy Committee review
08/20/2014 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 08/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means
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of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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