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A COMPREHENSIVE REVIEW ON FECAL MICROBIOTA TRANSPLANTATION THERAPY

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Abstract:

Over a decade fecal microbiota transplantation emerged as the best treatment approach in the therapy of dysbiosis-related diseases by improving or restoring the composition of the recipient's gut microbiota. FMT is highly recommended and effective in case of recurrent or refractory Clostridioides difficile infection (CDI) WITH 90% of cure rates. Despite the anticipated therapeutic advantages of FMT, the precise mechanism of action of FMT is not well understood. FDA released a safety alert regarding the potential life-threatening infections that may occur after a fecal microbiota transplant. Several RCT and clinical trials are performing on the FMT to understand the efficacy and safety in various other gut-related disorders. In this Review, we emphasized the mechanism of action, indications and contraindications, complications, and management of FMT in other diseases.

Keywords: *Fecal Microbiota Transplantation, Clostridium Infections, Gastrointestinal diseases.*

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INTRODUCTION:

Fecal microbiota transplantation (FMT) is the process of transferring healthy donor stool into a patient's gastrointestinal tract (GIT) in order to improve or restore the composition of the recipient's gut microbiota[1][]. FMT is also known as an intestinal microbiota transplant, Fecal transplantation, stool transplant, and bacteriotherapy. In the 4th century, fecal material was administered orally to treat diarrhea, food poisoning, and fever in china, and enteric flora transplantation was used in veterinary medicine in the 17th century[2]. According to reports, soldiers in World War 2 treated bacterial dysentery with fresh, warm camel feces[3]. In 1958 fecal enemas were used successfully to treat patients suffering from pseudomembranous colitis[4]. FMT was initially incorporated into the IDSA (Infectious Diseases Society of America)/SHEA(Society for Healthcare Epidemiology of America) guidelines in 2010[5]. In 2013 FMT was a conditional recommendation in the American college of gastroenterology (ACG)[6][]. In 2014 FMT was strongly recommended in the European Society of Clinical Microbiology and Infectious Diseases[6]. With overall success rates of 90% and evidence of safety and efficacy from RCT and meta-analyses, FMT is an emerging and highly effective, safe modality for the treatment of recurrent or refractory Clostridioides difficile infection (CDI). More than 300 studies evaluating FMT are currently available on ClinicalTrials.gov, with the majority of them focusing on gastrointestinal issues but also including evaluations of FMT for neurologic, behavioral, and metabolic issues[7].

GASTROINTESTINAL MICROBIOTA

An estimated 1000–1200 different bacterial species are found in the human gastrointestinal (GI) tract, with the majority of these species being found in the large intestine, roughly 3.9 x 10^{13} organisms, which is comparable to the number of cells in the human body, along with that fungus, archaea, protozoa, and viruses also present in git[8,9]. Species of Firmicutes and Bacteroides are among the most prevalent colonic microbes[10] Three important functions of the microbiota in the gut include (a) a wide range of metabolic processes, such as the production of vitamins, the breakdown of dietary carbohydrates, and bile processing; (b) the production of antimicrobial factors and the protective exclusion of some pathogens from growing; and (c) the maintenance of mucosal immunity through intricate interactions with the gut epithelium. This healthy microbiota, through colonization resistance, defends the body from invading bacterial pathogens[11].

FMT MECHANISM OF ACTION

The Fecal microbiota transplant act by reintroducing the healthy microorganisms which are destroyed by the pathogenic microorganisms and improper antimicrobial usage, by restoring the bactericidal/ bacteriostatic action of healthy bacteria by killing pathogenic bacteria and inhibiting their growth. FMT also restores normal gut metabolism and intestinal barrier function. Plays the main role in the eradication of C. difficile infections.

FMT INDICATIONS AND CONTRAINDICATIONS

Currently, fecal microbiota transplantation is predominately used for the treatment of refractory/recurrent CDI [4]. In general oral metronidazole is the first line of therapy for mild-moderate C. difficile infections, while vancomycin is advised for more severe infections or recurring infections[12]. Numerous randomized controlled trial studies have shown that FMT successfully treats patients with recurrent and resistant CDI[13,14]. This exceptional efficiency may be explained by the continuous restoration of the natural microbiota that occurs following FMT. In recurrent or refractory CDI, the cure rate of FMT is remarkably up to 90%, which is much better than extended anti-microbial treatment with 20 to 30 % cure rates[15]. The US Food and Drug Administration (US FDA) has been approved since 2013 and is already included in various expert guidelines of standard practice for the management of refractory and recurrent CDI[16]. Based on data from different case reports and clinical trials on FMT, indicated in gastrointestinal diseases (inflammatory bowel disorders, irritable bowel syndrome, constipation) and extra-gastrointestinal diseases (autoimmune disorders, obesity, Parkinson's disease, metabolic syndrome, multiple sclerosis, multidrug-resistant organisms infections, autism) but further evaluation and role of FMT in extra-gastrointestinal diseases is going on[15]. There are several comorbid illnesses that should be taken into account before undergoing FMT, even if there are presently no absolute contraindications for potential patients. When dealing with individuals using immunosuppressive medications or experiencing any illness process that causes severe immunodeficiency, extra care must be used. High-dose corticosteroids, posttransplant immunosuppression using drugs like calcineurin inhibitors and mammalian target of rapamycin inhibitors, as well as chemotherapeutic and anticancer drugs like tumor necrosis factor inhibitors, are all examples of immunosuppressive medications.

Decompensated liver cirrhosis, severe HIV/AIDS, and recent bone marrow transplantation are other immunodeficiency-related disease processes that should be taken into account as prospective (or relative) contraindications[17].

SCREENING PROTOCOL FOR FECAL MICROBIOTA DONOR

The screening of the donor was performed according to following approved guidelines by various Clinical trials[7].

- **Inclusion and exclusion criteria of fecal microbiota donor**[4,18–21]

➢ ***Inclusion criteria***

- Healthy person aged between 18-65 years
- no prior or present gastrointestinal illness symptoms and additional significant ongoing medical conditions
- Few frequent drugs, none of which may affect the viability of the feces, and none of which have been antimicrobials (antibiotics, antifungals, and antivirals) or probiotics in the last three months

➢ ***Exclusion criteria***

❖ Infectious agents risk

- The current and past history of Inflammatory bowel disease (IBD), chronic diarrhea and constipation, irritable bowel syndrome, malignancy of the gastrointestinal tract, and family history of colorectal cancer
- History of individual significant gastrointestinal surgery (eg: partial colectomy, gastric bypass)
- Hepatitis B and C infections, Human Immunodeficiency virus (HIV), and usage of illicit drugs
- Currently known communicable diseases (eg: Upper respiratory tract infections)
- The various risk factors for variant Creutzfeldt-Jakob disease (A degenerative brain disorder that leads to dementia and death).
- Travel during the past six months to regions of the world where diarrheal diseases are common or where there is a significant risk of developing travelers' diarrhea and Body piercing or a tattoo during the last six months
- Other diseases like atopic disease, multiple sclerosis, connective tissue diseases, fibromyalgia, chronic fatigue syndrome, neurological disorders, and a history of malignant disease.

❖ Numerous factors alter the gut microbiota

- Probiotics, Antimicrobials (antifungal, antibiotics, antiviral) within the last three months.
- Biological agents, calcineurin inhibitors, and systemic antineoplastic agents.
- Family members with active gastrointestinal diseases

➢ **Laboratory investigations**

- Complete blood picture (CBP)
- C-reactive protein test
- Antinuclear antibodies test
- Lipid profile test and metabolic panel test
- Human chorionic gonadotropin pregnancy test (Female)

➢ **Microbial and stool screening test**

- Gene identification for Clostridium difficile toxin by PCR test
- Identification of rotavirus antigen by ELISA
- The detection of enteric pathogens like shigella, salmonella, plesiomonas, aeromonas, campylobacter, yersinia, Escherichia coli O157, V. parahaemolyticus, and Vibrio cholera are done by stool culture.
- Vancomycin-resistant enterococci (VRE) rectal screen
- Helicobacter pylori antigen test
- Methicillin-resistant staphylococcus aureus (MRSA) screen
- Tests for parasites and ova, including cryptosporidium and giardia

➢ **Serological investigations**

- Hepatitis- A test (IgG+IgM antibodies)
- Hepatitis- B test
- Hepatitis- C test (IgG)
- Syphilis Trep-Sure ELISA
- HIV-1 and HIV-2 p24 antigen and antibody (IgG) test
- Plasma polymerase chain reaction assays for Cytomegalovirus, and Epstein-Barr viruses.

RECIPIENT PREPARATION AND FECAL MICROBIOTA PREPARATION

In order to prepare a patient for fecal microbiota transplantation, there is currently no standard procedure. No antibiotics of any kind should be given to the recipient 12 to 48 hours before fecal infusion[18]. Recipients of fecal microbiota transplants for C. difficile must take vancomycin for 5–10 days before stopping 24–36 hours prior to the procedure. According to certain research, loperamide should be taken one hour before FMT to make sure the

transplanted feces remain in the intestines for at least 4 hours[10]. The 30g to 50 g of fecal matter is mixed with 150 ml of sterile NaCl (sodium chloride) water in a blender[15]. The prepared solution is filtered to remove large particulate matter from the processed solution. Approximately 60 ml of fluid infused into the gastrointestinal tract of the recipient and the fecal preparation should be stored at -80°c[15].

FMT IN THE MANAGEMENT OF SEVERAL DISEASES

In the post-antibiotic age, the emergence of refractory antibiotic-related resistance has caused medical professionals and scientists to reconsider the utility of FMT in contemporary medicine[22]. The FMT is had played main role in the treatment of bacterial infections [clostridium difficile infection (CDI), multi drug resistance organisms (MDRO), urinary tract infections (UTI)] and other viral and fungal infections. The case reports and various research papers provide the effective role of management with FMT in several Gastrointestinal diseases [Crohn's disease(CD), Ulcerative colitis(UC), Constipation, Pouchitis, Irritable bowel syndrome (IBS), and other gastrointestinal diseases], Gastrointestinal-liver related diseases [Severe alcoholic hepatitis (SAH), Hepatic encephalopathy (HE), Cirrhosis, Non-alcoholic fatty liver disease (NAFLD), Primary sclerosing cholangitis (PSC), Hepatic myelopathy], Gastrointestinal-brain [Parkinson's disease (PD), Autism spectrum disorder (ASD)], metabolic diseases, Radiation enteritis (RE), Drug-associated colitis, Graft-versus-host diseases (GVHD) and skin, kidney and other diseases[22].

COMPLICATIONS AND ADVERSE EVENTS

According to recent reports, severe multidrug-resistant bacterial infections killed individuals who had received FMT. Because of this, one of the two immunodeficient patients who received FMT from donors who had not been tested for the gram-negative bacteria that produce the extended-spectrum -lactamase (ESBL) developed an invasive infection with ESBL-producing Escherichia coli, which ultimately led to his death. This instance has been brought to notice by the FDA[23]. The FDA provides safety alert for patients receiving FMT had a risk of developing potentially life-threatening infections caused by enteropathogenic Escherichia coli (EPEC) and Shigatoxin-producing Escherichia coli (STEC)[23].

The patients who are receiving fecal microbiota transplant experience various adverse events, the mild adverse events are Borborygmus, Nausea/Vomiting (FMT through oral route), Transient fever, Abdominal discomfort, Bloating, and Flatulence. Patients also experience severe adverse events like colon cancer, Inflammatory bowel disease, autism, asthma, non-alcoholic fatty liver disease, etc[15].

CONCLUSION:

Currently, refractory/recurrent clostridium difficile infection was predominantly treated by Fecal microbiota transplantation, due to the emergence of antibiotics resistance, but the role of FMT is not clearly known completely. Several clinical trials are going on to assess the role of FMT in the management of several other diseases. The FDA recently released a safety alert regarding the potential life-threatening infections that may occur after fecal microbiota transplant, so there is a need for further research to carry on for assessing the safety, efficacy, and role of FMT on all diseases.

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