

How and to Whom Should Fecal Transplantation be Applied?

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Fecal microbiota transplantation (FMT), also known as fecal bacteriotherapy, fecal transfusion, and stool transplantation, is a procedure that fecal matter from a healthy donor is transplanted into the gastrointestinal system (GIS) of the recipient.

The first use of fecal matter was given orally to treat food poisoning and severe diarrhea as the "Yellow Soup" in China at 4th century. In the 16th century, it was used to treat high fever, pain, vomiting, and chronic diarrhea/constipation. It was also employed in veterinary medicine in the 17th century. In the 20th century, "Hot camel feces" was recommended by Bedouins and used by German soldiers in Africa during World War II, confirming its therapeutic benefits. In Anatolia, "Dry horse-donkey and goat feces" were used to aid in the healing of injured tissues. In modern medicine, FMT was first used in humans in 1958 by Eiseman and colleagues.

The topic has gained increasing interest, and there has been a significant increase in research on the subject. For example, while the number of studies on the subject was 100 in 1990, it is noteworthy that more than 500 articles were published in 2010.

In the FMT procedure, the planted human gastrointestinal microbiota into the gastrointestinal system (GIS) of the recipient should be considered as tissue rather than an organ. Our bodies contain approximately 10^{14} microorganisms, which is 10 times more than the total number of cells in our bodies. Microorganisms are predominantly found in the GIS, skin, genitourinary system, and respiratory system. The colon alone hosts about 70% of the microorganisms in our bodies. Over 400 bacterial species have been cultured from the GIS, and this number can reach up to 36,000 using polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) methods. Most of these bacteria are facultative anaerobes, and a small number of them are aerobes. The GIS microbiota is diverse at birth but becomes relatively stable after the second year of life and remains until the end of life. There are four major types: Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria.

How should the donor and recipient be prepared for an FMT procedure?

For the recipient, the night before the procedure, before going to bed, it is recommended that they take a light laxative such as magnesium citrate. 1 hour before the procedure, the recipient should take 2 tablets of an antidiarrheal medication, preferably loperamide, to ensure that the transplanted material remains in the intestines for at least 4-6 hours. Healthy donors should be usually relatives and close friends, but stool can also be obtained from unrelated individuals through stool banks. The success rate of the treatment is slightly higher when the donor is a close relative (93%) compared to a stranger (84%). However, there is no significant statistical difference between these rates. Results obtained from operations conducted with randomly selected donors showed similarity to those obtained from relative donors. The gender of the donor does not have an effect on the success of the treatment. To prevent the recipient from being exposed to new diseases through FMT, the following factors should be investigated in detail in donors:

1. History of travel to regions with endemic diarrhea.
2. Sexual history.
3. History of previous surgeries.
4. History of blood transfusion.
5. The presence of malignancy in first and second-degree relatives should be queried.

When selecting a donor, screening should be conducted according to the Amsterdam protocol. Important points to consider during the anamnesis stated below:

1. Normal body mass index (18-25 kg/m²).
2. Use of antibiotics and proton pump inhibitors in the past 3 months.
3. Recent tattoos, piercings, or a history of imprisonment.
4. Engaging in high-risk sexual behavior or intravenous drug use in the past 3 months.
5. Presence of conditions such as irritable bowel syndrome, inflammatory bowel disease (Crohn's and ulcerative colitis), type 1 diabetes, Hashimoto's hypothyroidism, Graves' hyperthyroidism, rheumatoid arthritis, or celiac disease.
6. History of chronic diarrhea/constipation, colorectal polyps, or cancer.
7. Immunocompromised status (immunosuppressive therapy or chemotherapy).
8. Chronic fatigue syndrome.
9. Presence of allergies or food allergies.

These characteristics should be thoroughly investigated.

Additionally, both the donor's stool and blood should be examined.

In the donor's stool, tests should be conducted for followings.

Clostridium difficile toxin, Entemobae histolitica, Cryptosporidium.

Bacteria:

Helicobacter pylori antigen, Yersinia, Campylobacter, Shigella, Salmonella, Enteropathogenic E. Coli.

Viruses :

Rotavirus, adenovirus, enterovirus.

Parasites:

Astroviruses and Giardia.

In the donor's blood, the following tests should be performed:

1. Complete blood count, Full urine.
2. Liver function tests, albumin, total protein, Amilaz, Lipaz, LDL-KOL, HDL-KOL.
3. HIV-1 and 2 antibodies.
4. Human T-lymphotropic virus.
5. Hepatitis A, B, and C viruses. HBV-DNA, HCV-RNA.
6. CMV- PCR. and EBV-Ig M
7. Strongyloides, Amebiasis, Syphilis.

How should fecal transplant material be prepared?

Although there is no consensus on this matter, the Amsterdam protocol is mostly followed and preparation is done accordingly. The solution prepared according to this protocol is mixed manually or with a kitchen mixer, and then filtered through a coffee filter or a stainless-steel sieve to remove large particles and obtain a suspension. These suspensions are placed in 60 ml syringes. Fresh materials to be transferred can be cooled but should not be frozen.

Fecal material for transplantation can be infused through various ways. The mostly preferred method is colonoscopy, but transplantation can also be performed via a nasogastric tube, nasoduodenal route, upper gastrointestinal endoscopy, and retention enema.

There is no comparative study on methods of administration. Numerous research studies with conflicting results have been published. In fact, there are no significant differences among the results. The best and most effective route is the one selected based on the anatomical localization of the disease. For example, for the treatment of metabolic diseases (insulin resistance, celiac disease, small intestine diseases), the duodenal infusion route is the most effective. In colonoscopy, infusing fecal material up to the cecum and/or terminal ileum yields the best results. Regardless of the route of administration, for the transplantation to be effective, the material must remain in the lumen for at least 4 hours. To achieve this, the patient should be positioned on their left side after the procedure, and air should be aspirated from the colon to conclude.

What diluent should be used?

Different diluents have been used in various studies, but the recommended diluent is non-bacteriostatic 0.9% saline solution. At the same time, yogurt, buttermilk, milk, water, and egg can also be used.

How much stool is needed?

The amount of fecal material used affects the success and recurrence rate of the treatment. If less than 200 ml of fecal material is given, the treatment success rate is 80% and the recurrence rate is 6.2%. However, when more than 500 ml of fecal material is given, the treatment success rate increases to 97.3% and the recurrence rate decreases to 4.7%. For gastroscopy, 50-60 grams of stool with 250 ml of diluent should be used, while for colonoscopy, 200-300 grams of stool with 500 ml of diluent should be used.

Fresh or frozen? Which is better?

There is no significant difference found in the studies. Fresh stool should be given within 8 hours. In a study where previously collected and frozen stool was thawed and compared to fresh stool, the treatment success rate was 92% for fresh stool and 90% for frozen stool.

What are the indications?

FMT, which can be used for many different purposes nowadays;

Common Indications of FMT

Pseudomembranous enterocolitis associated with **Clostridium difficile**.

(IBD) **Ulcerative Colitis, Crohn's Disease.**

Irritable bowel syndrome,

Chronic diarrhea/constipation,

Chronic fatigue syndrome.

Rare and Investigational Indications of FMT

Multiple sclerosis

Tip-1 ve Tip-2 Diabetes Mellitus,

Obezite, İnsulin Resistance

Chronic diarrhea due to graft-versus-host disease

Autism, Parkinson and Alzheimer and Demans disease

Hepatik ansefalopati ve Cirrhosis of the liver

Primary Sclerosing Cholangitis

İTP, Ateroskleroz , Kolelitiazis

Çölyak disease

Hashimoto's thyroiditis

Multidrug-resistant organisms infections

Multiple organ dysfunction in critical patients

Is Fecal Microbiota Transplantation (FMT) safe?

It has been practiced in the world for 10-12 years. If the donor is chosen correctly and well. No major complications have been observed so far. For 8 years, We have applied Fecal Microbiota Transplantation to approximately 2100 patient with very different clinical conditions. We did not encounter any significant complications.

In conclusion

FMT is an effective and acceptable therapeutic approach for certain gastrointestinal and non-gastrointestinal diseases. As we gain a better understanding of the intestinal microbiota, its role in many diseases whose pathogenesis is currently unknown will be revealed.

So far (15-6-2023), 48 studies on FMT have been published in the world, including us. 14 of them are randomized and controlled trials. Except for one study. Successful results were obtained and published at different rates, varying between 27 % and 72.1 %. It was the same as placebo in only one study.

Fecal Microbiota Transplantation is safe and should be done in the early stages of diseases, that is, as soon as the diagnosis is made.

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