Protocol

Fecal Microbiota Transplantation

(20192)

Medical Benefit		**Effective Date**: 10/01/14	**Next Review Date**: 07/19
Preauthorization	Yes	**Review Dates**: 07/14, 07/15, 07/16, 07/17, 07/18	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With recurrent *Clostridium difficile* infection refractory to antibiotic therapy	Interventions of interest are: • Fecal microbiota transplantation	Comparators of interest are: • Standard antibiotic regimens	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity
Individuals: • With inflammatory bowel disease	Interventions of interest are: • Fecal microbiota transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity
Individuals: • With pouchitis, irritable bowel syndrome, constipation, or metabolic syndrome	Interventions of interest are: • Fecal microbiota transplantation	Comparators of interest are: • Standard of care	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity

DESCRIPTION

Fecal microbiota transplantation (FMT) 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 treatment-refractory Clostridium difficile infection (CDI) and other conditions, including inflammatory bowel disease.

SUMMARY OF EVIDENCE

For individuals who have recurrent CDI refractory to antibiotic therapy who receive FMT, the evidence includes randomized controlled trials (RCTs) and observational studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. The RCTs found that FMT was more effective than standard treatment or placebo for patients with recurrent CDI. Other RCTs did not find the superiority of any route of administration over another or the superiority of fresh vs. frozen feces. Case reports and case series have reported high rates of resolution of recurrent CDI following treatment with FMT. Few treatment-related adverse events have been reported. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have inflammatory bowel disease who receive FMT, the evidence includes two 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 poor data analysis for patients already enrolled. Of the two small RCTs, one found a statistically significant higher remission rate after active FMT than after a control intervention, but this trial had few patients in remission (n=11) and short follow-up (seven weeks); the other trial reported no difference in remission rates. Data on a small number of patients with Crohn disease are available; however, there are no controlled studies of FMT in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pouchitis, irritable bowel syndrome, constipation, or metabolic syndrome who receive FMT, the evidence 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 a limited number of patients, and there is a lack comparative studies. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

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

- There have been at least three episodes of recurrent infection; AND
- Episodes are refractory to appropriate antibiotic regimens, including at least one regimen of pulsed vancomycin.

Fecal microbiota transplantation is considered **investigational** in all other situations.

POLICY GUIDELINES

There is a lack of consensus on the number of recurrences that warrants consideration of FMT.

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 one recurrence of CDI; the other study, the Youngster study (2014), included patients with a relapse after at least three episodes of mild-to-moderate CDI or at least two episodes of severe CDI.

The 2013 American College of Gastroenterology guidelines recommended that FMT be considered second-line therapy for a third recurrence of CDI.

BACKGROUND

FECAL MICROBIOTA

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 the stool can be infused 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 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 the growth of pathogenic microbes, and stimulating the lymphoid tissue to produce antibodies to pathogens.

Applications

Clostridium difficile Infection

To date, the major potential clinical application of FMT is the 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.[1, 2]

It is unclear what causes C. difficile overgrowth, but disruption of the normal colonic flora and 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.[3]

Other Applications

Other potential uses of FMT include treatment of conditions in which altered colonic flora may play a role. They include inflammatory bowel disease, 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, published in 2013, evaluated a synthetic stool product in two patients with recurrent CDI.[4] The product is made from 33 bacterial isolates developed from culturing stool from a healthy donor.

REGULATORY STATUS

In July 2013, the U.S. Food and Drug Administration (FDA) issued guidance on investigational new drug requirements for the use of FMT to treat CDI not responsive to medication therapy.[5] The FDA guidance stated that the FDA is continuing to consider how to regulate FMT and that, during this interim period, the agency will use enforcement discretion regarding the 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 noted that selective enforcement does not apply to use of fecal transplant for treating conditions other than treatment-resistant CDI.

RELATED PROTOCOL

Fecal Analysis in the Diagnosis of Intestinal Dysbiosis

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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