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Fecal Microbiota Transplantation

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Fecal microbiota transplantation (FMT) also known as bacteriotherapy, fecal microbiota reconstitution, or human probiotic infusion is the transfer of stool from a healthy donor into the gastrointestinal tract of a recipient for the purpose of treating recurrent *Clostridium difficile* colitis[1]. The main aim is to restore the microbiota.
The precise mechanisms of FMT in the treatment of Clostridium difficile-associated Disease (CDAD) or *C. difficile* infection (CDI) remain unclear, but may involve the re-colonization of microbiota with missing components to generate colonization resistance or direct antagonistic activity of the normal microbiota to *C. difficile*. Unlike the transient use of antibiotics (e.g. vancomycin) for *C. difficile*, implanted microbiota may provide a prolonged presence of 'antagonistic' activity, break the cycle of antimicrobial use, and prevent future colonization by *C. difficile*[2].
FMT by nasogastric tube (NGT) showed that it is more effective than oral vancomycin in preventing further recurrences in individuals who have already had recurrent *C. difficile colitis*[3].

CDAD: *Clostridium difficile* is a Gram-positive, spore-forming bacteria, and the most important and common nosocomial pathogen of healthcare-associated diarrhea in hospitalized patients in developed countries. One fourth of all cases of antibiotic-associated diarrhea is due to this infection and causes almost all cases of pseudomembranous colitis. The infection can be mild to severe, ranging from mild diarrhea to life-threatening complications, such as ileal perforation, fulminant colitis, toxic megacolon, or brain empyema[4]. Recently CDAD has become more frequent and severe, more refractory to standard therapy, and more likely to relapse[5,6]. This pattern is widely observed in Canada, the United States, and Europe and is attributed to a new hypervirulent strain of *C. difficile* called NAP1/BI/027[7,8].
Mature colonic bacterial microbiota in a healthy adult is generally resistant to *C. difficile* colonization. Any factors associated with the alteration of normal intestinal microbiota increases the risk of *C. difficile* colonization after exposure to the bacteria[9].

Risk factors for CDAD:

1. Use of broad-spectrum antibiotics
2. Concomitant use of multiple and prolonged antimicrobials[9-11].
3. Advanced age (65 years or older).
4. Recent transplantation.
5. Gastrointestinal surgery.
6. Use of immunosuppressive drugs.
7. Use of proton pump inhibitors.
8. Prolonged hospitalization
9. Malnutrition.
10. Nasogastric tube feeding and presence of multiple co-morbidities[12-16].
11. The host immune response is considered the major determinant of outcome following exposure to *C. difficile*[17].

Standard treatment of CDAD includes: discontinuation of the offending/inducing antibiotics and *C. difficile* targeted antibiotic therapy with oral metronidazole, or vancomycin which is the only US FDA approved drug for CDAD[1,18-21]. Although generally effective in the majority of patients in achieving clinical improvement, the use of antibiotics (e.g. vancomycin) does not restore intestinal microbiota, nor does it reduce the exposure to *C. difficile* in the environment, co-morbidities or other host risk factors[22,23].
Despite the fact that more than 90% of patients respond to the treatment initially, 20% to 60% of patients will experience at least one recurrence within a few weeks of completion of the vancomycin treatment[19,23-25]. Therefore optimal management of multiple relapses remains clinically challenging.
Although there is limited evidence, FMT appears to be a safe and effective procedure. Symptoms improve immediately after FMT procedure and patients stay diarrhea free for several months or even years, indicating that FT could be an effective alternative in the treatment of patients with recurrent/refractory CDAD.

Indications for FMT:

1. Recurrent *Cl. difficile* infection.
2. Resistant *Cl. difficile* infection.
3. Irritable Bowel Disease[26,27].
4. Inflammatory Bowel Disease[28].

Potential Indications in the Future:
With renewed interest, presently work is being done on human microbiota and breakthrough has been made in three new fields:

1. Gut microbiota promote bone growth via IGF1[29].
2. Intestinal microbiota affects host physiology[30].
3. Mucin degrading bacteria Akkermansia muciniphila modulate glucose metabolism[31,32].

Donor Criteria for FMT:
A potential donor prior to fecal transplantation should have the following prerequisites:

1. No antibiotic exposure in the past six months.
2. Not immunocompromised.
3. Not have had any tattooing or body piercing in past six months.
4. Not have any history of drug use.
5. Not have any history of high-risk sexual behavior.
6. Not have any history of incarceration.
7. Not have recently traveled to endemic areas for Amebiasis or Giardiasis.
8. Not have any chronic GI disorders, such as inflammatory bowel disease.

In the majority of the cases, the donors can be family members or relatives. Unrelated healthy volunteers can also donate. However the donor criteria mentioned above must be fulfilled by all donors.

Screening of Donors for FMT:
A potential donor should be screened for:

1. Blood tests: Hepatitis A, B, and C serology; HIV; RPR for Syphilis.
2. Stool tests: Ova and parasites; C. difficile PCR; culture and sensitivity; Giardia cyst or antigen.
3. Any allergies.

FMT Procedure:
Before the procedure, patient has to follow specific preparation instructions.

1. Pre-transplantation use of Antibiotics. Drugs used against CDAD, such as vancomycin or metronidazole, are prescribed prior to FMT to suppress the pathogen burden.
2. Stop all antibiotics two days before the procedure.
3. Liquid diet followed by an enema or laxative preparation the night before the procedure.
4. Fecal transplantation is usually performed by Colonoscopy. As the colonoscope is withdrawn, the donor stool is delivered through the colonoscopy into the colon.
5. Other Methods of FMT delivery:

a) Gastroscopy
b) Nasogastric tube Insertion
c) Retention enema
d) Oral Capsule (Fresh and Frozen microbiota)

Delivery Methods
In all studies, fresh donor feces were used to prepare fecal suspensions. Polyethylene glycol (PEG) bowel preparation was performed in two studies[33,34] in which fecal suspensions were delivered by colonoscopy.
For most patients FMT was performed by clinical specialists either in hospitals or outpatient clinical centers, whereas in the Canadian study[35] patients or their family members administered the procedures in their homes.
Volumes of fecal suspension delivery varied across the studies depending on the method of delivery used. In two studies[36,37] a small amount (25–30 mL) fecal suspension was infused through a nasogastric tube, once only, whereas in other studies a larger amount of fecal suspensions (200–600 mL) were delivered via gastroscopy, colonoscopy, or rectal retention enema, once only. The majority of patients received a single FMT procedure.
Through NGT: 30 g feces in 50–70 mL saline/25 mL[37], or 30 g feces in 150 mL saline/30 mL[36].
By Gastroscopy: 50–100 g feces in 250 mL saline/200 mL[38].
By Colonoscopy: quantity of feces not specified and 300–600 mL used[33].
By Retention Enema: 50 mL feces in 200 mL saline/250 mL[35].
Only a small number of patients needed second FMT when the first FMT failed[34,38] or symptoms reccurred[36] after the initial success.

Newer Modalities of treatment:
FMT can now be delivered by a capsule. This mode of delivery has been recently used to treat recurrent *Clostridium difficile* infection. This was an unblinded, randomized trial conducted in three academic centers in Alberta, Canada, between October 2014 and September 2016, with follow-up to December 2016. Results were published by JAMA[39]. Among 116 patients, 57 were randomized to the capsule group and 59 to the colonoscopy group. One hundred and five patients (53 in the capsule group and 52 in the colonoscopy group) completed the trial. Recurrent *C. diff.* was prevented after a single treatment in 96.2% of the capsule group (51 of 53 patients) and the colonoscopy group (50 of 52 patients) (difference, 0%; $P<0.001$). FMT by capsule seems to be a safer, economical and convenient method of delivery. However rates of resolution of diarrhea following administration of FMT using frozen encapsulated inoculum from unrelated donors was 70% only[40] , though a recent study did not find any difference[41].

The various methods used to conduct FMT and their important features have been put up in the form of a table. See below for Table 1.

Various methods of Fecal Microbiota Transplantation and their salient features

Mode of Delivery	Gastroscopy	Colonoscopy	NGT	Enema	Capsule
Procedure	Less available/difficult	Less available/difficult	Available/Takes Less Time/Easy[36]	Easy	Easy
Advantage and Disadvantage	Check for stomach and Duodenum/Less volume	Check for Rectum and Colon & preferred sites[42]/Large volume/Better retention[(33,34)]	Larger area exposed[36]	Lesser retention	Not known
Risk	Gastritis	Sometimes dangerous[38]	Safe in most/Vomiting and aspiration of fecal matter[33]	Safe	Safest
Reproducible	Fast, safe, Less stressful[38]	Inconvenient/Costly	Yes/Economical	Yes/Self therapy at Home[35]	Yes/Self therapy at Home
Eradication of Cl. difficile	90%	95-100%[34]	90-100%[3]	100%[35]	96.2%[39]
Severe CDAD and Colonic Distention	Safe[19]	Avoid	Safe	Safe[19]	Safe

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Table 1. Various methods of FMT and their salient features.

Conclusion:

FMT will soon become the preferred treatment for recurrent or resistant CDI. More randomized controlled studies are underway to help us understand its role regarding the safety, efficacy and modes of delivery. These will help us to compare different delivery methods of the fecal microbiota suspensions to establish superiority of one over another. Most studies till date do suggest that FMT administered by nasogastric tube, gastroscopy, colonoscopy, or retention enema and capsule is safe. All studies have reported promising results indicated by high response rate. Newer indications of FMT will bring in lot of promise in solving many long standing riddles in medical science.

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Conflict of Interest: None declared.

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