Fecal Microbiota Transplantation: A Promising Therapeutic Approach for Recurrent Clostridium Difficile Infection and Other Disorders; Literature Review

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Abstract. Clostridium difficile infection is the most prevalent hospital-acquired infection following antibiotic administration. It represents a significant burden on the patient's morbidity, mortality, and the global healthcare system. Fecal microbiota transplantation was found to be an excellent alternative method for treating and preventing recurrent C. difficile infection. The exact mechanism is unknown, but it is thought to restore the diversity and composition of gut microbiota. We have identified the relevant studies using the PubMed database, the following mesh words were "fecal microbiota transplantation" and "recurrent Clostridium difficile infection. No quality assessment of individual studies was performed. In this literature review, we will try to determine the efficacy, safety, and cost-effectiveness of fecal microbiota transplantation in patients with recurrent Clostridium defficile infection compared to standard antibiotic therapy. High cure rate was reported regardless of the transplantation modality. Beyond recurrent C. difficile infection, we reviewed the use of fecal microbiota transplantation in other conditions such as primary C. difficile infection and inflammatory bowel diseases.

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1. Introduction and Background:

Clostridium difficile (C. difficile) is an obligate anaerobic gram-positive spore-forming, toxin-producing bacillus, officially renamed in 2016 to Clostridioides difficile (Messias et al., 2018; Czepiel & Drózd 2019). It was found to be disease-causing in 1978 (Messias et al., 2018). Infection caused by C. difficile is the most common hospital-acquired infection associated with antibiotic administration (Messias et al., 2018). Transmission occurs through the fecal-oral route, person-to-person, through fomites, and hospital instruments (Messias et al., 2018).

C. difficile has different virulence factors, mainly exotoxins, enterotoxin, and cytotoxin (Messias et al., 2018). These toxins are the leading cause of the intestinal epithelium destruction and mucosal injury, and ultimately, the development of pseudomembranous colitis (Messias et al., 2018). C.difficile is part of the healthy flora in the entire intestine of humans and animals (Czepiel & Drózd 2019). Approximately 5% of adults and 15–70% of infants are colonized by C. difficile (Czepiel & Drózd 2019). The colonization prevalence is several times higher in hospitalized patients and nursing home residents (Czepiel & Drózd 2019).

Most common presentations with toxin-producing C.difficile are non-bloody diarrhea, fever, and abdominal pain (Czepiel & Drózd 2019). Severe Clostridium difficile infection (CDI) are manifested by inflammatory markers elevation and hypoalbuminemia (Czepiel & Drózd 2019). Severe CDI leads to potentially fatal consequences such as toxic megacolon or spontaneous colon perforation, acute kidney injury, and hypotension (Czepiel & Drózd 2019; Konturek et al., 2016).

Recurrence of CDI occurs in 10%–25% of patients treated with metronidazole or vancomycin (Asempa & Nicolau, 2017). Furthermore, frequent recurrences have been reported in the same individual (Asempa & Nicolau, 2017). CDI represents a severe burden for the patient's morbidity, mortality, and the healthcare system globally (Li et al., 2012; Ma et al., 2017). Based on current incidence rates, annual costs for management of CDI amount to approximately $800 million in the USA and €3000 million in Europe (Li et al., 2012). Furthermore, the estimated cost of recurrent C.difficile infection (rCDI) can exceed that of primary CDI (Li et al., 2012). C. difficile was responsible for almost half a million infections and was associated with approximately 29,000 deaths in the united states in 2011 (Ma et al., 2017).

2. The Principle of gut dysbiosis and its influences on intestinal and extraintestinal disorders:

The term gut microbiota is described as the whole culture of bacteria, viruses, parasites, and fungi colonizing

small and large intestine (Ooijevaar et al., 2019). Roughly, the adult gut microbiota is composed of more than 2,000 species of bacteria (Ooijevaar et al., 2019). Gut microbiota contributes to essential metabolic and biological functions (Ooijevaar et al., 2019). Dysbiosis, by definition, is the impairment of the normal diversity and composition of the gut microbiota (Ooijevaar et al., 2019). It is thought to be a part of the pathogenesis of many other conditions, such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), multiple sclerosis (MS), hepatic encephalopathy (HE), metabolic syndrome, Parkinson disease and graft versus host disease (GVHD) (Ooijevaar et al., 2019); D'Haens & Jobin, 2019).

Large variety of therapeutic procedures used to normalize gut dysbiosis, including fecal microbiota transplantation (FMT) (Wang et al., 2019). By definition, FMT is the transplantation of stool from a healthy donor into a diseased patient's gut (Wang et al., 2019). The first successful FMT was reported in the healthcare literature by Eiseman et al. for treating *pseudomembranous colitis* in 1958 (Wang et al., 2019). Currently, the only indication for FMT is to treat rCDI (Wang et al., 2019). Several guidelines recommend the use of FMT as a second-line treatment of rCDI (Kelly et al., 2016). The European guidelines recommended considering FMT for severe CDI after the primary antibiotic regimen (Kelly et al., 2016). This Literature review will address the clinical use, cure rate, cost-effectiveness, and short-term safety of FMT for patients with rCDI in comparison to standard antibiotic regimens. Additionally, the future application and safety of FMT for immunocompromised individuals with rCDI, primary CDI, and rCDI in IBD patients.

3. Discussion and Result:

3.1. FMT in Recurrent and Refractory CDI

FMT has been used frequently in the last couple of years, especially for recurrent and refractory CDI (Messias et al., 2018). In 2010, a group of specialized medical centers established the main indications of FMT treatment described in Table1 (Messias et al., 2018).

Table 1. Indications for Fecal Microbiota Transplantation:

1. Recurrent *C. difficile* infection:
   - Three or more episodes of mild to moderate C. difficile infection and failure of 6-8-week cycle with vancomycin, with or without an alternative antibiotic, i.e., Rifaximin, Nitazoxanide or Fidaxomicin.
   - Minimum of two episodes of C. difficile infection resulting in hospitalization and associated with critical comorbidities.
2. Moderate *C. difficile* infection is not responding to standard therapy (vancomycin or fidaxomicin) for at least one week.
3. Severe *C. difficile* infection (even fulminant) without response to standard therapy after 48 hours.

The American College of Gastroenterology also recommended FMT as an option for rCDI in patients who did not respond to the vancomycin regimen (Messias et al., 2018). Recent studies showed that FMT was more cost-effective and clinically efficient than standard regimen for CDI; metronidazole, vancomycin, and fidaxomicin (Messias et al., 2018). The exact mechanism of FMT is unclear, but it was thought to restore the normal diversity and composition of the gut microbiota by reduction in Proteobacteria and Verrucomicrobia and increase in Bacteroidetes and Firmicutes (Reigadas et al., 2018). Additionally, the secondary bile acids are suggested of playing a major rule in the growth of C. difficile (Reigadas et al., 2018). FMT successfully restores the secondary and total bile acid components, which inhibit the reproduction of C. difficile in normal circumstances (Reigadas et al., 2018). The fecal sample taken from a healthy donor, processed and liquidized in the laboratory to form a bacterial suspension, and delivered into a patient's gut (Mullish & Williams, 2018).

Typically, donors must be investigated rigorously to prevent possible transmission of infectious agents, and full detailed history must be taken (Table 2) (Kelly & Tebas, 2018); Song & Kim, 2019; Satokari et al., 2015).

Table 2. Donors screening:

Laboratory investigations:
Serology test: HIV 1, HIV 2, Viral hepatitis B and C Complete blood count, C-reactive protein and Electrolytes Liver function test, Renal function test, Lipid profile C. difficile culture and toxin A/B Stool culture and sensitivity, ova and parasite *Tropenema pallidum* serum test
History required:
Illicit drug use and Sexual history History of GI diseases such as: IBD, IBS, GI malignancy and abdominal surgery Obesity/Metabolic syndrome Atopic diseases Recent antibiotic use

Abbreviations: GI: Gastrointestinal. IBD: Inflammatory bowel diseases. IBS: Irritable bowel syndrome. HIV: Human immunodeficiency virus.

Some fecal microbiota transplantation programs additionally exclude donors with personal or family histories of diseases associated with disrupted intestinal microbiota, such as obesity and depression (Hota & Poutanen, 2018). FMT becomes broadly available in public stool banks such as "OpenBioma" (Kelly & Tebas, 2018; Khoruts, 2018).

There is no recommended route of FMT administration (Song & Kim, 2019). However, FMT can be delivered in various ways, commonly through the upper

GI tract (endoscopy, nasogastric or Nasojejunal tube, or by capsule ingestion) and the lower GI tract (colonoscopy, recto sigmoidoscopy and enema or combined approach) (Messias et al., 2018; Song & Kim, 2019; Cammarota et al., 2017; Kim & Gluck, 2019). Table 3 compares the different administration method's strengths and weaknesses (Messias et al., 2018; Song & Kim, 2019; Cammarota et al., 2017; Kim & Gluck, 2019).

Table 3. Comparison between different FMT delivery methods

Method	Cure rate	Advantages	Disadvantages
Upper GI: NG/NJ tube, gastroscopy	81%	- Safe for patients contraindicated to colonoscopy - Sedation needless	- Nausea, vomiting, aspiration - Moral discomfort - SBBO - Less volume infused (25 – 50ml) compared to colonoscopy - Cannot reach distal colon
Capsule (Frozen and fresh)	>90%	- Easy storage and administration - Few side effects - Patient's comfort - Non-invasiveness	- Take longer time for clinical improvement compared to other modalities - Cost
Colonoscopy	90%	- High cure rate - Better visualization of affected/inflamed areas - Infusion of large volume (200 – 500ml) - Better retention, distal reach compared to enema infusion	- Sedation risk (vomiting or aspiration) - Risk of perforation (in severe colitis or ileus) - Cost - Endoscopist's skills needed
Retention enema	93%	- Sedation needless - Self-administration at home, availability - Low cost, less invasive	- Needs repetition to achieve clinical improvement - Poor retention, limited to the splenic flexure

Abbreviations: GI: gastrointestinal. NG: Nasogastric. NJ: Nasojejunal. SBBO: Small bowel bacterial overgrowth

The first successful randomized trial was published in 2013, where FMT was infused through a nasoduodenal tube into 16 patients with rCDI (Guery et al., 2019). With a single infusion, 13/16 had diarrhea resolution, and the remaining three patients received the second infusion, of which 2/3 had symptoms resolution, to achieve a total of 93.8% cure rate (Guery et al., 2019). In comparison to the control groups, the first group received vancomycin alone, and the second group received vancomycin with bowel lavage were cured in 31% and 23% of cases, respectively (Guery et al., 2019). In 2 randomized control trials, FMT showed a significantly higher cure rate than vancomycin (94% and 90% vs. 31% and 26%, respectively) (Cammarota et al., 2017). Another randomized clinical trial comparing 64 patients with documented rCDI, 24 patients were assigned for FMT (19 via colonoscopy and five via Nasojejunal tube), 24 patients treated with fidaxomicin and 16 patients received vancomycin (Hvas et al., 2019). The primary outcome was clinical resolution and negative C. difficile test (Hvas et al., 2019). FMT group achieved primary outcome of 71% (17/24), while fidaxomicin group 33% (8/24) and 19% (3/16) in the vancomycin group (P = .009 for FMTs vs. fidaxomicin; P = .001 for FMTs vs. vancomycin) (Hvas et al., 2019). A retrospective study was observing the response of FMT via colonoscopy from 2007 to 2014 in rCDI patients (Satokari et al., 2015). The assigned patients were divided into two groups, first one received fresh transplant, while the second group received frozen transplant (Satokari et al., 2015).

Clinical outcome was achieved during 12 weeks of follow up, of which 96% (25/26) of the fresh transplant group, and 96% (22/23) in frozen transplant group (Satokari et al., 2015). In many uncontrolled observational studies, the cure rate of FMT found to be >90% (Johnson & Gerding, 2017).

FMT also found to be effective and relatively safe in severe CDI (Rao & Safdar, 2016). Lagier et al. conducted a study for severe CID patients with a high mortality rate, which found FMT to be superior to standard therapy (Rao & Safdar, 2016). One death case reported as a result of aspiration pneumonia during sedation for FMT via colonoscopy (Rao & Safdar, 2016). Besides, a retrospective cohort study for 111 patients with severe CDI, including 66 patients treated with FMT compared with 45, were treated with a standard antibiotic regimen (Hocquart et al., 2018). The three-month mortality rate was found to be 12% (8/66) in FMT treated group versus 42% (19/45) with the standard regimen (P<0.003) (Hocquart et al., 2018). In one cohort study included 57 in patients with severe or severe-complicated

CDI were treated with FMT (Fischer et al., 2017). The overall treatment outcome at one month was accomplished by 91% (n = 52) of the patients, while the remaining five patients had treatment failure (Fischer et al., 2017). Two out of five patients had complete recovery after the second FMT in follow-up, one survived a septic shock, and two deaths were reported; one following colectomy after three failed FMTs and one had sepsis and died within 24 hours after the first FMT (Fischer et al., 2017).

The precise mechanism of FMT is unclear, but generally, it was suggested to replace the standard gut flora components to resist the overgrowth of C. difficile. FMT has different ways of delivery, and all need special preparations and recommendations. Before FMT, the recipient needs support and education about administration method, possible adverse outcomes, and procedure failure. All forms of FMT delivery are superior to the standard antibiotic regimen in the treatment and prevention of rCDI. Furthermore, it considered to be an easy procedure, mainly FMT capsules, with approximately the same cure rate of other methods and safety profiles. Ultimately, FMT showed its efficacy and safety in severe CDI in a small number of trials. Some mortality cases were reported, but it is not directly associated with FMT itself. Therefore, large RCTs are needed to understand the long-term efficacy, safety, and potential use in severe CDI cases.

3.2. Adverse Events, Complications, and Follow up

FMT considered to be a safe procedure with few and self-limiting adverse events (Shaukat & Reinink, 2017; 28]. Table 4 listed the frequent adverse events (Shaukat & Reinink, 2017; Liubakka & Vaughn, 2016).

Table 4. FMT Adverse Effects

Abdominal pain or discomfort
Belching/Flatulence
Diarrhea/Constipation
Nausea/Vomiting (After upper GI route OR colonoscopy sedation)
Transient fever, dizziness
IBD patients: Flares, Fever, raised CRP, bacteremia

Abbreviations. IBD: Inflammatory bowel diseases. CRP: C-reactive protein

The procedure is commonly performed in a specialized center under the supervision of a gastroenterologist or infectious disease specialist (Shaukat & Reinink, 2017). Caution must be taken in IBD patients with rCDI (Choi & Cho, 2015). De Leon et al. reported a flare-up of ulcerative colitis patients after FMT (Choi & Cho, 2015). Possible norovirus transmission after colonoscopic FMT has been reported but has not been proven definitely (Choi & Cho, 2015). Khoruts et al. reported >25% risk of a flare-up in IBD patients who underwent FMT therapy (Liubakka & Vaughn, 2016). Theoretically, conditions that might be affected by gut microbiota also can be transmitted include obesity, diabetes mellitus type 2, atherosclerosis, IBD, nonalcoholic fatty liver disease, irritable bowel syndrome, asthma and autism (Choi & Cho, 2015; Liubakka & Vaughn, 2016). Up to now, there is no clear standard guidelines for follow up after FMT (D'Haens & Jobin, 2019). Most physicians follow the patient response and complications by contacting them after 3-7 days after FMT (D'Haens & Jobin, 2019). One more follow-up contact at 4-8 weeks is strongly recommended (D'Haens & Jobin, 2019). Stool C.difficile toxin test is not recommended post-FMT if the patient is asymptomatic (D'Haens & Jobin, 2019).

Fecal microbiota transplantation is a safe alternative therapy for rCDI, with minor and self-resolved adverse events within hours. Most adverse events were noted in those with underlying gastrointestinal diseases such as IBD. FMT recipients need support and follow up to monitor the long-term adverse effects and complications. Due to the uncertainty of the long-term complication of FMT, large RCTs are recommended with extended follow up.

3.3. FMT in immunocompromised patients with rCDI

The risk of CDI recurrence is increased in immunodeficient patients, including those on immunosuppressant medications, patients with human immunodeficiency virus (HIV), and organ transplants (Shogbesan et al., 2018).

A Literature review was conducted by Oluwaseun Shogbesan et al. for 44 studies, including 234 patients with immunodeficiency who met the outcome and included in the efficacy analysis (Shogbesan et al., 2018). Among them, 206 (87.7%) had clinical recovery of CDI after a single FMT attempt, while 93% had clinical recovery after two or more FMT attempts (Shogbesan et al., 2018). Another analysis for 80 immunocompromised patients demonstrated that FMT is safe for such a population (Zhang et al., 2018). One of the studies reviewed the efficacy of FMT in patients with IBD, solid organ transplants on immunosuppression, HIV, and cancers (Quraishi et al., 2017).

The clinical resolution was achieved in 78% patients after a single FMT, with an overall resolution rate of 98% after a second FMT attempt (Quraishi et al., 2017).

Immune system competency is an essential factor in protecting the body from CDI and recurrences. While many studies had excluded immunocompromised patients, they estimated to be a large number of population. Due to the heterogeneity of the immunosuppression subtype, no precise data can be provided, such as indications, efficacy, or safety. Large RCTs are needed in every subtype of immunodeficiency to establish FMT efficacy and safety profile in such a community.

3.4. FMT in primary CDI treatment

Given the high cure rate of FMT as a treatment for recurrent and refractory CDI, using FMT for primary CDI becomes an area of interest. In small RCT, 20 patients with primary CDI were selected for the study, and the primary endpoint was a clinical resolution (In the form of firm stool consistency or <3 bowel motions per day) with no evidence of CDI at day 70 follow up (Juul et al., 2018). 9/20 patients were randomly selected for FMT and 11 for metronidazole (Juul et al., 2018). The primary endpoint was achieved in the 5/9 FMT group compared to 5/11 in the control group (P=1.00) (Juul et al., 2018). FMT also used in a small, randomized control trial for primary CDI (Paknikar & Pekow, 2018). The study showed that seven of nine (77.7%) patients responded well to FMT in compare to five of 11 (45.5%) treated with metronidazole *(P=0.20)* (Paknikar & Pekow, 2018). In another trial, a comparison between vancomycin and FMT as a treatment for primary CDI (Camacho-Ortiz et al., 2017). FMT was not found to be superior to vancomycin in terms of clinical resolution (Camacho-Ortiz et al., 2017).

Besides, a recent small trial comparing metronidazole to FMT via enema did not show a significant difference in the cure rate between the two groups (Allegretti et al., 2019). Clinical resolution in the FMT group reported in 5 patients (56%) and five patients (45%) in the metronidazole group *(P=1.00)* (Allegretti et al., 2019).

Despite the insignificant outcomes mentioned above, the comparison is limited because of the small sample size and the use of one delivery route such as enema infusion, which needs to be done repeatedly to achieve a curable rate.

Therefore, a bigger sample size and further centralized randomized clinical trials to establish the efficacy and cost-effectiveness of FMT for primary CDI. Keep in mind the variety of administration methods; trials must include the best FMT delivery method to avoid bias.

3.5. FMT in Inflammatory bowel diseases treatment

Crohn's disease (CD) and ulcerative colitis (UC) are characterized by chronic inflammation of the gastrointestinal (GI) tract and can extend to extraintestinal symptoms. Both CD and UC are characterized by an impairment of the gut microbiota diversity with a predominantly high population of Proteobacteria and low Bacteroidetes and Firmicutes Phyla (Wilson et al., 2019). Moreover, an increase in the pro-inflammatory form of Escherichia coli has been reported (Wilson et al., 2019). A recent systemic review and meta-analysis by Paramsothy et al. of 53 studies (four RCT, 30 cohorts, 19 case studies) for IBD patients received FMT (Wilson et al., 2019). The analysis of cohort studies reported the remission rate in CD patients was more compared to UC (52% vs. 33%, respectively) (Wilson et al., 2019). Anderson et al. conducted a systemic review in 2012 for 41 patients with IBD showed a clinical recovery in 63% after FMT (Hsu et al., 2019). Another systemic review conducted by Ruben J et al. for 122 IBD cases (79 UC; 39 CD; 4 IBD unclassified), the clinical recovery was achieved in 45% of patients after FMT (Colman & Rubin, 2014). A meta-analysis for 29 studies discussing the risk of IBD flare-up following FMT (Qazi et al., 2017). The overall risk of IBD flare-up was 14.3% (95% CI 11-19) (Qazi et al., 2017). The risk of flare appears to be high in FMT through lower gastrointestinal methods in comparison to transplantation through the upper gastrointestinal (Qazi et al., 2017). A comparison study was conducted by Rossen et al. using FMT via the nasoduodenal route did not show a significant difference in recovery rate between treatment and control group: 30.4% in the FMT group in comparison to 20.0% in the FMT-autologous group (Qazi et al., 2017).

The evidence of using FMT to induce clinical remission for IBD is poor due to the lack of RCTs and the fear of disease flares. Adverse events are more frequent in these populations, as mentioned above in the adverse effects section. FMT must be used with attention and closely monitor during hospitalization. Further RCTs are suggested with different FMT methods to understand the mechanism of restoring gut microbiota in IBD patients and short-term safety. Keep in mind many IBD patients receiving steroids or other immunosuppressant medications. Therefore, more caution must be taken in such individuals.

4. Conclusion

This review paper addresses the efficacy, safety, and cost-effectiveness of fecal microbiota transplantation in patients suffering from recurrent Clostridium difficile infection. It also reviews the potential use of fecal transplantation in immunocompromised patients with rCDI, primary CDI, and inflammatory bowel diseases. FMT showed to be highly effective compared to the standard antibiotic regimen in rCDI with few and self-resolved adverse events. In terms of cost-effectiveness, FMT showed superiority mainly in the enema and capsules modalities. To date, no solid evidence to use FMT for primary CDI, rCDI in immunodeficient patients, and IBD. Therefore, future randomized trials are required to establish the FMT efficiency for other rCDI disorders.

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