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AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Fecal Bacteriotherapy

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Policy

Aetna considers fecal bacteriotherapy medically necessary for persons with *Clostridium difficile* infection, with infection confirmed by a positive stool test for *C. difficile* toxin, that has recurrent following at least one course of adequate antibiotic therapy (10 or more days of vancomycin at a dose of greater than or equal to 125 mg 4 times per day or 10 or more days of metronidazole at a dose of 500 mg 3 times per day).

Aetna considers fecal bacteriotherapy experimental and investigational for all other indications including the following (not an all-inclusive list):

- Crohn's disease
- Idiopathic thrombocytopenic purpura
- Inflammatory bowel diseases
- Insulin resistance
- Irritable bowel syndrome
- Metabolic syndrome
- Multiple sclerosis
- Ulcerative colitis

Background

Fecal bacteriotherapy (FT, also known as fecal microbiota transplantation fecal transplant, fecal transfusion, and probiotic infusion) is the transfer of a liquid suspension of stool from a healthy donor to the patient and is proposed for the treatment of *Clostridium difficile* infection (CDI), which can result in mild diarrhea to life-threatening fulminant pseudomembranous colitis. Treatment involves discontinuation of the offending antibody and oral administration of metronidazole or vancomycin. In some cases, patients non-responsive to medical management are treated by surgical colectomy which has a mortality rate of 35 % to 57 %. One
of the risks with FT is the transfer of contagious agents (e.g., fungi, parasites, and viruses) from the donor (You et al, 2008; Bakken et al, 2009).

A randomized controlled clinical trial by van Nood, et al. (2013) found that infusion of donor feces was significantly more effective for the treatment of recurrent C. difficile infection than the use of vancomycin. Included in the study were patients who were at least 18 years of age and who had a life expectancy of at least 3 months and a relapse of C. difficile infection after at least one course of adequate antibiotic therapy (≥ 10 days of vancomycin at a dose of ≥ 125 mg four times per day or ≥ 10 days of metronidazole at a dose of 500 mg three times per day). C. difficile infection was defined as diarrhea (≥ 3 loose or watery stools per day for at least 2 consecutive days or ≥ 8 loose stools in 48 hours) and a positive stool test for C. difficile toxin. Available isolates were characterized by PCR. Investigators randomly assigned patients with recurrent C. difficile infection to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary endpoint was the resolution of diarrhea associated with C. difficile infection without relapse after 10 weeks. The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of C. difficile-associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. The investigators reported that resolution of C. difficile infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage (p < 0.001 for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroidetes species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species. An accompanying editorial (Kelly, 2013) stated that the study by van Nood et al. is an important confirmation of the efficacy of fecal microbiota transplant for recurrent C. difficile infection.

Baddour (2013) commented that the findings of this study by van Nood, et al. will garner much attention and will likely increase the use of fecal transplantation (FT) in the treatment of recurrent C. difficile infection. These happenings, coupled with our increasing understanding of the gut microbiome, should markedly advance our understanding of the pathogenesis and treatment of C. difficile infection.

This clinical trial is consistent with the results of earlier studies of fecal bacteriotherapy. Guo et al (2012) critically appraised the clinical research evidence on the safety and effectiveness of FT compared with standard care in the treatment of patients with clostridium difficile-associated disease (CDAD). A comprehensive literature search was conducted by a research librarian to identify relevant studies published between 2000 and 2011. The Cochrane Library, PubMed, EMBASE, CINAHL, Biological Abstracts, BIOSIS Previews and Web of Science were searched. Methodological quality of the included case series studies was assessed in terms of patient selection criteria, consecutive
recruitment, prospective data collection, reporting of lost to follow-up, and follow-up rates. No controlled studies were found. Based on the weak evidence from 7 full-text case series studies of 124 patients with recurrent/refractory CDAD, FT appears to be a safe and effective procedure. In most cases (83%) symptoms improved immediately after the first FT procedure, and some patients stayed diarrhea-free for several months or years. The authors concluded that although these results appear to be promising, the treatment effects of FT can not be determined definitively in the absence of a control group. Results from randomized controlled trials (RCTs) that compare FT to oral vancomycin without or with a taper regimen will help to better define the role of FT in the management of recurrent CDAD.

Brandt and Reddy (2011) stated that with the increasing prevalence of recurrent/refractory CDI, alternative treatments to the standard antibiotic therapies are being sought. One of the more controversial of such alternative treatments is fecal microbiota transplantation (FMT). Although the notion of FMT is foreign -- even startling -- and not esthetic to most people, the concept has been around for many decades. Its benefit and effectiveness dated back more than 50 years to its use for staphylococcal pseudomembranous colitis, and now FMT is showing a great promise as an inexpensive, safe, and highly efficient treatment for recurrent and refractory CDI. Moreover, with a better understanding of the intricacies of the colonic microbiome and its role in colonic pathophysiology, FMT has the potential to become the standard of care for CDI treatment, and a potential answer to other intestinal disorders in years to come.

Smits et al (2013) stated that there has been growing interest in the use of fecal microbiota for the treatment of patients with chronic gastro-intestinal infections and inflammatory bowel diseases (IBD). Lately, there has also been interest in its therapeutic potential for cardio-metabolic, autoimmune, and other extra-intestinal conditions that were not previously considered to be associated with the intestinal microbiota. Although it is not clear if changes in the microbiota cause these conditions, these researchers reviewed the most current and best methods for performing FMT and summarized clinical observations that have implicated the intestinal microbiota in various diseases. They also discussed case reports of FMT for different disorders, including CDI, irritable bowel syndrome, IBD, insulin resistance, multiple sclerosis, and idiopathic thrombocytopenic purpura. There has been increasing focus on the interaction between the intestinal microbiome, obesity, and cardio-metabolic diseases, and these investigators explored these relationships and the potential roles of different microbial strains.

Kump et al (2013) examined if patients with ulcerative colitis (UC) would benefit from FMT and if dysbiosis can be reversed. A total of 6 patients with chronic active UC non-responsive to standard medical therapy were treated with FMT by colonoscopic administration. Changes in the colonic microbiota were assessed by 16S rDNA-based microbial community profiling using high-throughput pyrosequencing from mucosal and stool samples. All patients experienced short-term clinical improvement within the first 2 weeks after FMT. However, none of the patients achieved clinical remission. Microbiota profiling showed differences in the modification of the intestinal microbiota between individual patients after FMT. In 3 patients, the colonic microbiota changed toward the donor microbiota; however, this did not correlate with clinical response. On phylum level, there was a
significant reduction of proteobacteria and an increase in bacteroidetes after FMT. The authors concluded that FMT by a single colonoscopic donor stool application is not effective in inducing remission in chronic active therapy-refractory UC. Changes in the composition of the intestinal microbiota were significant and resulted in a partial improvement of UC-associated dysbiosis. They stated that the results of this small study suggested that dysbiosis in UC is at least in part a secondary phenomenon induced by inflammation and diarrhea rather than being causative for inflammation in this disease.

Zhang et al (2013) stated that the concept of FMT has been used in traditional Chinese medicine at least since the 4th century. Evidence from recent human studies strongly supports the link between intestinal bacteria and IBD. These investigators proposed that standardized FMT might be a promising rescue therapy for refractory IBD. However, there were no reports of FMT used in patients with severe Crohn's disease (CD). These researchers reported the successful treatment of standardized FMT as a rescue therapy for a case of refractory CD complicated with fistula, residual barium sulfate and formation of intra-peritoneal large inflammatory mass. The authors concluded that this was the first case of severe CD treated using FMT through mid-gut.

In a pilot study, Cui and colleagues (2014) evaluated the safety, feasibility and effectiveness of FMT through mid-gut for refractory CD. These researchers established standardized laboratory protocol and clinical work-flow for FMT. Only refractory CD patients with Harvey-Bradshaw Index (HBI) score greater than or equal to 7 were enrolled for this study. All included patients were treated with single FMT through mid-gut and assessed during follow-up. Meta-genomics analysis showed a high concordance between feces sample and purified fecal microbiota from same donors. Standardized fecal microbiota preparation and clinical flow significantly simplified the practical aspects of FMT. A total of 30 patients were qualified for the present analysis. The rate of clinical improvement and remission based on clinical activity at the 1st month was 86.7 % (26/30) and 76.7 % (23/30), respectively, which was higher than other assessment points within 15-month follow-up. Patients' body weight increased after FMT, and the lipid profile improved as well. Fecal microbiota transplantation also showed a fast and continuous significant effect in relieving the sustaining abdominal pain associated with sustaining CD. The authors concluded that these findings demonstrated that FMT through mid-gut might be a safe, feasible, and efficient rescue therapy for refractory CD.

van Nood et al (2014) reviewed the current evidence on FMT for recurrent CDIs, metabolic syndrome and IBD. These investigators noted that recently, a randomized trial confirmed the effectiveness of this treatment strategy in patients with recurrent CDI. For other disorders, evidence is still limited. To-date, studies have been performed to try and influence the course of metabolic syndrome and IBD. The authors concluded that there is increasing interest in the role of altered microbiota in the development of a myriad of diseases. Together with new insights comes an interest in influencing this altered microbiota as a potential target for therapy. Fecal microbiota transplantations are effective against recurrent CDI. Restoration of intestinal flora and thereby restoration of colonization resistance is thought to be the mechanism responsible for cure. With the developments in FMT and the extension of this treatment modality to both intestinal and extra-intestinal
diseases, a new field of targeted therapy awaits. The authors concluded that currently, FMT should only be given in a strict experimental setting for other conditions than CDI.

Colman and Rubin (2014) conducted a systematic review and meta-analysis to evaluate the effectiveness of FMT as treatment for patients with IBD. A systematic literature search was performed through May 2014. Inclusion criteria required FMT as the primary therapeutic agent. Clinical remission (CR) and/or mucosal healing were defined as primary outcomes. Studies were excluded if they did not report clinical outcomes or included patients with infections. A total of 18 studies (9 cohort studies, 8 case studies and 1 RCT) were included. A total of 122 patients were described (79 UC; 39 CD; 4 IBD unclassified). Overall, 45% (54/119) of patients achieved CR during follow-up. Among the cohort studies, the pooled proportion of patients that achieved CR was 36.2% (95% CI: 17.4% to 60.4%), with a moderate risk of heterogeneity (Cochran's Q, p = 0.011; I² = 37%). Subgroup analyses demonstrated a pooled estimate of CR of 22% (95% CI: 10.4% to 40.8%) for UC (p = 0.37; I² = 0%) and 60.5% (95% CI: 28.4% to 85.6%) for CD (p = 0.05; I² = 37%); 6 studies performed microbiota analysis. The authors concluded that this analysis suggested that FMT is a safe, but variably effective treatment for IBD. They stated that more RCTs are needed and should investigate frequency of FMT administration, donor selection and standardization of microbiome analysis.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:
44705

HCPCS codes covered if selection criteria are met:
G0455 Preparation with instillation of fecal microbiota by any method, including assessment of donor specimen

ICD-9 codes covered if selection criteria are met:
008.45 Intestinal infections due to clostridium difficile

The above policy is based on the following references:


outcomes. Participating providers are independent contractors in private practice and are neither employees nor agents of Aetna or its affiliates. Treating providers are solely responsible for medical advice and treatment of members. This Clinical Policy Bulletin may be updated and therefore is subject to change.

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