Clinical Policy Title: Fecal transplantation for the treatment of clostridium difficile infection

Clinical policy number: 08.02.02

Effective Date: October 1, 2014
Initial Review Date: June 18, 2014
Most Recent Review Date: June 15, 2016
Next Review Date: June 2017

Policy contains:
- Fecal microbiota transplantation (FMT).
- Treatment of Clostridium difficile infection.

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of fecal microbiota transplantation (FMT) therapy for *Clostridium difficile* infection (CDI) to be clinically proven and, therefore, medically necessary when both of the following criteria are met:

- Confirmed positive stool for CDI.
- Failure of appropriate antibiotic therapy.

**Example of appropriate recommended regimen of antibiotic therapy**

- Metronidazole 500 mg three times daily or 250 mg four times daily for 10 to 14 days; intravenous metronidazole at a dose of 500 mg every eight hours may also be used for treatment of CDI in patients for whom oral therapy is not feasible.
- Oral vancomycin, 125mg four times daily for 10 – 14 days, followed by 125mg daily pulsed every three days for 10 doses (Curry 2009).
- If there is a third recurrence after a pulsed vancomycin regimen, FMT should be considered.
Limitations:

All other uses of FMT are not medically necessary, including but not limited to:

- Ulcerative colitis.
- Crohn's disease.
- Irritable bowel syndrome.
- Inflammatory bowel diseases.
- Idiopathic constipation.
- Other gastrointestinal functional diseases.
- Non-gastrointestinal diseases.

NOTE: The following codes are not included in the Medicaid medical fee schedule in Pennsylvania

44705 - Preparation of fecal microbia for instillation, including assessment of donor specimen

Alternative covered services:

- Primary physician office visits.
- Gastroenterologist visits.
- Other therapeutic options for CDI are being developed, and drugs used for other infections are being studied as alternatives to metronidazole and vancomycin.

Background

Clostridium difficile (C. difficile or C. diff) is a Gram-positive, spore-forming bacteria that produces enterotoxin (toxin A), cytotoxin (toxin B), and binary toxin responsible for diarrhea and inflammation in infected patients. It is the most important and common nosocomial pathogen of health care-associated diarrhea in hospitalized patients in developed countries and causes millions of human infections worldwide annually. It is the cause of at least 25 percent of all cases of antibiotic-associated diarrhea and accounts for nearly all cases of pseudomembranous colitis. CDI can cause a wide range of diseases, from mild diarrhea to life-threatening complications, especially in the elderly. Patients with CDI typically have extended lengths of stay in hospitals, and CDI is a frequent cause of large hospital outbreaks of disease.

There is growing recognition that CDI may occur and recur because antibiotics perturb patients' intestinal microflora, now called the microbiome. When the microbiome is altered unfavorably, patients are in a state of dysbiosis, and the community of living organisms in the intestine will no longer be able to protect the host against CDI. By reintroducing a healthy diversity of bacteria, fecal transplantation can re-establish colonization resistance to prevent C. difficile from gaining a foothold and becoming a dominant organism in the environment of the gut.

FMT, also known as fecal bacteriotherapy, fecal microbiota reconstitution, and human probiotic infusion, is the process of instilling a liquid suspension of stool from a healthy donor into the patient’s upper gastrointestinal tract through a nasogastric/nasoduodenal catheter or gastroscopy, or into the colon through a colonoscopy or rectal catheter. The current rationale for using FMT for CDI is that introducing microbes from a healthy donor will allow restoration of a normal microbial community in the diseased host with consequent suppression of C. difficile colonization and disease pathogenesis.
The first clinical use of FMT reported in English-language publications was a 1958 case series of four patients with pseudomembranous enterocolitis, three of whom were critically ill. *C. difficile* had not yet been recognized as a cause of pseudomembranous colitis and *Micrococcus pyogenes* (hemolytic, coagulase-positive *Staphylococcus aureus*) was cultured from each patient’s stool. Fecal enemas were administered as an adjunct to antibiotic treatment and all four patients had “dramatic” resolution of symptoms within 24 – 48 hours of FMT.

The first case of confirmed CDI treated with FMT was reported in 1983, and treatment was curative (Schwan, 1983). Until 1989, retention enemas were the most common technique for FMT. Alternative methods for delivering FMT have included fecal infusion via duodenal tube (1991), rectal tube (1994), and colonoscopy (1998). FMT for recurrent CDI has been administered by nasogastric tube, colonoscopy, and rectal tube, including self-administration at home by enema.

Increasingly, interest is emerging in the changes in the intestinal microbiota associated with CDI. In 2008, Chang et al. constructed small (< 200 sequences per subject) 16S rRNA gene libraries from the stools of four patients with first-time CDI and three patients with recurrent CDI (Chang, 2008). Based on 16S rRNA gene classification, they found the fecal microbiomes of patients with an initial episode of CDI were similar at the phylum level to healthy subjects (i.e., the majority of sequences belonged to dominant fecal phyla *Bacteroidetes* and *Firmicutes*), while they observed a major reduction or loss of *Bacteroidetes* in patients with recurrent CDI. The loss of the *Bacteroidetes* was accompanied by the expansion of other phyla, including *Proteobacteria* and *Verrucomicrobia*, normally minor constituents of the fecal microbiota.

Khoruts et al. compared the microbiota of a patient with recurrent CDI before and after FMT using terminal-restriction fragment-length polymorphism and clone-based 16S rRNA gene sequencing (Khoruts, 2010). Before transplantation, the patient's microbiota were deficient in members of *Bacteroides* and instead comprised atypical fecal genera such as *Veillonella*, *Clostridium*, *Lactobacillus*, *Streptococcus*, and unclassified bacteria similar to *Erysipelothrix*. Two weeks after infusion of donor fecal suspension, the bacterial composition of the feces approached normal and was dominated by *Bacteroides* sp. strains.

In 1989, Tvede and Rask-Madsen used a combination of nine normal fecal organisms to treat six patients with chronic relapsing *C. difficile* diarrhea (Tvede, 1989). These investigators cultivated 10 strains of bacteria, including *Enterococcus* (*Streptococcus* faecalis (1108-2), *Clostridium innocuum* (A27-24), *Clostridium ramosum* (A31-3), *Bacteroides ovatus* (A40-4), *Bacteroides vulgatus* (A33-14), *Bacteroides thetaiaotaomicron* (A33-12), *Escherichia coli* (1109 and 1108-1), *Clostridium bifermentans* (A27-6), and *Blautia producta* (*Peptostreptococcus productus*) (1108-2), in broth for 48 hours to a concentration of approximately $10^9$ bacteria/mL. Two mL from each bacterial culture were admixed with 180 mL saline that had been pretreated in an anaerobic chamber for 24 hours; the bacterial suspension was then instilled rectally. This procedure was followed promptly by a decline of *C. difficile* to undetectable levels by culture and the loss of detectable toxin from the stool. Normal bowel function was restored within 24 hours, and abdominal symptoms disappeared. Stool cultures and toxin assays for *C. difficile* remained negative during a year of follow-up. It is especially important to note that feces from none of the six patients contained *Bacteroides* sp. These results suggest FMT may restore both the structure and function of the normal microbiome present, breaking the cycle of recurrent *C. difficile*-associated disease (CDAD), usually after treatment with pulsed or tapered vancomycin therapy has failed.

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
• Agency for Healthcare Research and Quality Guideline Clearinghouse and evidence-based practice centers.
• The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on May 11, 2016. Search terms were: “fecal transplantation, C. difficile” and “bacteriotherapy.”

We included were:
• Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
• Guidelines based on systematic reviews.
• Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

The clearest indication for FMT is recurrent or refractory disease, but this is not universally accepted as many await confirmation from randomized controlled trials (RCTs). In the only long-term follow-up of FMT to date, a five-medical center cross-country joint effort followed 77 patients who had FMT for more than three months. The patients experienced a 91 percent primary cure rate and a 98 percent secondary cure rate, the latter defined as a cure enabled by the use of antibiotics to which the patient hadn’t responded before the FMT, or by a second FMT. It is interesting that 97 percent of these patients stated they would have another FMT were they to develop CDI again, and 58 percent said they would choose to have FMT rather than antibiotics. It is not unusual for patients to develop some gastrointestinal complaints or altered bowel habits for several days after FMT, including absence of bowel movement, abdominal cramping, gurgling bowel sounds and/or increased gas. Of the 77 subjects in this study, four developed an autoimmune disease (rheumatoid arthritis, Sjogren syndrome, idiopathic thrombocytopenic purpura or peripheral neuropathy) at some point after the FMT, though a clear relationship between the new disease and FMT was not evident. These results and clinical experience suggest FMT can correct the dysbiosis that characterizes chronic CDI and effect a seemingly safe, relatively inexpensive and rapidly effective cure in the vast majority of patients.

In addition, FMT has been proposed as a treatment of other gastrointestinal and non-gastrointestinal disorders, although experience in these other non-CDI diseases is in its infancy. It may have a role as first-line treatment for patients with CDI rather than antibiotics because of its rapid effect, minimal risk, relatively low cost, and reestablishment of a “balanced” colonic microbiota. FMT has been used to treat patients with severe CDI manifested by toxic megacolon or ileus; in these patients, abdominal distention, fever, and white blood cell count decreased and relief from discomfort increased, occasionally within hours of the procedure. In none of these cases was the patient’s condition or course of disease worsened by FMT. More research is needed with FMT to ensure its safety and optimal route of administration. Future studies are certain to narrow the spectrum of organisms that need to be given to patients to cure the disease.
Summary of clinical evidence:

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                        |  - Results: No controlled studies were found. Based on the weak evidence from seven full-text case series studies of 124 patients with recurrent/refractory CDAD, FMT appears to be a safe and effective procedure. In most cases (83%), symptoms improved immediately after the first FMT procedure, and some patients stayed diarrhea-free for several months or years.  
                        |  - Conclusions: Although these results appear promising, the treatment effects of FMT cannot be determined definitively in the absence of a control group. Results from RCTs that compare FMT to oral vancomycin with or without a taper regimen will help better define the role of FMT in the management of recurrent CDAD. |
| Kassam (2012)             | Key points:<br>  - Systematic review and meta-analysis with robust methods to determine the efficacy and safety profile of FMT in CDI. Studies that used FMT via any delivery modality for laboratory or endoscopically proven CDI with clinical resolution as primary outcome were included. A sample size of 10 or more patients was a further criterion.  
                        |  - Results: Eleven studies with a total of 273 CDI patients treated with FMT were identified; no RCTs were found, as none have been published. Two-hundred and forty-five out of 273 patients experienced clinical resolution (UPR 89.7%; WPR 89.1% [95% CI 84 to 93%]). There was no statistically significant heterogeneity between studies (Cochran Q test P = 0.13, I² = 33.7%). A priori subgroup analysis suggested lower gastrointestinal FMT delivery (UPR 91.4%; WPR 91.2% [95% CI 86 to 95%]) led to a trend toward higher clinical resolution rates than the upper gastrointestinal route (UPR 82.3%; WPR 80.6% [95% CI 69-90%]) (proportion difference of WPR was 10.6% [95% CI -0.6 to 22%]). No difference in clinical outcomes was detected between anonymous vs. patient-selected donors. No reported adverse events were associated with FMT and follow-up was variable from weeks to years.  
                        |  - Conclusions: FMT holds considerable promise as a therapy for recurrent CDI, but well-designed RCTs and long-term follow-up registries are still required. These are needed to identify the right patient, efficacy and safety profile of FMT before this approach can be widely advocated. |
| Postigo (2013)            | Key points:<br>  - A review and pooled analysis of treatment efficacy for articles published up to December 2011. Studies that reported cases of FMT for recurrent CDI using either colonoscopy or NGT-guided fecal infusion were reviewed.  
                        |  - Results: A total of 182 patients from 12 published studies were identified; 148 patients received FMT via colonoscopy (colonoscopy group) and 34 patients received FMT via NGT (NGT group). The median age in the colonoscopy group compared with the NGT group was 72 and 82 years, respectively. There were differences regarding pre-FMT treatment for CDI: 134 patients (90.5%, 134/148) received lavage with/without antibiotic in the colonoscopy group and 34 patients (100.0%, 34/34) received antibiotic without lavage in the NGT group, P < 0.001. A higher stool volume was used for FMT in the colonoscopy group (121 patients, 81.8%, used 100 – 400 ml) than in the NGT group (33 patients, 97.0%, used <100 ml), P < 0.001. The treatment efficacy did not differ significantly: 93.2% (138/148) success for the colonoscopy group compared to 85.3% success (29/34) for the |
NGT group, P = 0.162. Recurrence of CDI after FMT was also similar in both the colonoscopy group (8/148 5.4%) versus the NGT group (2/34, 5.9%), P = 1.000.

- Conclusions: Despite procedural differences, FMT via colonoscopy or NGT appears to be highly effective and safe for the management of recurrent CDI.

Policy updates

AmeriHealth Caritas Pennsylvania identified two new systematic reviews and one evidence-based guideline for this policy. Both systematic reviews found FMT was associated with symptom resolution of recurrent CDI but its role in primary and severe CDI has not been established (Bagdasarian, 2015; Sha, 2014). Existing research in pediatric populations consists of seven publications reporting a total of 11 patients with chronic constipation, recurrent CDI, or ulcerative colitis (Sha 2014). The European Society of Clinical Microbiology and Infectious Diseases updated its CDI treatment guidance, issuing a strong recommendation for FMT for multiple recurrent CDI (Debast 2014). These new findings would not alter the current policy. Therefore, no changes to the policy are warranted.

No policy updates were made in May 2016.

Glossary

Bacteria — A large domain of prokaryotic microorganisms (i.e., cells without an organized nucleus). They were among the first life forms to appear on Earth and are present in most of its habitats. Bacteria also live in symbiotic and parasitic relationships with plants and animals. The majority of bacteria in the human body are harmless or beneficial, the largest number being in the gut. However, some species of bacteria are pathogenic and cause infectious diseases.

Bacteroides — A phylum of bacteria commonly found in the human intestine, where they have a symbiotic host-bacterial relationship with humans. They assist in breaking down food and producing valuable nutrients and energy the body needs. However, Bacteroides can be pathogenic when introduced to parts of the body other than the gastrointestinal area. They can cause or exacerbate abscesses and other infections. Bacteroides are increasingly regarded as specialists for the degradation of proteins and carbohydrates.

Clostridium difficile (or C. difficile) — A bacterium that can cause symptoms ranging from diarrhea to life-threatening inflammation of the colon. C. difficile most commonly affects older adults in hospitals or in long-term care facilities and typically occurs after use of antibiotic medications. When the normal gut microbiota have been suppressed or destroyed (usually after a broad-spectrum antibiotic has been used), the gut becomes overrun with C. difficile. The bacteria release toxins that can cause bloating and diarrhea with abdominal pain, which may become severe. However, in recent years, C. difficile infections have become more frequent, severe and difficult to treat.

Dysbiosis — (Also called “dysbacteriosis.”) Microbial imbalance resulting from a change in the number or types of bacteria on or inside the body. Dysbiosis is most prominent in the digestive tract or on the skin, but can also occur on any exposed surface or mucous membrane. Researchers speculate it may have a role in illnesses such as inflammatory bowel disease, chronic fatigue syndrome, obesity or certain cancers. One cause of dysbiosis is antibiotic exposure.

Fecal transplant — (Also known as “fecal microbiota transplant” or “stool transplant.”) The process of transplanting fecal bacteria from a healthy individual into a recipient. The aim is to reestablish healthy
microbiota in the gut of the recipient. It has been proven a highly effective treatment for patients suffering from \textit{C. difficile}. It involves restoration of the intestinal microbiome by introducing healthy microbiota through an infusion of stool from a healthy human donor.

\textbf{Gut flora} — An older term that refers to plants or plant-like organisms, though it is now known that many of the microorganisms that inhabit our bodies are not related to plants. The term microbiota is now preferred and should be used instead of flora or microflora. Many, however, continue to use these terms interchangeably.

\textbf{Gut microbiota} — The community of microorganisms that live in the gastrointestinal tract. Gut refers to the intestine. Gut microbiota consist of tens of trillions of microorganisms, including at least 1,000 different species of known bacteria with millions of genes. Gut microbiota in a single person can, in total, weigh up to 4.5 pounds. Research suggests the relationship between gut microbiota and humans is not merely commensal, but rather a mutualistic relationship. The metabolic activities performed by these bacteria resemble those of an organ.

\textbf{Human Microbiome Project (HMP)} — An organization that develops tools and datasets for the research community studying the roles of these microbes in human health and disease. The first phase of HMP characterized the composition and diversity of microbial communities which inhabit major mucosal surfaces of the human body, including nasal passages, oral cavities, skin, gastrointestinal tract, and urogenital tract, and evaluated the genetic metabolic potential of these communities. The current phase of HMP focuses on creating the first integrated dataset of biological properties from both the microbiome and the host from cohort studies of microbiome-associated diseases. This project uses a new field of research, metagenomics, which allows the comprehensive examination of microbial communities without the need for cultivation.

\textbf{Medically necessary} — A service or benefit is medically necessary if it is compensable under the Medical Assistance program and if it meets any one of the following standards:

- The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition, or disability.
- The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury, or disability.
- The service or benefit will assist the member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the member and those functional capacities that are appropriate for members of the same age.

\textbf{Microbiota (or microbiome)} — The community of microorganisms that typically inhabits a bodily organ or part. The human body contains more than 10 times as many microbial cells as human cells. These microorganisms may be \textit{commensal} (living in close association that allows one species to benefit without harming the other), \textit{symbiotic} (having an interdependent relationship), or \textit{pathogenic} (disease-producing). Human beings have clusters of bacteria in different parts of the body, such as the skin, the mouth, the vagina, and the intestine.

\textbf{Prebiotics} — Non-digestible food components that pass undigested through the upper part of the gastrointestinal tract and stimulate the growth and/or activity of advantageous bacteria (e.g., \textit{Bifidobacteria} and \textit{Lactobacilli}) that colonize the large intestine. As a functional food component, prebiotics, like probiotics, are conceptually intermediate between foods and drugs.
**Probiotics** — Live micro-organisms similar to those found naturally in the human body which may be beneficial to health when administered in sufficient quantities. Probiotics help maintain the balance of microbiota in the intestines. They are commonly consumed as part of fermented food (e.g., yogurt, kefir, dietary supplements). The largest group of probiotic bacteria in the intestine is made up of lactic acid bacteria, of which *Lactobacillus acidophilus*, found in yogurt with live cultures, is the best known. Some yeast may also act as probiotics.

**Recurrent *Clostridium difficile* infection (CDI)** — Recurrence is defined by complete abatement of CDI symptoms while on appropriate therapy, followed by subsequent reappearance of diarrhea and other symptoms after treatment has been stopped. Recurrence should be distinguished from persistent diarrhea without resolution during initial therapy, which should prompt an evaluation for other causes. In the absence of an alternative diagnosis, such patients should be considered to have refractory illness.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


**Clinical trials**

Searched clinicaltrials.gov on May 11, 2015 using terms fecal microbiota transplantation | Open Studies. 10 studies found, 5 relevant.


NCT02435160 The Study of Efficacy and Mechanism in Fecal Microbiota Transplantation in the Treatment of Ulcerative Colitis. Available at:

CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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