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A Patient's Guide to Fecal Microbiota Transplantation (FMT) for Recurrent *C. difficile* Infection

Clostridium difficile, or *C. difficile* for short, is the most common hospital acquired infection and can be a very aggressive intestinal bug. Each year, these bacteria infect roughly 500,000 people in the U.S., sending more than 347,000 to the hospital for treatment. In extreme cases, *C. difficile* infection can be fatal, with estimates of *C. difficile*-associated death ranging from 14,000 to 30,000 annually. *C. difficile* infection costs the U.S. $4.8 billion each year.

The contents of this pamphlet were produced by The American Gastroenterological Association unless otherwise noted. The full text is available online at fmt.gastro.org.

What is Clostridium difficile?

C. difficile can be found in the soil, air, water, and human and animal feces. As many as 10% of the population carry the bacteria with no ill effects or symptoms. However, these individuals shed the bacteria through their feces. When people who carry *C. difficile* do not wash their hands after going to the bathroom, they can contaminate the food they handle and they can leave the bacteria on things they touch. The bacteria then produce spores (a dormant form of the bacteria) that can survive for months unless the area is thoroughly cleaned with products specifically designed to kill the spores, such as cleansers that contain bleach. If you touch a surface contaminated with *C. difficile*, you may accidentally ingest the spores when you touch your food or your mouth.

C. difficile is most common in hospitals and long-term care facilities, like nursing homes. Studies suggest that up to 20% of hospital patients and 50% of people in long-term care facilities carry *C. difficile*, even if they do not have any symptoms. Unless a hospital or facility follows special procedures for cleaning and disinfection, the spores can remain on beds, toilets and medical equipment. Healthcare providers and other facility staff help prevent transmission of the bacteria from patient to patient by washing their hands properly. As many hospital patients and long-term care residents are already in a weakened condition because of illness, injury or age, *C. difficile* can spread throughout these facilities very quickly if prevention strategies are poor.

If you are healthy, you will most likely not develop an infection with *C. difficile*. Other organisms normally present in your gastrointestinal (GI) tract keep it in check by occupying the sites where *C. difficile* could attach and multiply. Think of these sites as parking spaces — if another organism is already there, *C. difficile* has nowhere to park.

However, taking antibiotics can wipe out these helpful organisms. With fewer organisms to occupy sites on the intestinal lining, *C. difficile* can establish itself in

the intestine and grow. It then produces toxins that injure cells and cause inflammation, resulting in symptoms such as diarrhea and abdominal pain.

Infection Symptoms

The symptoms of *C. difficile* infection usually begin with the following:

- Watery diarrhea three or more times a day for more than two days.
- Abdominal pain.
- Mild to moderate nausea.
- Loss of appetite.

In more serious cases, the degree of inflammation in the colon may be more extensive and may cause bleeding, the formation of pus and destruction of the lining of the intestine. In this case, symptoms may include:

- Watery diarrhea as often as 15 times per day.
- Severe abdominal pain and intestinal cramping.
- Dehydration.
- Fever.
- Weight loss.

Severe *C. difficile* can be dangerous. Rapid dehydration may affect your organs and cause your blood pressure to be very low. If you get dehydrated extremely fast, it can damage your kidneys and lead to kidney failure.

In the most severe cases, the lining of the large intestine may get severly swollen (toxic megacolon) and may develop holes (bowel perforation). When bacteria or feces from your intestines escape into other areas of the body, through bowel perforation, it is a medical emergency that usually requires immediate surgery, because it can be fatal.

Risk Factors

The main trigger of *C. difficile* infections is antibiotic use, especially if you have been taking antibiotics for a long time or take a "broad spectrum" antibiotic

that kills a wide variety of bacteria. Because *C. difficile* is more common in hospitals, nursing homes and other care facilities, being a patient or resident of these facilities is also a risk.

Other risk factors include:

- Being at least 65 years old.
- Having abdominal surgery.
- Existing problems or disease in your intestines, such as inflammatory bowel disease or colon cancer.
- Having a weakened immune system because of chemotherapy or other drugs that suppress the immune system, or AIDS.
- Previous infection with *C. difficile*, especially recent.

Diagnosis and Testing

If you develop diarrhea within a few days of being admitted to or released from a hospital, or within two months of taking an antibiotic, and you have had three or more unformed stools or bouts of diarrhea in 24 hours, *C. difficile* may be the culprit. There are several ways to test for *C. difficile*. Which one your doctor chooses will depend on your symptoms and medical history and whether you are currently in a hospital.

Stool tests

The simplest and best test is a stool test, where you provide a stool sample in a sterile container provided by your doctor's office or lab. The lab will run tests on the sample to detect the bacteria. Stool tests can take 24 to 48 hours to provide results.

Blood tests

Blood tests can help tell a doctor how severe the infection is. Signs that doctors may look for might include: a high white blood cell count, which is a sign of

infection in the body; elevated kidney tests, which show dehydration; and low albumin (blood protein), highlighting poor nutrition.

Endoscopic examination

In a very few cases, an examination of your colon by colonoscopy or sigmoidoscopy may be needed. A gastroenterologist (a doctor who specializes in treating the digestive system) should be the one to decide if this test is necessary. A colonoscopy allows the doctor to examine the entire colon and rectum while a sigmoidoscopy only examines the lower part of the colon and the rectum.

A colonoscopy can help rule out other causes of diarrhea or reveal areas of inflammation that indicate infection with *C. difficile* called "pseduomembranes". It will also enable the doctor to take tissue samples if necessary. If you are in the hospital and need to have urgent surgery, stool tests may take too long to provide results, and your doctor may opt for a colonoscopy in order to save time.

CT Scan

If your doctor suspects you may be developing complications from *C. difficile*, he or she may order a computerized tomography (CT) scan to look for thickening of the wall of your intestines. During this test you may receive an intravenous injection of a special dye, which will enable the CT machine to take better pictures of your intestines. If you have an allergy to iodine or shellfish, tell your doctor, because people with these allergies may have a reaction to the dye.

Treatment

If you develop a *C. difficile* infection while taking an antibiotic, your doctor may advise you to stop taking it or switch to another type. Depending on how long you've been coping with diarrhea or how sick you are, your doctor may want

you to receive IV fluids and electrolyte supplementation so you do not get dehydrated. Unfortunately, *C. difficile* can be stubborn, so treatment often requires several steps.

Antibiotics

Stopping the antibiotics that allow *C. difficile* to grow and receiving fluids resolves the infection in about 20 percent of people who are infected with the bacteria. However, if that is not successful, your doctor may prescribe a different type of antibiotic to specifically treat the *C. difficile* infection. For a mild or moderate infection, the first choice is usually metronidazole for 10 to 14 days. For a severe infection, the first choice is usually vancomycin for 10 to 14 days. If those don't work, your doctor may try vancomycin for a longer period of time. Fidaxomicin is also another antibiotic that may be used at the discretion of your doctor.

Many people who take antibiotics to treat *C. difficile* infection start to feel better within three days, but it is important to continue taking the medication until you finish it. Otherwise, it may not kill all of the *C. difficile* organisms and you may suffer a relapse. Approximately 20% of people with *C. difficile* will need a second round of antibiotics. Those who have one relapse have a 40% chance of another relapse, and those who have had two relapses have a 60% chance of another relapse.

Probiotics

Probiotics are living microscopic organisms (microorganisms) that research has shown may benefit your health. Most often they are bacteria, but they may also be other organisms such as yeasts. In some cases they are similar to, or the same as, the helpful organisms in your GI tract.

There is evidence that taking certain probiotics may help treat *C. difficile* infection. *Saccharomyces boulardii* has been shown to decrease the frequency of relapses in people who have had several bouts of the disease, especially if it is taken along with vancomycin. There is also some evidence to suggest that

Lactobacillus plantarum 299v helps prevent relapses when taken with metronidazole. In general, probiotics are thought to work against *C. difficile* by competing for the space it occupies in the GI tract.

Probiotics are widely available over the counter in pharmacies and health food stores. However, there are many different types of probiotics, and not all of them have been studied for preventing *C. difficile* infection or have been shown to be helpful. Also, there have been cases of serious illness and death in people who were critically ill or who had a weakened immune system who took probiotics. Therefore, if you have *C. difficile*, it is extremely important for you to ask your doctor about probiotics before you take them.

Surgery

In extremely severe, life-threatening cases, it may be necessary for a surgeon to remove the infected or damaged part of the GI tract.

Fecal microbiota transplantation (FMT)

In this procedure, stool from a healthy donor is processed into a liquid preparation and transferred into the colon of the infected individual in an effort to reintroduce or boost helpful organisms.

How FMT works[1]

The human body contains 10 bacterial cells for every human cell, and 100 unique bacterial genes for every human gene. This vast, hidden bacterial majority is known as the microbiome. Recent advances in molecular microbiology have revealed the critical role of the microbiome in a variety of important processes ranging from nutrition to immunology.

[1] The "How FMT works" section was prepared by OpenBiome and is an addition to the AGA's content

Fecal transplantation, whereby the bacterial community from a healthy donor is administered to a patient in need, has great promise to treat some diseases related to the microbiome that are otherwise difficult or impossible to treat.

During FMT, stool from a carefully screened, healthy donor is introduced either through the lower gastrointestinal tract (e.g. by colonoscope/sigmoidoscope or enema) or through the upper gastrointestinal tract (e.g. via nasogastric/nasoduodenal tube or upper endoscope). Both routes of administration work and have their own advantages and drawbacks.

Although FMT is being researched as a treatment for a variety of diseases, C. difficile is the only disease that has been meaningfully explored and has promising clinical evidence supporting its use.

FMT: What's Old Is New

In 1958, Benjamin Eisman, MD, a surgeon in Denver, CO, first tried FMT when four of his patients had colitis he suspected of being caused by C. difficile. All four patients recovered. For several decades thereafter, FMT remained relatively obscure. But at the turn of this century, a new and particularly tough strain of C. difficile emerged, and infections began to climb steadily. Faced with treating more frequent and more stubborn cases of infection, doctors have since revisited FMT as a treatment option. In 2011, the American Gastroenterological Association (AGA) published an article that provides gastroenterologists with information on determining who might benefit from FMT, screening donors and performing the procedures.

Who is a Candidate for FMT?

According to the American Gastroenterology Association, FMT may be an option for people who have had one of the following:

- At least three episodes of mild to moderate C. *difficile* infection that have not responded to six to eight weeks of treatment with antibiotics.
- Have had at least two episodes of severe C. *difficile* infection that required them to be admitted to the hospital.

- Moderate *C. difficile* infection that did not respond to antibiotics (namely vancomycin or fidaxomicin) for at least a week.
- Severe *C. difficile* infection or severe colitis caused by *C. difficile* that did not respond to antibiotics within two days.

Not everyone is a good candidate for FMT. The procedure may be risky for people who are taking drugs that suppress the immune system, have had a recent bone marrow transplant, have cirrhosis of the liver or advanced HIV or AIDS. If you fall into one of these categories, your doctor may advise against it, depending on how severe your C. difficile infection is and whether you have other complications.

OpenBiome, the first stool bank[2]

We founded OpenBiome, a nonprofit 501(c)(3) organization, after watching a dear friend suffer through 18 months of C. difficile and 7 rounds of Vancomycin before finally receiving a successful, life-changing FMT. The remarkable effectiveness of this treatment and the great lengths our friend had to go through to receive it convinced us that we needed to help expand access. After many conversations with local clinicians and the FDA, we launched OpenBiome in 2012 to make FMT faster and easier for patients and doctors alike. We provide hospitals with screened, filtered, and frozen material ready for clinical use. This service eliminates the time, staff, protocols, and facilities needed to screen and prepare material from new donors for each treatment. It also helps lower costs by spreading the price of donor screening across many treatments. OpenBiome now works with more than 150 hospitals and clinics around the country, providing material for FMT at the price it takes to cover costs. More information about OpenBiome, including how to support someone's treatment, is available at **www.openbiome.org.**

[2] The "OpenBiome, the first stool bank" box was prepared by OpenBiome

Preparing for the Transplant

Although the actual procedures for FMT will depend on the health of the recipient and the preferences of the doctor performing the transplant, there are several things recipients and donors will have to do to prepare. Doctors use different techniques to perform FMT, including colonoscopy/sigmoidoscopy, enema or infusion through a nasogastric/nasoduodenal tube (a tube the runs from your nose down into your stomach/intestine) or upper endoscope. Each of these procedures has some risk. For colonoscopy and enema, there is a very low risk of bowel perforation. For transfer via a nasogastric tube, there is a small chance that some of the fluid containing the stool could end up in the lungs and cause an infection there.

Though there have been some cases of successful "do-it-yourself" stool transplants involving enemas at home this is not advised. Transplants must be overseen by a doctor because of the risk of contamination by improper handling of the stool, and because the donor's GI tract may contain bacteria and organisms harmful to the recipient. In addition, both the donor and the recipient must be screened as though the procedure was going to take place in a hospital.

Donors

Donors who provide the stools for transplantation must be screened carefully to avoid transmitting dangerous viruses, parasites or bacteria into the person infected with C. difficile. Doctors first screen potential donors by asking them similar questions they would ask of potential blood donors. Donors will also be tested for diseases that can be spread through the blood, such as hepatitis, HIV and syphilis. The donor's stool will be tested as well, especially for infections that can be transmitted.

Patients have the option of using stool from a universal stool bank, or of selecting their own donors for screening. Donor screening may not be covered by health

insurance and can cost up to $500. Donors should check with their insurance companies and plan accordingly.

Because the long-term effects of FMT are not known, the Food and Drug Administration requires that the recipient sign an informed consent form. It is possible that a registry of patients who have had FMT may be established to enable them to be followed over time. If and when such a registry is developed, patients are strongly encouraged to be a part of it.

Recipients

Usually, people who are going to receive FMT should have a completely empty GI tract, especially if the FMT is being given by colonoscopy. Usually, this means drinking only clear fluids and not eating anything for 12-24 hours before the procedure, although one should speak to their doctor. People with mild or moderate C. difficile may also be asked to drink a laxative liquid that will make them defecate until their entire digestive system is empty. However, those with severe infection, colitis, pseudomembranous colitis or toxic megacolon should not drink these preparations.

Recipients who will receive the transplant by enema or colonoscopy may be given loperamide (Imodium®) the day of the procedure. This drug slows down the muscle contractions in the intestines and colon so that the donor stool stays in the body longer and the helpful organisms in the stool have a chance to take hold.

If the transplant is to be delivered by a nasogastric tube, the recipient will be given a drug to prevent the stomach from secreting acid that can potentially destroy the helpful organisms in the donor stool.