Minireview Article

Fecal Microbiota Transplant

ABSTRACT

Aims: The fecal microbiota transplantation (FMT) may be a possible solution for symptoms reduction and improvement of the clinical condition in Inflammatory bowel diseases (IBDs), such as Ulcerative Colitis (UC) and Crohn's Disease (CD). In addition to being effective in other conditions associated with disequilibrium in gastrointestinal microbiota, such as recurrent Clostridium difficile infection (RCDI) and Metabolic Syndrome (MS).
Study design: Minireview.
Place and Duration of Study: Faculty of Medical Sciences of São José dos Campos - Humanitas, between June 2021 and August 2022.
Methodology: To verify the FMT applications in different conditions, a narrative review was conducted to update information on FMT area and explore the possibilities of using this practice in patients with IBD, RCDI and MS. The studies have been shown that FMT can be useful in the treatment of RCDI and represent a possible alternative to antibiotic therapy in cases of primary infection by C. difficile.
Results: Regarding the treatment of UC, FMT seems to be effective in inducing remission, but its durability and long-term safety are still not well defined. Furthermore, in the treatment of Crohn's disease and metabolic syndrome FMT is still questionable, and further studies are needed.
Conclusion: In conclusion, the studies are optimistic and, even if modest, suggest that FMT has the potential for treatment and/or remission of different inflammatory and infectious conditions.

Keywords: Fecal microbiota transplant, inflammatory bowel diseases, Clostridium difficile and microbiome.

1. INTRODUCTION

THE GASTROINTESTINAL MICROBIOTA IS A COMPLEX ECOSYSTEM COMPOSED OF HUNDREDS OF THOUSANDS OF MICROORGANISMS, INCLUDING BACTERIA, VIRUSES AND FUNGI.1 THESE MICROORGANISMS PARTICIPATE IN SEVERAL METABOLIC AND IMMUNOLOGICAL INTERACTIONS, CONTRIBUTING TO THE MAINTENANCE OF HEALTH OF THE HOST.2 HOWEVER, IN SITUATIONS OF DYSBIOSIS, THAT IS, CHANGES IN THE COMPOSITION AND FUNCTION OF THE MICROBIOTA, ITS COMPONENTS CAN CAUSE INFLAMMATORY GASTROINTESTINAL DISEASES.3

FECES LARGELY REFLECT THE INDIVIDUAL'S MICROBIOME AND ITS POSSIBLE CHANGES.4 THUS, IN CASES OF DYSBIOSIS, ONE OF THE OPTIONS FOR RESTORING THE HEALTHY MICROBIOME (EUBIOSIS) IS THE TRANSPLANTATION OF FECAL MICROBIOTA (FMT), TRANSFERRING THE FECAL CONTENT OF A HEALTHY ORGANISM (IN EUBIOSIS) TO AN ORGANISM WITH AN ALTERED MICROBIOME, A POSSIBLE CAUSE OF THE DISEASE.5

FMT IS AN EMERGING PROCEDURE IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASES SUCH AS ULCERATIVE COLITIS, CROHN'S DISEASE AND CLOSTRIDIUM DIFFICILE INFECTION, DEMONSTRATING EFFICACY IN THE REMISSION AND/OR IMPROVEMENT OF CLINICAL MANIFESTATIONS.

In addition, FMT seems to promote detectable beneficial changes in the composition of the intestinal microbiota of patients with Metabolic Syndrome.6,7,8,9
The first records of FMT are from the fourth century, in China, where it was used to treat patients with severe diarrhea.10 However, despite not being a current practice, there are still questions about the function and effectiveness of FMT in the treatment of different inflammatory and infectious diseases. Thus, the aim of this study was to analyze the applicability and some results of FMT: in Crohn's Disease, Ulcerative Colitis, Clostridium difficile Infection and Metabolic Syndrome.

2. MATERIAL AND METHODS

A mini narrative review was conducted to update information on FMT area and explore the possibilities of using this practice in patients with IBD, RCDI and MS. A literature search was performed in the PubMed database for clinical trial studies and review articles published in the last 10 (ten) years. The remission of clinical conditions was established as the primary outcome and exclusion criteria was not blind or incomplete blinding studies. In total, 53 (fifty three) articles were chosen.

3. RESULTS AND DISCUSSION

Fecal Microbiota Transplantation in the Treatment of Clostridium difficile Infection

C. difficile is a Gram-positive bacillus transmitted mainly by the fecal-oral route, whose clinical manifestation is characterized by three or more watery stools in 24 hours, for at least two consecutive days.11,12 Long-term use of antibiotics and the consequent increase in the growth of antibiotic-resistant microorganisms is associated with the development of recurrent C. difficile infection (RCDI). Thus, in these cases, FMT has a great therapeutic potential, in addition to being used as an alternative therapy to antibiotic in cases of primary infection by C. difficile13,14(Figure 1).
Millan et al., in a single-center study in which 20 patients with RCDI received FMT from universal donors via colonoscopy, observed that these individuals had a greater number of antibiotic-resistant microorganisms and that healthy fecal microbiota introduced through transplantation could eliminate these microorganisms, eradicate resistance genes, and restore antibiotic susceptibility.14
Youngster et al., studying different administration routes of FMT in RCDI patients, demonstrated, through a randomized-controlled trial, that the administration of fecal microbiota by nasogastric tube was as effective as administration via colonoscopy.15 Youngster et al., also demonstrated that the oral administration of frozen FMT capsules in a small group of patients with IRCDI, led to a clinical resolution of 90% in diarrheal conditions. Thus, the authors suggested the possibility of application in a wider population and in a safer way, although larger studies were needed to confirm the data.16
Likewise, Kao et al., studying patients aged 18 to 90 years, with at least three documented episodes of C. difficile infection, observed that the use of fresh stool was more effective compared to antibiotic therapy or placebo and that frozen stools transported by colonoscopy presented themselves as an alternative treatment to the use of fresh stools.17 Kelly et al., in a randomized, controlled and double-blind clinical trial, concluded that donor stools administered by colonoscopy seemed safer and more effective in preventing new episodes of C. difficile infection than FMT made from the feces of infected patients themselves.18 However, with regard to FMT in patients with RCDI treated with vancomycin, a study conducted by Hota et al.,

compared 14 days of oral vancomycin followed by a single FMT via enema with step-down oral vancomycin and concluded that there was no significant difference between them.19Another study, performed by Hvas et al., 2019, compared the efficacy of FMT to fidaxomicin and vancomycin in patients with RCDI and concluded that clinical resolution rates were significantly higher in patients who received FMT as treatment (92% vs 42% and 19% for fidaxomicin and vancomycin, respectively). 20

The applications of FMT in patients who underwent solid organ transplantation have also been studied. In an experience of Lin et al., 2018, five of these patients with RCDI had a cure rate of 80% after one FMT, and 100% cure rate after two FMTs. 21

FMT also seems to be an effective treatment for elderly and very sick patients, with colonoscopy being the preferred infusion route. Concerns about the safety of this method is rare, even in patients with many comorbidities.22

The cure rate of FMT in cases of RCDI can range from 85% to 90% and has been shown to be able to restore the phylogenetic diversity of the bacterial microbiome, even if the long-term effect is not yet very well understood.23 FMT seems to constitute a safe and effective approach in the management of recurrent and refractory C. difficile infection, although there may be a difference between primary and secondary cure rates, as restoration may be insufficient with the administration of a single FMT.24

Fecal microbiota transplant in the treatment of ulcerative colitis

Ulcerative colitis (UC) is an inflammatory disease of the large intestine, especially from transverse colon, with unknown origin. It is featured by inflammation and ulceration at intestinal mucosa and submucosa.25

Very typical symptoms are diarrhea, generally with rectal bleeding and often abdominal pain. This disease has a high risk to symptomatic relapse and can persist for weeks or months. Further, the ulcerative colitis, when extended, raises the risk of developing colon cancer, compared to not affected individuals.26

The innate and adaptive immunity of the host, under normal circumstances, is capable to prevent the invasion of harmful bacteria and to tolerate the normal microbiota. However, if the microbiota is not balanced and/or immunity is compromised, so the intestinal mucosal immune response is overstimulated, which can lead to disease. The barrier function of the intestinal mucosa decreases as the intestinal microbiota is translocated, which causes further damage to the intestinal mucosa barrier, causing a vicious cycle and accentuating the intestinal inflammatory response.27,28

The treatment of ulcerative colitis by FMT aims to induce clinical remission through the progressive transformation of the inflamed mucous into normal, reestablishing the tissue's histological architecture, reducing morbidity and mortality and improving the quality of life of individuals who have this pathology.29(Figure 1)

FMT can reduce permeability of the intestinal barrier and increase short chain fatty acids, which could help to keep the epithelial barrier intact. FMT has the ability to restore immune dysbiosis because it can inhibit T cell and other leukocytes activity and the production of inflammatory factors.30

Warren et al. studied the efficacy of UC regression, based on the use of FMT by endoscopic and capsule routes. Of the 30 patients undergoing FMT by endoscopy, 15 kept treatment using capsules, and in all patients, there was control of UC. Only four had adverse effects such as diarrhea, constipation and nausea, showing that FMT can be an innovative, safe and efficient alternative for the treatment of UC.31

Paramsothy et al., analyzed 53 studies and compared the efficacy of FMT in three different clinical conditions, UC, CDI and pouchitis, resulting in 555 patients. The authors concluded that the greatest clinical remission occurred in CDI when compared to UC. However, there was a significant benefit in clinical remission of UC.

Costello et al., in a systematic review and meta-analysis of four existing randomized clinical trials, concluded that, even without solid evidence, FMT seems to be effective in inducing UC remission, without signs of short-term insecurity.32 Corroborating these data, another systematic review and meta-analysis demonstrated an increase in clinical and endoscopic UC remission by FMT compared to placebo, with an NNT=5. Furthermore, there was no statistically significant increase in serious adverse effects compared to the control groups. Based on the observed efficacy and safety, the short-term use of FMT has shown promising as a therapeutic to induce remission of active UC.

Fecal microbiota transplant in the treatment of Crohn's disease

Crohn's disease (CD) is a chronic inflammatory condition with transmural involvement of the gastrointestinal tract, may occurring extraintestinal manifestations. Although treatment options have expanded in recent years, they focus primarily on lowering the immune response, thus bringing notable risks associated with long-term immunosuppression.33

Its pathogenesis is not fully understood, but it is now recognized that it is related to an abnormal activation of the gastrointestinal immune system against microorganisms of the intestinal microbiota, in genetically susceptible hosts and under the influence of environmental factors.34

According to a recent meta-analysis, after minimizing publication bias, patients with inflammatory bowel disease who received FMT had a 36.2% remission rate: 22% for UC and 60.5% for CD.35 The central mechanism for the effectiveness of TMF is probably the establishment of intestinal bacterial strains and antimicrobial components, such as adhesins, immunomodulatory molecules, bacteriocins, etc., produced by these associated strains. Thus, adhesin molecules can compete for sites with pathogenic bacteria, leading them to be prevented from colonizing the intestine and possible rehabilitation of the intestinal microbiota.36(Figure 1) Xiang et al. studied 174 patients with CD who underwent FMT by endoscopy, nasojejunal tube or colonic transendoscopic enteral tube. The median duration of follow-up was 43 months. The authors noted that 75.3% of patients achieved a clinical response one month after FMT. Of these, 9.2% of patients achieved sustained remission after a single FMT, while 10.7% of patients switched therapy due to loss of response. In total, 109 patients underwent multiple courses of FMT during follow-up. Of these, 58.7% of patients achieved clinical response with FMTs and 21.1% of patients achieved sustained clinical remission with FMTs. The overall average attendance of the FMT courses was 3.5. The average time between the first and second FMT course was 123 days.37

Li et al., carrying out a study with sixty-nine patients with active CD, observed a significant benefit already in the first FMT. Four weeks after the first FMT, 63 patients achieved a clinical response, of which 47 achieved clinical remission. In addition, 8.7% of patients showed partial improvement in symptoms related to CD. Just before these patients received the second FMT, 62.3% of them still maintained a clinical response, among which 43.5% still maintained clinical remission.38 Susking et al. selected nine families for a study of FMT in patients with active CD. These patients received the fecal transplant, whose donors were the parents. Two weeks after FMT, 7 of 9 patients were in clinical remission based on PCDAI score. At 6 and 12 weeks, 5 of 9 patients who did not receive additional therapy were still in remission. Only two subjects required additional standard medical therapies before the end of the study.39

Fecal microbiota transplant in the treatment of Metabolic syndrome

Metabolic syndrome (MS) is characterized by a set of symptoms strongly associated with the development of cardiovascular diseases, type 2 diabetes and nonalcoholic fatty liver disease, being characterized by insulin resistance, dyslipidemia, high blood pressure and increase of abdominal waist.40 It is believed that the gut microbiota plays a key role in maintaining the physiological function of the host, and dysbiosis caused by various factors leads to extensive physiological changes and increases the risk of MS. Studies have shown that it is possible that an increased frequency of the phylum Firmicutes, and reduced frequency of Bacteroidetes could be related to an obese phenotype. However, the underlying mechanisms by which gut microbiota affects host metabolism still need to be defined.41 It has been observed that FMT alters and increases the biodiversity of intestinal microbiota, modulates bacterial proportion, increases the release of glucagon like peptide 1 (GLP-1), modulates the paths of biliary acid and interferes with the production of short-chain fatty acids. It can also be responsible for complex effects like immune cells regulation, alteration of intestinal gluconeogenesis, reduction of tumor necrosis factors - alfa, change in the metabolism of lipids and glucose, among other mechanisms 35. Because of that, a hypothesis was raised that FMT might contribute to the treatment of MS/obesity by increasing the insulin sensitivity, decreasing body fat and modulating the metabolism of lipids and cholesterol42(Figure 1). Kotte et al.43, studied the effects of FMT in 38 men with MS - aleatory divided into a treatment group (26 men who received transplant from a healthy donor) and control group (12 men who received autologous fecal transplant). The authors observed that six weeks after the FMT there was an alteration in the composition of duodenal and fecal microbiota in the treatment group, associated with a better peripheral sensibility to insulin and a slightly, but significant, decrease in quantity of glycated hemoglobin, when compared to the control group. However, when the samples were collected and analyzed again, 18 weeks after the FMT, the microbiota composition had returned to the base composition, evidencing a short-term benefit non-sustained in long-term.44 In turn Allegretti et al., studying 11 obese men who received the FMT by oral capsules, with the dose reinforced twice every four weeks, observed significant change in the curve of glucose after 12 weeks, when compared to the placebo's group curve. It was also observed an alteration in the levels of insulin 6 weeks after the FMT.36 Therefore, the authors suggested that FMT might have preventive role in the development of MS in obese pacients.45

Studies have shown that FMT alters the receptors' microbiota making it similar to the donor's composition, but without any functional effect or metabolic change.44, 45, 46

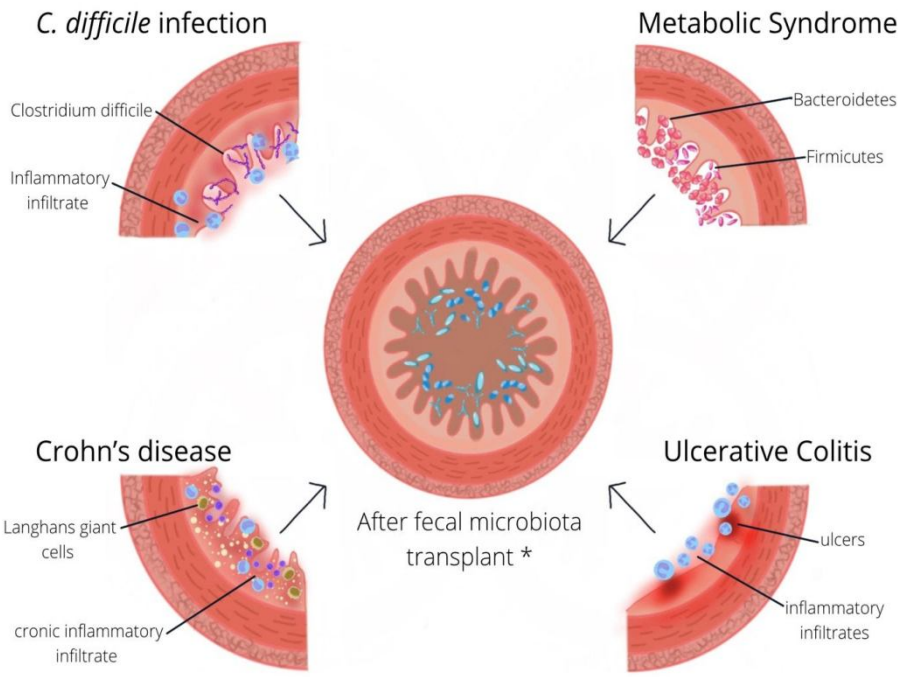

FIGURE 1: MECHANISMS OF SUCCESSFUL TREATMENT OF CLOSTRIDIUM DIFFICILE INFECTION, CROHN'S DISEASE, ULCERATIVE COLITIS AND METABOLIC SYNDROME WITH FECAL MICROBIOTA TRANSPLANT. IMPROVEMENT IN SYMPTOMS AFTER FMT HAS BEEN ASSOCIATED WITH RESTORING THE HEALTHY MICROBIOME (EUBIOSIS) AND REDUCTION OF INFLAMMATION AND TISSUE DAMAGE.

THE STUDIES HAVE SHOWN THAT FMT CAN BE USEFUL IN THE TREATMENT OF RCDI WITH CURE RATES RANGING FROM 85% TO 90% AND REPRESENT A POSSIBLE ALTERNATIVE TO ANTIBIOTIC THERAPY IN CASES OF PRIMARY INFECTION BY C. DIFFICILE. REGARDING THE TREATMENT OF UC, FMT SEEMS TO BE EFFECTIVE IN INDUCING REMISSION, BUT ITS DURABILITY AND LONG-TERM SAFETY ARE STILL NOT WELL DEFINED.31,32,46. FURTHERMORE, THE STUDIES SUGGEST THAT FMT IN THE TREATMENT OF CROHN'S DISEASE AND METABOLIC SYNDROME IS STILL QUESTIONABLE, AND FURTHER STUDIES ARE NEEDED TO PROVE THE FEASIBILITY OF THIS PROCEDURE IN THESE AND OTHER CONDITIONS.

IT IS IMPORTANT TO HIGHLIGHT THAT ALL THE STUDIES HAVE LIMITATIONS AND BIAS. IT IS OBSERVED, FOR EXAMPLE, THAT ALL STUDIES WERE CARRIED OUT IN MEN AND FOLLOW-UP BEYOND 6 MONTHS IS NOT YET AVAILABLE. FURTHERMORE, NONE OF THE STUDIES REPORTED DIETARY CONTROL, A FACTOR THAT DIRECTLY AFFECTS THE COMPOSITION OF THE MICROBIOTA. FOR EXAMPLE, A DIET RICH IN PROTEIN IS ASSOCIATED WITH INCREASED MICROBIOTA DIVERSITY47, THIS DIVERSITY MAKES COMMUNITIES CONSIDERED MORE RESILIENT, MANAGING TO BUILD MORE RESOURCES, REDUCING THE OPPORTUNITY FOR BACTERIAL INVASION. THIS CAN BE A BARRIER TO THE REVERSAL OF DYSBIOSIS BY TMF, AS IT OFFERS MORE RESISTANCE TO COLONIZATION.48 ANOTHER STUDY POINTED OUT THE IMPORTANT ROLE OF THE VIRAL COMMUNITY IN RECEIVING TREATMENT WITH TMF, AS PATIENTS WHO DID NOT RESPOND TO TREATMENT HAD A GREATER DIFFERENCE IN THEIR VIRAL COMMUNITIES WHEN COMPARED TO THEIR RESPECTIVE DONORS.49

IT IS ALSO IMPORTANT TO CONSIDER THE LIMITATIONS AND THE RISKS OF THE PROCEDURE. RISK OF INFECTION TRANSMISSION FROM FMT HAS BEEN OF GREAT CONCERN, ALTHOUGH INFECTIOUS COMPLICATIONS AFTER FMT APPEAR TO BE RARE.50 OTHER ADVERSE EVENTS AFTER FMT CAN BE

THE RESULT OF THE NASODUODENAL ADMINISTRATION, AS ASPIRATION PNEUMONIA.51 AS OTHER PROCEDURES ALSO HAVE THEIR RELATED COMPLICATIONS, THE BEST WAY OF FMT ADMINISTRATION MUST BE VERIFIED FOR EACH PATIENT AND ACCORDING TO THE PROFESSIONAL EXPERIENCE.52 TO PROVIDE LONG-TERM ASSESSMENT FOR UP TO 10 YEARS TO ANSWER THE MOST PRESSING SAFETY QUESTION REGARDING FMT, GLIKLICH ET AL., 2014, DEVELOPED THE FMT NATIONAL REGISTRY TO PROVIDE A REAL-WORLD VIEW OF CLINICAL PRACTICE, PATIENT OUTCOMES, SAFETY, AND COMPARATIVE EFFECTIVENESS.53

4. CONCLUSION

IN CONCLUSION, ALTHOUGH OTHER STUDIES ARE NECESSARY TO CONFIRM ALL THE BENEFITS OF FMT IN PATIENTS WITH ICD, UC, CD AND MS, THE RESULTS ARE OPTIMISTIC AND, EVEN IF MODEST, SUGGEST THAT TMF HAS POTENTIAL FOR THE TREATMENT OF DIFFERENT INFLAMMATORY AND INFECTIOUS DISEASES.

REFERENCES

1-BLASER MJ. THE MICROBIOME REVOLUTION. JOURNAL OF CLINICAL INVESTIGATION. 2014;124(10), 4162–4165. HTTPS://DOI.ORG/10.1172/JCI78366

2- NAGAO-KITAMOTO H, KITAMOTO S, KUFFA P, KAMADA N. PATHOGENIC ROLE OF THE GUT MICROBIOTA IN GASTROINTESTINAL DISEASES. INTESTINAL RESEARCH. 2016; 14(2), 127–138. HTTPS://DOI.ORG/10.5217/IR.2016.14.2.127

3- PASSOS M DO CF, MORAES-FILHO JP. INTESTINAL MICROBIOTA IN DIGESTIVE DISEASES. ARQUIVOS DE GASTROENTEROLOGIA. 2017; 54(3), 255–262. PORTUGUESE. HTTPS://DOI.ORG/10.1590/S0004-2803.201700000-31

4- SAFFOURI GB, SHIELDS-CUTLER RR, CHEN J, YAN Y, LEKATZ HR, HALE VL, ET AL. SMALL INTESTINAL MICROBIAL DYSBIOSIS UNDERLIES SYMPTOMS ASSOCIATED WITH FUNCTIONAL GASTROINTESTINAL DISORDERS. NATURE COMMUNICATIONS. 2019; 10(1), 1–11. HTTPS://DOI.ORG/10.1038/S41467-019-09964-7

5- VINDIGNI SM, SURAWICZ CM. FECAL MICROBIOTA TRANSPLANTATION. GASTROENTEROLOGY CLINICS OF NORTH AMERICA. 2017; 46(1), 171–185. HTTPS://DOI.ORG/10.1016/J.GTC.2016.09.012. PMID: 28164849.

6- FANG H, FU L, WANG J. PROTOCOL FOR FECAL MICROBIOTA TRANSPLANTATION IN INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS. BIOMED RESEARCH INTERNATIONAL. 2018; HTTPS://DOI.ORG/10.1155/2018/8941340

7- PARAMSOTHY S, PARAMSOTHY R, RUBIN DT, KAMM MA, KAAKOUSH NO, MITCHELL HM, ET AL. FAECAL MICROBIOTA TRANSPLANTATION FOR INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS. JOURNAL OF CROHN'S AND COLITIS. 2017; 11(10), 1180–1199. HTTPS://DOI.ORG/10.1093/ECCO-JCC/JJX063

8- SMITS LP, KOOTTE RS, LEVIN E, PRODAN A, FUENTES S, ZOETENDAL EG, ET AL. EFFECT OF VEGAN FECAL MICROBIOTA TRANSPLANTATION ON CARNITINE- AND CHOLINE-DERIVED TRIMETHYLAMINE-N-OXIDE PRODUCTION AND VASCULAR INFLAMMATION IN PATIENTS WITH METABOLIC SYNDROME. JOURNAL OF THE AMERICAN HEART ASSOCIATION. 2018; 7(7). HTTPS://DOI.ORG/10.1161/JAHA.117.008342

9- Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial. Ann Intern Med. 2016 Nov 1;165(9):609-616. https://doi.org/10.7326/M16-0271

10- Wang JW, Kuo CH, Kuo FC, Wang YK, Hsu WH, Yu FJ, et al. Fecal microbiota transplantation: Review and update. Journal of the Formosan Medical Association. 2019; 118, S23–S31. https://doi.org/10.1016/j.jfma.2018.08.011

11- Jiang ZD, Jenq RR, Ajami NJ, Petrosino JF, Alexander AA, Ke S, et al. Safety and preliminary efficacy of orally administered lyophilized fecal microbiota product compared with frozen product given by enema for recurrent Clostridium difficile infection: A randomized clinical trial. PLoS ONE. 2018; 13(11), 1–12. https://doi.org/10.1371/journal.pone.0205064

12- Mada PK, Alam MU. Clostridium Difficile. [Updated 2021 Aug 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431054/

13- Baudou E, Lespine A, Durrieu G, André F, Gandia P, Durand C, et al. Fecal Microbiota Transplantation for Primary Clostridium difficile Infection. N Engl J Med. 2018; 378:2535-2536. doi: 10.1056/NEJMc1803103

14- Millan B, Park H, Hotte N, Mathieu O, Burguiere P, Tompkins TA, et al. Fecal Microbial Transplants Reduce Antibiotic-resistant Genes in Patients With Recurrent Clostridium difficile Infection. Clinical Infectious Disease. 2016; 62(12), 1479–1486. https://doi.org/10.1093/cid/ciw185

15- Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, Smith MB, et al. Fecal microbiota transplant for relapsing clostridium difficile infection using a frozen inoculum from unrelated donors: A randomized, open-label, controlled pilot study. Clinical Infectious Diseases. 2014; 58(11), 1515–1522. https://doi.org/10.1093/cid/ciu135

16- Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing Clostridium difficile Infection. JAMA - Journal of the American Medical Association. 2014; 312(17), 1772–1778. doi: 10.1001/jama.2014.13875

17- Kao D, Roach B, Silva M, Beck P, Rioux K, Kaplan GG, et al. Effect of oral capsule–vs colonoscopy-delivered fecal microbiota transplantation on recurrent Clostridium difficile infection: A randomized clinical trial. JAMA - Journal of the American Medical Association. 2017; 318(20), 1985–1993. doi: 10.1001/jama.2017.17077

18- Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Mortadha Abd, Alani M, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection. HHS Public Access. 2016; 165(9). https://doi.org/10.1186/s40168-018-0549-6

19- Hota SS, Sales V, Tomlinson G, Salpeter MJ, McGeer A, Coburn B, et al. Oral vancomycin followed by fecal transplantation versus tapering oral vancomycin treatment for recurrent clostridium difficile infection: An open-label, randomized

CONTROLLED TRIAL. CLINICAL INFECTIOUS DISEASES. 2017; 64(3), 265–271. HTTPS://DOI.ORG/10.1093/CID/CIW731

20- HVAS CL, DAHL JØRGENSEN SM, JØRGENSEN SP, STORGAARD M, LEMMING L, HANSEN MM, ET AL. FECAL MICROBIOTA TRANSPLANTATION IS SUPERIOR TO FIDAXOMICIN FOR TREATMENT OF RECURRENT CLOSTRIDIUM DIFFICILE INFECTION. GASTROENTEROLOGY. 2019 APR;156(5):1324-1332.E3. DOI: 10.1053/J.GASTRO.2018.12.019. EPUB 2019 JAN 2. PMID: 30610862.

21- HVAS CL, DAHL JØRGENSEN SM, JØRGENSEN SP, STORGAARD M, LEMMING L, HANSEN MM, ET AL. FECAL MICROBIOTA TRANSPLANTATION IS SUPERIOR TO FIDAXOMICIN FOR TREATMENT OF RECURRENT CLOSTRIDIUM DIFFICILE INFECTION. GASTROENTEROLOGY. 2019 APR;156(5):1324-1332.E3. DOI: 10.1053/J.GASTRO.2018.12.019. EPUB 2019 JAN 2. PMID: 30610862.

22- HVAS CL, DAHL JØRGENSEN SM, JØRGENSEN SP, STORGAARD M, LEMMING L, HANSEN MM, ET AL. FECAL MICROBIOTA TRANSPLANTATION IS SUPERIOR TO FIDAXOMICIN FOR TREATMENT OF RECURRENT CLOSTRIDIUM DIFFICILE INFECTION. GASTROENTEROLOGY. 2019 APR;156(5):1324-1332.E3. DOI: 10.1053/J.GASTRO.2018.12.019. EPUB 2019 JAN 2. PMID: 30610862.

23- ZUO T, WONG SH, LAM K, LUI R, CHEUNG K, TANG W, ET AL. BACTERIOPHAGE TRANSFER DURING FAECAL MICROBIOTA TRANSPLANTATION IN CLOSTRIDIUM DIFFICILE INFECTION IS ASSOCIATED WITH TREATMENT OUTCOME. GUT. 2018; 67(4), 634–643. HTTPS://DOI.ORG/10.1136/GUTJNL-2017-313952

24- PONTE A, PINHO R, MOTA M, SILVA J, VIEIRA N, OLIVEIRA R, ET AL. INITIAL EXPERIENCE WITH FECAL MICROBIOTA TRANSPLANTATION IN CLOSTRIDIUM DIFFICILE INFECTION - TRANSPLANT PROTOCOL AND PRELIMINARY RESULTS. REV ESP ENFERM DIG. 2015 JUL;107(7):402-7. PORTUGUESE. DOI: 10.17235/REED.2015.3767/2015. PMID: 26140631.

25- CÊRCA IDA. TRANSPLANTE DE MICROBIOTA FECAL. UNIVERSIDADE FERNANDO PESSOA PORTO, 2018. PORTUGUESE.

26- CRAVO M. SUPORTE NUTRICIONAL NA DOENÇA INFLAMATÓRIA DO INTESTINO.ASSOCIAÇÃO PORTUGUESA DE NUTRIÇÃO ENTERICA E PARENTERICA. VOL.VII – N.º 1 – ABRIL 2013 ISSN: 1646-7183. PORTUGUESE.

27- ZHANG YJ, LI S, GAN RY, ZHOU T, XU DP, LI HB. IMPACTS OF GUT BACTERIA ON HUMAN HEALTH AND DISEASES. INT J MOL SCI. 2015;16:7493–7519).

28- SHEN ZH, ZHU CX, QUAN YS, YANG ZY, WU S, LUO WW, ET AL. RELATIONSHIP BETWEEN INTESTINAL MICROBIOTA AND ULCERATIVE COLITIS: MECHANISMS AND CLINICAL APPLICATION OF PROBIOTICS AND FECAL MICROBIOTA TRANSPLANTATION. WORLD J GASTROENTEROL. 2018 JAN 7;24(1):5-14. DOI: 10.3748/WJG.V24.I1.5. PMID: 29358877; PMCID: PMC5757125

29- SOBRADO CW SOBRADO LF. MANEJO DA COLITE ULCERATIVA AGUDA GRAVE: ATUALIZAÇÃO TERAPÊUTICA. ARTIGO DE REVISÃO. ABCD ARQ BRAS CIR DIG 2016;29(3):201-205. PORTUGUESE. HTTPS://DOI.ORG/10.1590/0102-6720201600030017

30- SHEN ZH, ZHU CX, QUAN YS, YANG ZY, WU S, LUO WW, ET AL. RELATIONSHIP BETWEEN INTESTINAL MICROBIOTA AND ULCERATIVE COLITIS: MECHANISMS AND CLINICAL APPLICATION OF PROBIOTICS AND FECAL MICROBIOTA TRANSPLANTATION. WORLD J GASTROENTEROL. 2018 JAN 7;24(1):5-14. DOI: 10.3748/WJG.V24.I1.5. PMID: 29358877; PMCID: PMC5757125

31 - Warren S, Sommers SC. Pathogenesis of Ulcerative Colitis. Am J Pathol. 1949; 25(4): 657–679. PMid: 18152861

32 - Costello SP, Hughes PA, Waters O, Bryant RV, Vincent AD, Blatchford P, et al. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis. JAMA. 2019; 321(2): 156-164. doi:10.1001/jama.2018.20046.

33 - Höie O, Wolters F, Riis L, Aamodt G, Solberg C, Bernklev, T, et al. European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD). Ulcerative colitis: patient characteristics may predict 10-yr disease recurrence in a European-wide population-based cohort. Am J Gastroenterol. 2007; 102(8): 1692-701. https://doi.org/10.1016/j.crohns.2008.01.007

34- Sokol H, Landman C, Seksik P, Berard L, Montil M, Nion-Larmurier I, et al. Fecal microbiota transplantation to maintain remission in Crohn's disease: A pilot randomized controlled study. Microbiome. 2020;8(1):1–14. https://doi.org/10.1186/s40168-020-0792-5

35- Zou, M., Jie, Z., Cui, B., Wang, H., Feng, Q., Zou, Y., et al. (2020). Fecal microbiota transplantation results in bacterial strain displacement in patients with inflammatory bowel diseases. FEBS Open Bio, 10(1), 41–55. https://doi.org/10.1002/2211-5463.12744

36- Xu, M. Q. et al. Fecal microbiota transplantation broadening its application beyond intestinal disorders.World J Gastroenterol, v. 21, n.1, p. 102–111, 2015.

37- Xiang L, Ding X, Li Q, Wu X, Dai M, Long C, et al. Efficacy of faecal microbiota transplantation in Crohn's disease: a new target treatment? Microb Biotechnol. 2020;13(3):760–9. https://doi.org/10.1111/1751-7915.13536

38- Li P, Zhang T, Xiao Y, Tian L, Cui B, Ji G, et al. Timing for the second fecal microbiota transplantation to maintain the long-term benefit from the first treatment for Crohn's disease. Appl Microbiol Biotechnol. 2019;103(1):349–60. https://doi.org/10.1007/s00253-018-9447-x

39- Suskind DL, Brittnacher MJ, Wahbeh G, Shaffer ML, Hayden HS, Qin X, et al. Fecal microbial transplant effect on clinical outcomes and fecal microbiome in active Crohn's disease. Inflamm Bowel Dis. 2015;21(3):556–63. https://doi.org/10.1097/MIB.0000000000000307

40- de Groot PF, Frissen MN, de Clercq NC, Nieuwdorp M. Fecal microbiota transplantation in metabolic syndrome: History, present and future. Gut Microbes. 2017 May 4;8(3):253-267. doi: 10.1080/19490976.2017.1293224. Epub 2017 Feb 27. PMID: 28609252; PMCID: PMC5479392. https://pubmed.ncbi.nlm.nih.gov/28609252/

41- Fukuda S, Ohno H. Gut microbiome and metabolic diseases. Semin Immunopathol. 2014 Jan;36(1):103-14. doi: 10.1007/s00281-013-0399-z. Epub 2013 Nov 6. PMID: 24196453.

42- Proença IM, Allegretti JR, Bernardo WM, de Moura DTH, Ponte Neto AM, Matsubayashi CO, et al. Fecal microbiota transplantation improves metabolic syndrome parameters: systematic review with meta-analysis based on randomized clinical trials. Nutr Res. 2020 Nov;83:1-14. doi: 10.1016/j.nutres.2020.06.018. Epub 2020 Jul 3. PMID: 32987284. https://pubmed.ncbi.nlm.nih.gov/32987284/

43- Kootte RS, Levin E, Salojärvi J, Smits LP, Hartstra AV, Udayappan SD, et al. Improvement of Insulin Sensitivity after Lean Donor Feces in Metabolic Syndrome Is Driven by Baseline Intestinal Microbiota Composition. Cell Metab. 2017 Oct 3;26(4):611-619.e6. doi: 10.1016/j.cmet.2017.09.008. PMID: 28978426. https://pubmed.ncbi.nlm.nih.gov/28978426/

44- Allegretti JR, Kassam Z, Hurtado J, Marchesi JR, Mullish BH, Chiang A, et al. Impact of fecal microbiota transplantation with capsules on the prevention of metabolic syndrome among patients with obesity. Hormones (Athens). 2021 Mar;20(1):209-211. doi: 10.1007/s42000-020-00265-z. Epub 2021 Jan 9. PMID: 33420959. https://pubmed.ncbi.nlm.nih.gov/33420959/

45- Smits LP, Kootte RS, Levin E, Prodan A, Fuentes S, Zoetendal EG, et al. Effect of Vegan Fecal Microbiota Transplantation on Carnitine- and Choline-Derived Trimethylamine- N-Oxide Production and Vascular Inflammation in Patients With Metabolic Syndrome. J Am Heart Assoc. 2018 Mar 26;7(7):e008342. doi: 10.1161/JAHA.117.008342. PMID: 29581220; PMCID: PMC5907601. https://pubmed.ncbi.nlm.nih.gov/29581220/

46- Hirten RP, Grinspan A, Fu SC, Luo Y, Suarez-Farinas M, Rowland J, et al. Microbial Engraftment and Efficacy of Fecal Microbiota Transplant for Clostridium Difficile in Patients With and Without Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019 May 4;25(6):969-979. https://doi.org/10.1093/ibd/izy398

47- Lee P, Yacyshyn BR, Yacyshyn MB. Gut microbiota and obesity: An opportunity to alter obesity through faecal microbiota transplant (FMT). Diabetes Obes Metab. 2019 Mar;21(3):479-490. https://doi.org/10.1111/dom.13561

48- Mallon CA, Elsas JDV, Salles JF. Microbial invasions: the process, patterns, and mechanisms. Trends Microbiol. 2015 Nov;23(11):719-729. https://doi.org/10.1016/j.tim.2015.07.013

49- Manrique P, Zhu Y, van der Oost J, Herrema H, Nieuwdorp M, de Vos WM, et al. Gut bacteriophage dynamics during fecal microbial transplantation in subjects with metabolic syndrome. Gut Microbes. 2021 Jan-Dec;13(1):1-15. https://doi.org/10.1080/19490976.2021.1897217

50- Wang S, Xu M, Wang W, Cao X, Piao M, Khan S, et al. Adverse Events of Fecal Microbiota Transplantation.PLoS One. 2016; 11(8):e0161174. https://doi.org/10.1371/journal.pone.0161174

51- Baxter M, Ahmad T, Colville A, Sheridan R. Fatal Aspiration Pneumonia as a Complication of Fecal Microbiota Transplant. Clin Infect Dis. 2015 Jul 1; 61(1):136-7. https://doi.org/10.1093/cid/civ247

52- Kelly CR, Yen EF, Grinspan AM, Kahn SA, Atreja A, Lewis JD, et al. Fecal Microbiota Transplantation Is Highly Effective in Real-World Practice: Initial Results From the FMT National Registry. Gastroenterology. 2021 Jan;160(1):183-192.e3.
https://doi.org/10.1053/j.gastro.2020.09.038

53- Gliklich RE, Dreyer NA, Leavy MB, editors. Registries for Evaluating Patient Outcomes: A User's Guide [Internet]. 3rd ed. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. Report No.: 13(14)-EHC111. PMID: 24945055.