GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(REVIEW ARTICLE)

Check for updates

Fecal microbiota transplantation as a novel approach for *Clostridium difficile* infection: A review

Harshini k [1], Sathya A [2, *], Swathi G [3], Bhuvanesh M [1], Mariyammal R [4] and Nepolean R [5]

[1] *Thanthai Roever college of pharmacy, Perambalur, Tamil Nadu, India.*
[2] *Department of pharmacology, Thanthai Roever college of pharmacy, Perambalur, Tamil Nadu, India.*
[3] *Department of pharmacy practice, Thanthai Roever college of pharmacy, Perambalur, Tamil Nadu, India.*
[4] *Department of pharmacology, Thanthai Roever college of pharmacy, Perambalur, Tamil Nadu, India.*
[5] *Department of pharmaceutics, Thanthai Roever college of pharmacy, Perambalur, Tamil Nadu, India.*

GSC Biological and Pharmaceutical Sciences, 2025, 31(03), 351-358

Publication history: Received on 17 May 2025; revised on 25 June 2025; accepted on 27 June 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.31.3.0248

Abstract

Clostridium difficile infection (CDI) remains a leading cause of antibiotic-associated diarrhea and pseudomembranous colitis, especially within healthcare environments. The growing frequency of recurrent and antibiotic-resistant CDI presents a considerable challenge to treatment efforts. Faecal microbiota transplantation (FMT) has gained recognition as a highly effective treatment for recurrent or treatment-resistant CDI by reestablishing a healthy gut microbiota. This review examines the underlying mechanisms, risk factors, diagnostic methods, and available treatments for CDI, with particular emphasis on the clinical effectiveness and safety of FMT. Clinical evidence consistently demonstrates that FMT is more effective in preventing recurrence than standard antibiotic therapies. Additionally, the review discusses the historical development of FMT, procedural techniques, donor screening practices, and its potential use in other conditions related to microbiota imbalance. In summary, FMT offers a promising, safe, and cost-efficient option for managing recurrent CDI, although further research and standardized protocols are necessary for broader clinical implementation

Keywords: *Clostridium difficile*; Faecal microbiota transplantation; Recurrent CDI; Antibiotic-associated diarrhoea; Gut microbiota; Pseudomembranous colitis

1. Introduction

Clostridium difficile (C. difficile) is a Gram-positive, anaerobic, toxin producing bacillus that forms spores and is commonly found in the intestinal tract of humans and animals, as well as in the environment. C. difficile was first described in 1935 by Hall and O'Toole who were investigating the acquisition of normal bacterial flora in healthy newborns [1]. In 2016, it was officially renamed Clostridium difficile [2]. A colon infection caused by the Gram-positive bacterium *Clostridium difficile* carries a potentially fatal risk, particularly in elderly individuals and those with dysbiosis of the gut microbiota as a result of antibiotic exposure. The most common cause of infectious diarrhea linked to medical care is C. difficilewith significant morbidity and mortality [3]. High temperatures, UV light, strong chemicals, and antibiotics cannot harm C difficile spores. Additionally, due to their resistance to antibiotics, spores may persist in the gastrointestinal tract and perhaps have a role in the recurrence of sickness [4]. Two protein exotoxins called toxin A and toxin B, which induce inflammation and damage to the colonic mucosa, are produced by pathogenic strains of *Clostridium difficile* [5]. The depletion of beneficial gut flora b antibiotics and a weakened immune response to C. difficile as a result of age and medical comorbidities are risk factors for C. difficile. *Clostridium difficile* infection (CDI) is an important healthcare-associated disease worldwide [6]. C. difficile has been a well-established pathogen in North

* Corresponding author: Sathya A

America and Europe for decades, but is just emerging in Asia [7]. *Clostridium difficile* can result an infection in a variety of illnesses, including toxic megacolon, colitis, multi-organ failure and occasionally even death [8]. Infectious diarrhea is increasingly being caused by *Clostridium difficile*. Since 2000, there has been a sharp rise in incidence, which has been linked to a novel strain that produces more toxins and is more resistant to antibiotics [9]. This bacterium is spread through the faeco-oral route and causes disease in humans through the production of two toxins.

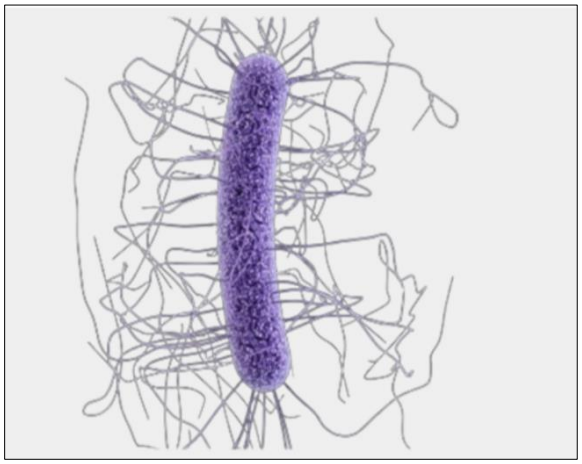

Figure 1 *Clostridium difficile* Bacterium

Aim and objective

The purpose of this review is to evaluate FMT's safety and effectiveness as a new treatment for recurrent or refractory CDI and investigate its potential as a standard therapeutic approach.

2. Methodology

A thorough search of the literature was done with Google Scholar, ScienceDirect, and PubMed. To get up-to-date information, peer-reviewed publications, meta-analyses, clinical trials, and recommendations pertaining to CDI and FMT were examined.

3. Pathophysiology

Exotoxins A (308 kDa) and B (275 kDa), which are secreted by pathogenic strains of C. difficile, cause cytoskeletal disintegration, impair cellular function, and trigger inflammatory reactions. Because antibiotics alter the normal gut flora, C. difficile can multiply and release toxins.

3.1. Pathogenesis of *C. difficile* infection

- **Microbial Suppression:** Antibiotics disrupt normal flora.
- **Ingestion of Spores:** From environmental sources.
- **Toxin Production:** Germination and proliferation in the colon.
- **Mucosal Damage:** Toxins lead to inflammation.
- **Recurrence:** Persistent spores and microbiota imbalance increase relapse risk.

3.2. Antibiotics associated diarrhoea(aad)

AAD is a common side effect that affects 5–35% of people who take antibiotics. Ten to twenty percent are caused by C. difficile. Osmotic imbalances, pathogen overgrowth, and disruption of gut flora are all implicated. When antibiotics are stopped, mild AAD goes away; in more severe cases, specialized treatment may be necessary.

4. Pseudomembranous colitis

Mucosal pseudomembranes are a defining feature of PMC, a severe kind of colitis associated with C. difficile. It frequently occurs after taking antibiotics and manifests as fever, leukocytosis, diarrhea, and cramping in the abdomen. Imaging or endoscopy are used to confirm the diagnosis.

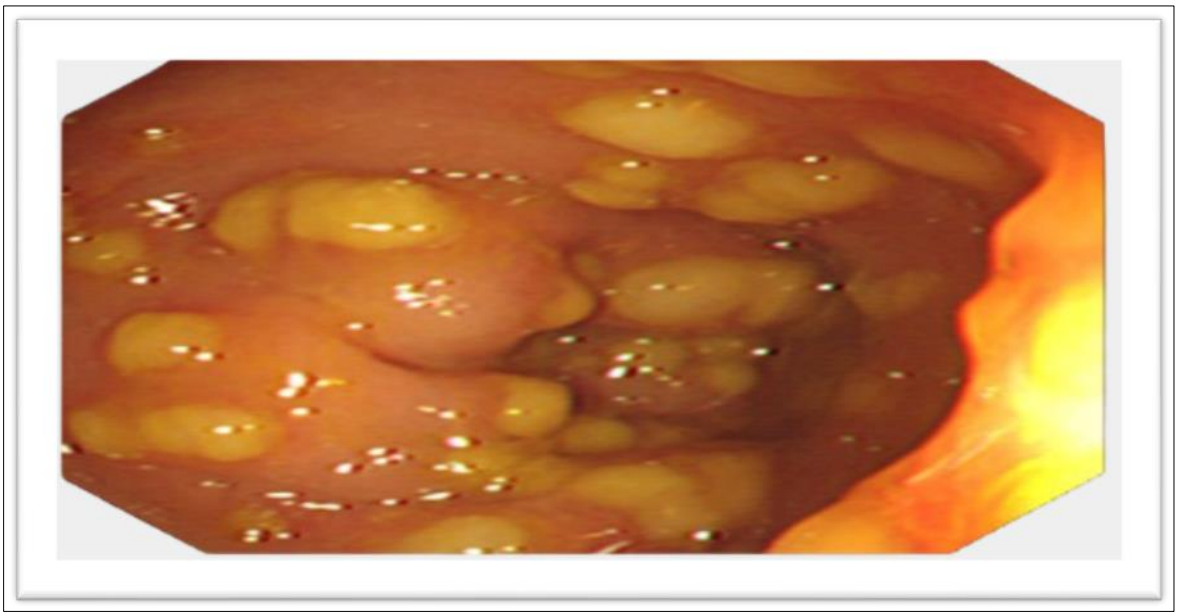

Figure 2 Pseudomembranous Colitis

4.1. Diagnosis

Diagnosis combines clinical presentation with laboratory confirmation of *C. difficile* toxins or DNA. Enzyme immunoassays (EIA), nucleic acid amplification tests (NAAT), and cytotoxicity assays are common tools. Endoscopy and imaging are adjuncts in complicated cases.

Table 1 Diagnosis tests

Test	Indication
Glutamate dehydrogenase (GDH) EIA (TAT <2 hours)	Initial screening test with high sensitivity and high negative predictive value; GDH-positive samples must undergo a confirmation test for the toxigenic infection.
Toxin A and B EIA (TAT <2 hours)	Confirmation test for toxigenic infection in GDH-positive samples (2-step algorithm); good correlation with severe infections, limited sensitivity; NAAT (3-step algorithm) recommended if no toxin detected.
Cytotoxin neutralization assay (CTNA) (TAT <24 hours)	Standard test for evidence of toxins in stool; CTNA is rarely used for routine diagnosis, however, due to its longer TAT and low potential for standardization and automation.
NAAT of toxin genes (TAT <4 hours)	Confirmation test for toxigenic infection. NAAT (e.g. PCR) not recommended as screening test, as asymptomatic C. difficile carriers not requiring treatment or isolation may also be detected.
Anaerobic toxigenic culture (TAT >3 days)	Diagnostic gold standard as confirmation test for toxigenic infection; of limited use in early diagnosis of CDI due to long TAT; culture is required for ribotype testing and antibiotic resistance testing in critically ill patients and in outbreaks.

4.2. Risk factor

Risk factors for which there was evidence suggestive or consistent with an association with *C. difficile* diarrhoea were;

- Advanced age

- Hospitalization
- Antibiotic exposure
- Gastric acid suppression therapy
- Immunocompromised status
- Gastrointestinal procedures

4.3. Treatment

Initial CDI is treated with metronidazole or oral vancomycin. For severe cases, fidaxomicin or newer agents may be used. Emerging options include**:** Cadazolid, Surotomycin, Ridinilazole, Bezlotoxumab (monoclonal antibody).

Recurrent cases are increasingly managed with FMT.

4.4. Recurrence after antibiotic therapy

Recent data demonstrate clinical success rates of 66.3% for metronidazole vs 78.5% for vancomycin for severe CDI. Newer therapies show promising results, including fidaxomicin (similar clinical cure rates to vancomycin, with lower recurrence rates for fidaxomicin, 15.4% vs vancomycin, 25.3%; *P* = .005) and fecal microbiota transplantation (response rates of 83%-94% for recurrent CDI) [30].

Recurrent CDI (rCDI) is usually defined as an episode of CDI occurring within 8 weeksof a previous episode. rCDI may be due to relapse of the previous CDI by the same strain or reinfection by a different strain. About 15% to 30% of patients who initially respond to antimicrobial therapy experience rCDI.After the first recurrence has improved, the risk of further recurrence significantly increases. A second recurrence rate of 40% has been reported among patients with resolved first recurrence. The subsequent recurrence rate of patients who have already recurred more than twice is approximately 45% to 65%. The high recurrence rate of CDI contributes to increased health care costs [31].

Table 2 Management of recurrent "Clostridium difficile" infection by Treatment episode

Episode	**Therapy**
First recurrence	Mild to moderate CDI: metronidazole 500 mg orally 3 times a day for 10 days vancomycin 125 mg orally 4 times a day for 10 days fidaxomicin 200 mg orally 2 times a day for 10 days Severe CDI: vancomycin 125 mg orally 4 times a day for 10 days fidaxomicin 200 mg orally 2 times a day for 10 days
Second recurrence	Tapered and/or pulsed vancomycin regimen Fidaxomicin 200 mg orally 2 times a day for 10 days
Third or more recurrence	Fecal microbiota transplant

5. Result and Discussion

5.1. Fecal microbiota transplant for recurrent CDI

Fecal microbiota transplantation (FMT) has been utilized sporadically for over 50 years. In the past few years, *Clostridium difficile* infection (CDI) epidemics in the USA and Europe have resulted in the increased use of FMT, given its high efficacy in eradicating CDI and associated symptoms. As more patients request treatment and more clinics incorporate FMT into their treatment repertoire, reports of applications outside of CDI are emerging, paving the way for the use of FMT in several idiopathic conditions [32].

There has been increasing interest in understanding the role of the human gut microbiome to elucidate the therapeutic potential of its manipulation. Fecal microbiota transplantation (FMT) is the administration of a solution of fecal matter from a donor into the intestinal tract of a recipient in order to directly change the recipient's gut microbial composition and confer a health benefit. FMT has been used to successfully treat recurrent *Clostridium difficile* infection [33].

Many different groups of diseases are connected to the gut microbiota, including infectious conditions (infectious gastroenteritis, *Clostridium difficile* infection (CDI)), autoimmune diseases (allergic disease, diabetes, inflammatory bowel disease (IBD)), some general conditions (overweight, functional GI disorders), and behavioral diseases [34].

5.2. History of FMT

Table 3 Historical development of fecal microbiota Transplantation (FMT)

Year	author	author's conclusion
IVth century	Ge Hong (CHINA)	FMT's first use in a human patient, administered orally to a patient for food poisoning or severe diarrhea.
XVIth century	Li Shizhen	Described how stool products were used for treating GI symptoms such as constipation, abdominal pain, diarrhea.
XVIIth century	Fabricius Acquapendente	FMT is to be used in veterinary medicine for the first time.
1958	Eiseman et al.	Performed and reported the first human fecal transplant to treat cases of pseudomembranous colitis in 4 patients.
1981	Bowden et al.	A second series of pseudomembranous colitis cases with 16 patients successfully treated with retention enemas.
1983	Schwan et al	CDI case was treated with FMT for the first time

Almost 40 years later, in 2021, Microbiota transplantation as a treatment in a large number of CDI patients, recorded very low rates of recurrence.

The study realized by **Konturek et al.** outlined a significant CRP reduction after FMT therapy in all treated patients. FMT proved its benefits in recurrent CDI, being considered a salvatory option for patients that developed severe and recurrent CDI infection, despite proper antibiotic use [35].

5.3. Procedures for FMT

5.3.1. Donor selection

To minimize the risk of infection or other disease transmission, potential donors undergo rigorous screening including thorough history taking, serological tests, and fecal tests for parasitic, virologic, and bacterial pathogens [36].Donor stool is provided from 2 sources: patient-directed donors and universal donorsthrough stool banks [37]. There are some existing accepted protocols for donor screening [36].

5.3.2. Exclusion criteria

- Age<18 yr or>65 yr
- BMI>30 kg/m^2
- Metabolic syndrome
- Moderate to severe undernutrition
- History of antibiotics use in the last 6months
- Diarrhea within the last 3-6 months

Owing to the cost-effectiveness and convenience of use of fecal material from universal donors, stool banks such as OpenBiome have emerged. OpenBiome uses strict protocols for the recruitment of healthy volunteers: the volunteers are screened, standardized products are generated, and the products are stored after freezing and can be delivered rapidly to 99% of the entire United States. The additional advantages of stool banks are the ability to track registries and perform research on larger data obtained from multiple sites that conduct FMT, with the goal of assuring safety and efficacy [38].

5.4. Procedure for recipient and process

5.4.1. Donor Selection and Screening

Donors are rigorously screened for infections, metabolic disorders, and recent antibiotic use. Stool banks (e.g., Open Biome) standardize screening and supply.

5.4.2. Administration Routes

- **Upper GI**: Nasogastric, duodenal tubes, or capsules.
- **Lower GI**: Colonoscopy, enema, or rectal infusion.

5.4.3. Preparation

Donor stool is diluted, homogenized, filtered, and delivered via syringes or capsules after freezing.

5.5. Adverse events

In certain instances, the absence of controlled data prevented the establishment of a reliable relationship. Standardized, randomized controlled trials are required in order to identify and measure the risks related to FMT [40]. Abdominal pain, bloating, and changed bowel habits were among the frequent minor side effects. There were three significant side effects: two new cases of ulcerative colitis (UC), one of which was suspected prior to FMT treatment, and one incidence of a brief fever [43].

5.6. Safety of FMT

In addition to being a good treatment for rCDI, FMT may also be useful in treating metabolic syndromes, mental health issues, and inflammatory bowel disease (IBD), among other microbiota-related illnesses. However, for wider acceptance, reliable randomized.

6. Conclusion

This review shows that *Clostridium difficile* infection (CDI) remains a significant healthcare burden, with recurrent infections and antibiotic-resistant strains posing considerable challenges. Fecal microbiota transplantation (FMT) has emerged as a promising therapeutic approach, leveraging the restorative potential of gut microbiota to combat CDI. Fecal Microbiota Transplantation (FMT) is a groundbreaking therapy. Enhances gut barrier function and immune response by restoring the beneficial microbial diversity and composition. FMT is a safe and effective method with low risk of adverse events. FMT has potential applications in inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and mental health. Standardization of protocols and donor screening is crucial.

This conclusion highlights the potential of FMT as a novel approach for CDI treatment, emphasizes the need for further research, and underscores the clinical implications of this therapeutic strategy.

Compliance with ethical standers

Conflict of interest statement

The authors declare no conflicts of interest.

References

[1] Castagliuolo, I., and LaMont, J. T. (1999). Pathophysiology, diagnosis and treatment of *Clostridium difficile* infection. The Keio Journal of Medicine, 48(4), 169-174.

[2] Czepiel, J., Dróżdż, M., Pituch, H. et al. *Clostridium difficile* infection: review. Eur J Clin Microbiol Infect Dis 38, 1211–1221 (2019). https://doi.org/10.1007/s10096-019-03539-6

[3] smits, W., Lyras, D., Lacy, D. et al. *Clostridium difficile* infection. Nat Rev Dis Primers 2, 16020 (2016). https://doi.org/10.1038/nrdp.2016.20

[4] Heinlen, Latisha, and Jimmy D. Ballard. "*Clostridium difficile* infection." The American journal of the medical sciences 340.3 (2010): 247-252.

[5] Kelly, Ciarán P., and J. Thomas LaMont. "*Clostridium difficile* infection." Annual review of medicine 49.1 (1998): 375-390.

[6] Vuotto C, Donelli G, Buckley A, Chilton C. *Clostridium difficile* Biofilm. Adv Exp Med Biol. 2018;1050:97-115. doi: 10.1007/978-3-319-72799-8_7. PMID: 29383666.

[7] Burke KE, Lamont JT. *Clostridium difficile* infection: a worldwide disease. Gut Liver. 2014 Jan;8(1):1-6. doi: 10.5009/gnl.2014.8.1.1. Epub 2014 Jan 13. PMID: 24516694; PMCID: PMC3916678

[8] Mullish BH, Williams HR. *Clostridium difficile* infection and antibiotic-associated diarrhoea. Clin Med (Lond). 2018 Jun;18(3):237-241. doi: 10.7861/clinmedicine.18-3-237. PMID: 29858434; PMCID: PMC6334067.

[9] Knight CL, Surawicz CM. *Clostridium difficile* Infection. Med Clin North Am. 2013 Jul;97(4):523-36, ix. doi: 10.1016/j.mcna.2013.02.003. Epub 2013 Apr 24. PMID: 23809712.

[10] Owens Jr, Robert C., et al. "Antimicrobial-associated risk factors for *Clostridium difficile* infection." Clinical Infectious Diseases 46. Supplement1 (2008): S19-S31.

[11] Johnson, Stuart. "Recurrent *Clostridium difficile* infection: a review of risk factors, treatments, and outcomes." Journal of Infection 58.6 (2009): 403-410.

[12] . McFarland, Lynne V. "Antibiotic-associated diarrhea: epidemiology, trends and treatment." (2008): 563-578.

[13] Högenauer, Christoph, et al. "Mechanisms and management of antibiotic-associated diarrhea." Clinical infectious diseases 27.4 (1998): 702-710.

[14] Ros, Pablo R., et al. "Pseudomembranous colitis." Radiology 198.1 (1996): 1-9.

[15] Farooq, Priya D., et al. "Pseudomembranous colitis." Disease-a-month 61.5 (2015): 181-206.

[16] Surawicz, ChristinaM, and LynneV McFarland. "Pseudomembranous colitis: causes and cures." Digestion 60.2 (1999): 91-100.

[17] Alam, Seema, and Mudasir Mushtaq. "Antibiotic associated diarrhea in children." Indian pediatrics 46.6 (2009).

[18] Bartlett, John G., and Dale N. Gerding. "Clinical recognition and diagnosis of *Clostridium difficile* infection." Clinical infectious diseases 46.Supplement_1 (2008): S12-S18.

[19] .Brar, Harpreet S., and Christina M. Surawicz. "Pseudomembranous colitis: an update." Canadian Journal of Gastroenterology and Hepatology 14.1 (2000): 51-56.

[20] Peng, Zhong, et al. "Advances in the diagnosis and treatment of *Clostridium difficile* infections." Emerging microbes and infections 7.1 (2018): 1-13.

[21] Hernández, Luis Alcalá, Elena Reigadas Ramírez, and Emilio Bouza Santiago. "*Clostridium difficile* infection." Medicina Clínica (English Edition) 148.10 (2017): 456-463.

[22] Gerding, Dale N., Thomas M. File Jr, and L. Clifford McDonald. "Diagnosis and treatment of *Clostridium difficile* infection." Infectious Diseases in Clinical Practice 24.1 (2016): 3-10.

[23] .Lübbert C, John E, von Müller L. *Clostridium difficile* infection: guideline-based diagnosis and treatment. Dtsch Arztebl Int. 2014 Oct 24;111(43):723-31. doi: 10.3238/arztebl.2014.0723. PMID: 25404529; PMCID: PMC4238315.

[24] Bignardi, Giuseppe E. "Risk factors for *Clostridium difficile* infection." Journal of Hospital Infection 40.1 (1998): 1-15.

[25] Wilcox, Mark H. "Treatment of *Clostridium difficile* infection." The Journal of antimicrobial chemotherapy 41.suppl_3 (1998): 41-46.

[26] Gerding, Dale N., Carlene A. Muto, and Robert C. Owens Jr. "Treatment of *Clostridium difficile* infection." Clinical Infectious Diseases 46.Supplement_1 (2008): S32-S42.

[27] Leffler, Daniel A., and J. Thomas Lamont. "Treatment of *Clostridium difficile*-associated disease." Gastroenterology 136.6 (2009): 1899-1912.

[28] Cammarota, Giovanni, et al. "Emerging drugs for the treatment of *Clostridium difficile*." Expert Opinion on Emerging Drugs 24.1 (2019): 17-28.

[29] McCollum, David L., and J. Martin Rodriguez. "Detection, treatment, and prevention of *Clostridium difficile* infection." Clinical gastroenterology and hepatology 10.6 (2012): 581-592.

[30] Bagdasarian, Natasha, Krishna Rao, and Preeti N. Malani. "Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review." Jama 313.4 (2015): 398-408.

[31] Song, Jung Hoon, and You Sun Kim. "Recurrent *Clostridium difficile* infection: risk factors, treatment, and prevention." Gut and liver 13.1 (2019): 16.

[32] Borody, Thomas J., and Alexander Khoruts. "Fecal microbiota transplantation and emerging applications." Nature reviews Gastroenterology and hepatology 9.2 (2012): 88-96.

[33] Gupta, Shaan, Emma Allen-Vercoe, and Elaine O. Petrof. "Fecal microbiota transplantation: in perspective." Therapeutic advances in gastroenterology 9.2 (2016): 229-239.

[34] Wang, Jiunn-Wei, et al. "Fecal microbiota transplantation: Review and update." Journal of the Formosan Medical Association 118 (2019): S23-S31.

[35] Boicean, A.; Birlutiu, V.; Ichim, C.; Anderco, P.; Birsan, S. Fecal Microbiota Transplantation in Inflammatory Bowel Disease. Biomedicines 2023, 11, 1016. https://doi.org/10.3390/biomedicines11041016

[36] Kelly, Brendan J., and Pablo Tebas. "Clinical practice and infrastructure review of fecal microbiota transplantation for *Clostridium difficile* infection." Chest 153.1 (2018): 266-277.

[37] Allegretti, Jessica R., et al. "The 5D framework: a clinical primer for fecal microbiota transplantation to treat *Clostridium difficile* infection." Gastrointestinal endoscopy 87.1 (2018): 18-29.

[38] Kim, Kyeong Ok, and Michael Gluck. "Fecal microbiota transplantation: an update on clinical practice." Clinical endoscopy 52.2 (2019): 137-143.

[39] Wang, Zi-Kai, et al. "Intestinal microbiota pathogenesis and fecal microbiota transplantation for inflammatory bowel disease." World journal of gastroenterology: WJG 20.40 (2014): 14805.

[40] Brandt, Lawrence J., and Olga C. Aroniadis. "An overview of fecal microbiota transplantation: techniques, indications, and outcomes." Gastrointestinal endoscopy 78.2 (2013): 240-249.

[41] Rossen NG, MacDonald JK, de Vries EM, D'Haens GR, de Vos WM, Zoetendal EG, Ponsioen CY. Fecal microbiota transplantation as novel therapy in gastroenterology: A systematic review. World J Gastroenterol. 2015 May 7;21(17):5359-71. doi: 10.3748/wjg.v21.i17.5359. PMID: 25954111; PMCID: PMC4419078.

[42] Choi, Hyun Ho, and Young-Seok Cho. "Fecal microbiota transplantation: current applications, effectiveness, and future perspectives." Clinical endoscopy 49.3 (2016): 257-265.

[43] Baxter, Melissa, and Alaric Colville. "Adverse events in faecal microbiota transplant: a review of the literature." Journal of Hospital Infection 92.2 (2016): 117-127.

[44] Park, Seon-Young, and Geom Seog Seo. "Fecal microbiota transplantation: is it safe?." Clinical Endoscopy 54.2 (2021): 157-160.

[45] Agrawal, Manasi, et al. "The long-term efficacy and safety of fecal microbiota transplant for recurrent, severe, and complicated *Clostridium difficile* infection in 146 elderly individuals." Journal of clinical gastroenterology 50.5 (2016): 403-407.