

Fecal Microbiota Transplantation for Clostridium Difficile Infection

DOSIEAH POOJA
DOOKHUN MUHAMMAD NABEEL
LIN HUI-HUA
ZHANG ZHEN-YU

Department of Gastroenterology, Nanjing First Hospital
Nanjing Medical University

Abstract:

The increased prevalence of Clostridium difficile infection (CDI) has caused significant clinical and economic burden. There has been a major challenge for recurrent CDI due to poor response to standard therapeutic approach. Following antibiotic treatment, the intestinal flora is disturbed and this constitutes a major risk of CDI. The emergence of fecal microbiota transplantation (FMT) has brought an efficient treatment concept towards CDI. FMT involves the reconstitution of the normal intestinal microbial homeostasis. The use of FMT has become an acceptable and successful treatment for recurrent CDI where conventional therapy has failed. CDI is the main cause of pseudomembranous colitis and is associated with high mortality and morbidity. Risk of CDI is highly due to the use of broad-spectrum antibiotic, increasing age and hospitalization. Ensuring a normal colonization of healthy intestinal microbiota can alleviate the symptoms of recurrent CDI and this can be done by FMT techniques. Recently, FMT has become an interesting therapeutic technique clinically for a variety of diseases.

Key words: Clostridium difficile infection (CDI), fecal microbiota transplantation (FMT), treatment CDI.

INTRODUCTION

Gastrointestinal bacterial flora microbiota is a chain of non-organic tissues that can be applied within Fecal Microbiota Transplantation (FMT) for the means of implantation in the patients' gastrointestinal tract (GIT) in order to get a sufficient knowledge of FMT usage. Basically, it is highly critical to appreciate the components of the gastrointestinal flora complex in accordance to its functional implications. Approximately, there are more than 1000 bacterial cells existing in the body of humans and the majority of them are located within the GIT (1). Less than 40 percent of them can be detected via culture-based methods (2). Many types of research have been conducted in this field and it has been shown that a range of fifteen thousand to thirty-six thousand of bacterial cells have the ability to interfere with the human GIT (3,4). A human gut microbe-catalogue has been established via the metagenomic sequencing and more than 3 million have been identified as non-redundant microbial genes, within an extremely large number than that of the whole human gene complex (5). The GI Microbiota associated with the genetic components are presented in a complex, balanced mechanism of homeostasis showing a highly important role in nutrition, metabolism of the energy, the defense of the host, as well as the enhancement of the immune system (6, 7, 8, 9). Dysbiosis or any unpleasant disturbance in the homeostasis composition including several diseases states are highly potential to be treated with FMT technique in order to compensate for these changes.

Fecal Microbiota transplantation (FMT) is defined as the process in which the fecal matter is presented to the GIT of the patient for the means of re-colonization within the natural bacterial-preface of the gut that undergone profound removal or suppression. One of the major applications of this procedure is the Clostridium difficile infections treatment (10). Recently FMT has been of great interest due to its therapeutic potential in

certain disease conditions including that of inflammatory bowel diseases (IBD) and chronic gastrointestinal infections.

The basic objective of this review is to figure out whether FMT is a reasonable, secured as well as an efficient way of treatment for the infections associated with Clostridium difficile or not in addition to investigate the recent feedback, indication criteria, as well as the way of FMT administration, to recommend a reasonable outcome for future studies and therapy maneuver.

CLOSTRIDIUM DIFFICILE INFECTIONS:

Patients undergoing hospitalization are capable of catching strong infections known as healthcare-associated infections. Among them is the anaerobic, gram-positive Clostridium difficile bacterium, that has been stated to be a major cause of infections globally, is now thought to be the leading cause of hospital-associated gastrointestinal illness.(11,12) Patients at high risk include old people under antibiotic therapy or those who are receiving a medical care.(13) Biologically, C.difficile is defined as being a spore capable of forming gram-positive anaerobic bacillus having the ability to produce either a single or double toxin or both Toxin A (an enterotoxin) & Toxin B (a cytotoxin).(14) Once the organism induces the infection of the intestine it might be a direct cause of diarrhea in addition to other intestinal complications, as an example; colitis of the pseudomembranous, as well as an increased inflammation of the colon with distension in addition to sepsis (15). Treatment with current antibiotic regimens causes alteration in the gut's composition thus opening a window for the opportunistic clostridium difficile to colonize. It is a highly correlated nosocomial infection in elderly people associated with high morbidity and mortality even in those with no recent antibiotic intake. (13)

The spores that have been produced by *C. difficile* present a reasonable significance for the implications of infection control. These environmental criteria could be maintained for several months within the ability of resistance against drying in addition to various antiseptics. Many studies conducted a direct relationship between patients suffering *C. difficile* diarrhea and the broad spread of the environmental contaminants (16).

The way of *C. difficile* transmission happens primarily by the fecal and oral route, through the infusion of spores capable of overcoming the stomach acidity. Moreover, the spores undergo the process of germination in the gut. The *Clostridium difficile* bacterial flora is represented in the fecal materials leading to contamination of areas and any surface in direct contact with feces. The bacteria produce toxins that could be a reason of causing diseases. This bacterium can be expressed in two forms either as a spore form or as a vegetative form. The spores could be maintained alive without existence in the body on close layers for several months. Prior to that, people can be infected through contacting the contaminated surfaces with feces or spores (17).

Nowadays, the infections correlated with *Clostridium difficile* is considered to be a critical problem all over the world. According to the recent statistical analysis done in the United States of America, approximately more than 450,000 patients have been infected by *Clostridium difficile* resulting in a gradual increase of mortality, especially for patients aged 65 and above (18,19,20) Thus, infections show a high rate of severity resulting in treatment difficulty.

Recently, Food and drug administration (FDA) has declared that the infections co-ordinated with *C. difficile* are highly resistant to drugs globally, especially in the US. This aspect identically influences not only patients with a high age range (especially those who undergo hospitalization) but also the younger ones. Fecal-oral transmission is one of the ways for

the bacterial spread that leads to infect patients undergoing antibiotic treatment.(21)

Toxin is discharged as a result of the initiation of colonization of *C. difficile* in the colon enhancing the inflammatory symptoms to be reflected, for example, high risk of diarrhea, fever in addition to a referred pain to the abdominal region leading to kidney failure and dehydration causing death in case of improper treatment (16,20). The borderline of treatment includes intake of metronidazole and vancomycin. The latter is used for severe cases while fidaxomicin is considered to be reservoir in case of recurrence. There is a percentage of recurrence ranges between 20 to 60 percent after antibiotic intake and numerous recurrences lead to an increased rate of antibiotic resistance (20,22).

FECAL MICROBIOTA TRANSPLANTATION:

Fecal microbiota transplantation (FMT) is identified to be a conductive way of treatment methodology for the infections correlated to *C.difficile* infections especially for the recurrent infected patients in addition to those who show a high resistance towards the antibiotic intake (16,18,25). FMT is an efficacious, safe, inexpensive and readily available treatment option.(13) Case reports of previous *C.difficile* infections have shown positive clinical resolutions of >90% upon transplantation. (23,24) Even though this way of treatment has been known for a long time, it has just been highly applied clinically. Fecal insertion from a non-infected patient to the GIT of an infected one is considered to be a way for the natural gut flora to be restored leading to the destruction of *C.difficile*. Before this process, the donor feces undergo screening in order to assure the lack of any sexually transmitted diseases (as for example hepatitis and human immune deficiency viruses). (26) With the usage of nasogastric tube, the process of transplantation can be easily performed and fecal material can

either be in a fresh or a frozen form. FMT is highly recommended for treatment against infections co-ordinated with C.difficile resulting in a good prognosis for almost all of the patients who underwent a single procedure (16,18,19).

Fecal transplantation has been widely used for recurrence of Clostridium Difficile. Many researchers recommend further studies to obtain other clinical uses for fecal transplantation while focusing on safety measures. Colonoscopy is the preferred method of transplantation as compared to duodenal infusion as it has been debated to be a more effective way. (27)

FMT METHODOLOGY FEEDBACK

According to several studies done to compare between the standard way of treatment and FMT, the latter showed a high significance resulting in the absence of all the symptoms within a shorter duration of time that that for the standard one (based on the antibiotics intake. (20,30) More trials are being conducted to assess the efficacy and safety of this practice as a treatment approach for C.difficile infection. These trials will give a better insight about FMT in terms for mode of delivery and other most effective practical choice. (28,29)

PROGNOSIS OF FMT

Fecal Microbiota Transplantation has been applied in the late 1950s and it showed a high success rate regarding patients suffering from antibiotics-induced diarrhea with the lack of any respond towards other ways of treatment. Moreover, the mentioned technique has been broadly utilized globally especially in the last ten years because of the reason that C.difficile infections express a relatively high prevalence rate in addition to increased resistance to the antibiotic therapy. Based on the recent statistics, 20 percent of patients suffering from

C,difficile infections undergo relapses leading to aggressive symptoms such as toxicity, septic shock that may lead to death. (31,32). No treatment to date has such a high-resolution rate of >90 %. Based on a study conducted by Brandt et al., most of the patients stated that they would prefer to opt for another FMT instead of the conventional antibiotic therapy and approximately half of the patients stated they would rather choose FMT as first line treatment. (23)

FMT TECHNIQUE OF USAGE:

The mechanism of FMT is initiated with the infusion of the fecal material of a donor with a free medical history through colonoscopy, nasogastric tube or enema. The major target is to restore the nature bacterial flora of the gut that is capable of creating an efficient defending way towards C. difficile (33).

The FMT method includes proper intake of fecal samples from a completely healthy donor, most often one of the family members. Test for immunological matching is not required as for transplantation of organs and blood transfusion. Nowadays, some protocols have been set up for the means of proper donor selection and screening. Basically, all the donors should be free from any GIT complications such as colon polyps or malignancy. Furthermore, patients receiving antibiotic treatment, recent antibiotic treatment, surgical interference to the bowel, patients with a systemic autoimmune diseases or metabolic dysfunction, as well as frequent traveling are not recommended donors. The experimental screening of donor fecal samples involves many pathogens of the intestine, parasites in addition to C.difficile. Donor blood is required for testing regarding any kind of chronic viral infections (as for example hepatitis, human immunodeficiency virus, cytomegalovirus and Epstein-Barr virus).

For patients undergoing FMT via nasogastric tube group, application of omeprazole orally is required two days

before the procedure while those using colonoscopy should go through a profound process of standard bowel preparation.

Fecal material is mixed with sodium chloride in addition to 10 percent of glycerol. The fecal material is frozen for a period of time not less than 156 days. It is highly predicted that each inoculum is extracted from more than 35 grams of feces for the nasogastric tube application. The tube delivery is reassured with radiograph measures followed by material administration. Then, this tube is taken out and all patients are highly required to immediately drink water. While for the colonoscopy technique, fecal material is delivered to the right colon, followed by the dilution process.

RELATED FMT RESEARCH WORK

Currently, there are a few randomized clinical trials in progress regarding the usage of FMT for difficile-associated long-standing diarrhea (FECAL) removal. This approach is being applied in Holland and till now the number of patients reached 120. It was initiated in 2008 and the main aim was to compare the efficacy of this technique against the antibiotic therapy.

Another trial is being performed in Canada and started in 2010 in order to investigate whether it is necessary or not to take oral vancomycin prior fecal bacteriotherapy via tapering methodology in a sample of 146 patients suffering CDI recurrence but till now no conclusions have been revealed.

It was also suggested to use FMT in several bowel diseases correlated with the C.difficile infection. Cases of 6 patients in which 4 of them were suffering colitis and the other two have been diagnosed with Crohn's disease and the results of FMT usage revealed complete disappearance of any colitis symptoms (33). A review done by Anderson et al. (34) highlights the good prognosis of patients treated with FMT. He selected sample of some case reports including fifteen patients who underwent FMT for the treatment of C.difficile infections. 9 of

them were suffering from colitis while the rest was Crohn's syndrome and it was concluded that those suffering from C.difficile infections have a better prognosis. Another study performed by Reddy et al. (35) who extended some more knowledge in the field of FMT. He demonstrated that the existence of C.difficile infection with IBD needed further processes of infusions to enhance the treatment process. (36)

CONCLUSION:

C.difficile has become an emerging epidemic with a high prevalence rate. Recurrent CDI as a major management challenge not only is difficult to treat but also may affect patients for a long time. The high therapeutic efficacy of FMT for recurrent CDI is an important proof of concept that substantial modification of the gut microbiota can be an effective modality of treatment in humans. This method has been used frequently in the last decade and it was proven that it is a highly favorable way of treating the Clostridium difficile infections as compared to that of antibiotic therapy. FMT is therefore the first and crudest way to alter the intestinal microbiome, and both patients and providers have become more aware of this highly effective option for CDI. Although FMT appears to be safe, with few short-term adverse effects or complications directly attributed to the procedure yet reported, more robust data on safety are certainly needed, as is better understanding of the mechanisms by which FMT is effective. This procedure has also been recently applied to other GIT diseases including dysbiosis. Many ongoing clinical trials are being done in this field to obtain a better insight about the FMT technique.

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