

Cure Rates Remain High With Fecal Transplant for *C difficile*

Pam Harrison | October 20, 2014

PHILADELPHIA — Both initial and sustained responses to fecal microbiota transplant (FMT) for the treatment of refractory *C difficile* infection remain high out to 18 months' follow-up, provided patients do not require antibiotics for the treatment of an unrelated infection, new research shows.

"FMT is a well-established and effective option in treating *C difficile* colitis, especially if it is recurrent or refractory to antibiotics, but we don't have a lot of data in terms of long-term outcomes," Daniel Greenwald, MD, internal medicine resident, Lahey Hospital and Medical Center, Burlington, Massachusetts, told *Medscape Medical News* in advance of his presentation at the American College of Gastroenterology (ACG) 2014 Annual Scientific Meeting.

"We looked at a very sick cohort of patients, in that they had either recurrent or refractory *C difficile*, and we saw a 91.4% primary response rate at 3 months, an 86.2% response rate at 6 months, and an 80.5% response rate at 18 months, which I think is very telling of the effectiveness of FMT, even in sick patients who had failed primary, secondary, and in some cases, tertiary treatment options with antibiotics."

The researchers looked at 58 patients who had previously undergone FMT for recurrent or refractory *C difficile* infection. During the 18-month follow-up period, they observed that patients with comorbid gastrointestinal illnesses such as celiac disease were more likely to have a recurrent episode of *C difficile*.

We looked at a very sick cohort of patients, in that they had either recurrent or refractory *C difficile*, and we saw a 91.4% primary response rate. Dr Daniel Greenwald

They also found that in patients who did not have a sustained treatment response to FMT, there was a coincident use of antibiotic therapy after treatment for other conditions. A large percentage of these patients also happened to be on pretransplant immunosuppressive therapy, both well-established independent risk factors associated with susceptibility to *C difficile*.

In contrast, patients who took probiotics prior to receiving FMT were more likely to be disease-free at follow-up than patients who had relapsed ($P = .0186$).

"Recurrent *C difficile* is typically seen in patients who need antibiotics for some other condition down the road, so I think overall, this study just adds more data to the experience of the efficacy of FMT."

In a separate study evaluating safety outcomes after FMT, 45 patients with refractory or recurrent *C difficile* infection who had received treatment were prospectively followed. Symptoms and adverse events were assessed at multiple time points, including at 6 months after FMT.

"The most common symptoms prior to FMT were diarrhea (69%), fatigue (20%), and weight loss (13%)," report investigators led by Desmond Wilson, MD, from the Alpert Medical School of Brown University, Providence, Rhode Island. At various time points after FMT, patients reported gastrointestinal symptoms to varying degrees.

Table. Gastrointestinal Symptoms After Fecal Transplant

Time	Diarrhea, Loose Stool (%)	Bloating and Flatus (%)	Constipation (%)	Abdominal Pain (%)	Gastroesophageal Reflux (%)

Day 1	16%	11	—	—	—
Week 1	27%	—	24	16	—
Week 4	20%	—	13	11	—
Six months	13%	—	16	—	11

Most of the diarrhea that occurred after treatment was transient and lasted less than a day, say investigators, and 38% of the group members reported at least one side effect that was likely not related to FMT; these included 10 infections.

In all, 8 patients reported a serious adverse event within 12 weeks of receiving FMT, and 4 others reported a series of side effects later on, but again, none were related to the transplant, Dr Wilson told *Medscape Medical News*.

At 4 weeks, 87% of patients were cured of their *C difficile* infection. Four patients underwent repeat FMT, all of whom were cured of the infection, for an overall cure rate of 96% 6 months post FMT.

"People think of feces being dirty and ripe with bacteria — which they are — they are just not ripe with bacteria that are infective or malignant," Dr Wilson told *Medscape Medical News*. "Donors are screened for major bacterial pathogens as well as for viruses, such as hepatitis C. And from our data, it appears that FMT is generally well tolerated and is not associated with acquiring procedure-related infections or serious adverse outcomes."

Patients with inflammatory bowel disease (IBD) are at higher risk of acquiring *C difficile*, and once they have it, the infection is more challenging to treat than usual. Spurred on by individual case reports of IBD flaring after several patients received FMT, Monika Fischer, MD, from Indiana University–Purdue University, in Indianapolis, and her team retrospectively collected data involving IBD patients from 6 different academic centers who had developed *C difficile* infection and who had been treated with a colonoscopy or sigmoidoscopy FMT.

Inflammatory Bowel Disease

Out of the 41 cases identified, about half of the patients had Crohn's disease, 46% had ulcerative colitis, and one had indeterminate colitis. One month prior to FMT, 59% of the group had active IBD, and 41% were in clinical remission. Some 63% of patients were also immunosuppressed at the time of treatment and were receiving a variety of immunosuppressive agents.

Most patients, 83%, received FMT for recurrent *C difficile* infection, 10% were treated for refractory disease, and the remaining 7% were treated for recurrent-refractory colitis. The median number of *C difficile* episodes in the group was four; the median duration of *C difficile* infection was 9.5 months, and more than half of the group had failed vancomycin taper.

"After a single FMT, the cure rate was 71%, cure being defined as no recurrence of *C difficile* symptoms 3 months post FMT," Dr Fischer told *Medscape Medical News*. "And after repeat FMT was done in eight patients, the cure rate went up to 90%, using the same definition." Dr Fischer cautioned that improvement in disease activity was not uniform after treatment.

Three months after FMT, the clinical course of IBD did not change in 34% of patients; it improved in 49%, but it worsened in 17%. Although Dr Fischer suggested that disease severity rather than the FMT itself was responsible for disease worsening, "there is a small chance that the disease is going to flare after patients get an FMT, at least

that is our hypothesis, as you are introducing patients to a totally different microbiota, and they may have a reaction to it," she said.

In a statement to the press, Herbert DuPont, MD, from the University of Texas, in Houston, said that using fresh donor stool has its practical limitations, including difficulty in preparation, administration, and standardization. Frozen fecal microbial extracts or freeze-dried FMT, in contrast, may be more convenient and pleasant to use.

Fresh Donor Stool

Dr DuPont and his team compared the efficacy of fresh, frozen, or lyophilized FMT from the same donors administered by colonoscopy to 33 patients with recurrent *C difficile* infection. "We found equivalent success rates in FMT in the three methods of handling donor stools," they reported.

The investigators also observed dramatic shifts in fecal flora in FMT recipients regardless of the form received, with a decrease in Proteobacteria from 62% before transplant to 7% after treatment. They saw an increase in both Firmicutes (27% to 48%) and Bacteroidetes (0% to 25%).

"Showing frozen FMT is as effective as fresh in the same donor provides evidence that the more convenient frozen fecal flora can be used routinely in patients with recurrent *C difficile* infection," Dr DuPont reported. "And since lyophilized FMT is effective in the treatment of recurrent *C difficile* infection as well, it should be possible to deliver a powder form of the product orally in capsules to recipients with recurrent *C difficile* infection and to explore the value of easily administered oral FMT in other indications, such as IBD."

Speaking during a virtual press briefing organized by the ACG, Russell Cohen, MD, from the University of Chicago, in Illinois, pointed out that a number of groups have been experimenting with FMT to treat IBD in the absence of *C difficile*, but results have not been all that encouraging so far.

"The fact that the first FMT was successful in 80% of patients in the Fischer et al study and then 75% successful in those who did not get better on the first try meant the group did reach a 90% cure rate," Dr Cohen said. "So this is very encouraging for our IBD patients with *C difficile*." Part of the success of this particular study might be explained by the route of FMT delivery, through colonoscopy or sigmoidoscopy.

In one previous study in which IBD patients with *C difficile* received an FMT, Dr Cohen noted that the transplant was delivered by enema, and treatment was not successful.

"We're hoping that by using either a colonoscopy or a sigmoidoscopy to deliver the spray of feces to the lining of the bowel, we will be able to get rid of *C difficile* and keep it away in patients with IBD," Dr Cohen said.

Almost Identical Results

Also speaking at the press briefing, Mark Mellow, MD, a gastroenterologist in Oklahoma City, said that cure rates achieved by Dr Greenwald's team were "almost identical" to results he and his colleagues achieved in another long-term follow-up study (*Am J Gastroenterol.* 2012;107:1079-1087).

Of the 94 patients who had received colonoscopic FMT for recurrent *C difficile* infection, the primary cure rate was 91%, with a secondary cure rate of 98%, either with the use of vancomycin with or without probiotics or repeat FMT.

At a mean follow-up of 17 months, "the only patients who developed late recurrent *C difficile* were patients who needed antibiotics for some other condition, whereas nobody developed late recurrent *C difficile* if they did not need subsequent antibiotics," Dr Mellow explained. "So the message to physicians, especially those caring for people in long-term care facilities, is to use antibiotics very, very judiciously, to use as narrow-spectrum an antibiotic as possible, and for as short a period of time."

Dr Mellow also cautioned that the lingering GI symptoms reported by Dr Wilson and colleagues following FMT suggest that minor alterations in gut function do occur after FMT, just as they do after treatment of other enteric infections.

"The concept of a postinfectious irritable bowel syndrome is well known," Dr Mellow said. "And I think it is worth counseling patients about this before they receive an FMT, because if they have a loose bowel movement after, they'll think their disease is back, but the majority of the bowel dysfunction is not related to *C difficile* recurrence, and patients need to be aware of that bowel function will not always return to normal immediately after FMT."

Medscape Medical News © 2014 WebMD, LLC

Send comments and news tips to news@medscape.net.

Cite this article: Cure Rates Remain High With Fecal Transplant for *C difficile*. *Medscape*. Oct 20, 2014.