UDC 579.61 + 616.34-008.87 https://doi.org/10.15407/biotech14.01.46

FECAL MICROBIOTES TRANSPLANTATION TECHNOLOGIES: MEDICAL, BIOTECHNOLOGICAL AND REGULATORY ASPECTS

M. M. BAKALCHUK, O. B. BESARAB

National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute"

E-mail: bakalchukmaria@gmail.com

Received 17.11.2020
Revised 11.01.2021
Accapted 26.02.2021

Fecal microbiota transplantation (FMT) is a treatment method based on donor's fecal solution injection into the patient's gastrointestinal tract. FMT is effectively used in the treatment of recurrent *Clostridium difficile* infection. There is also growing interest in the therapeutic application of the method to treat metabolic, autoimmune and other disorders that was not previously associated with intestinal microbiota. Despite the promising results of FMT use, the organizational and legal matters and that of the safety FMT application have not yet been resolved in the European and Ukrainian medical community. The purpose of this review was to summarize information on the FMT application and the regulatory aspects of its use. in accordance with the applicable legal provisions. The analysis of the practical instructions provisions of for FMT applying in clinical practice was carried out, and the bioethical problems associated with the FMT use were investigated.

Key words: intestinal microbiota, fecal microbiota transplantation, *Clostridium difficile*, inflammatory bowel disorder.

The important role of the gastrointestinal tract microbiota in maintaining normal physiological processes in the human body has been generally accepted fact for a long time. The idea of a direct link between human health and the activity of intestinal microorganisms was formulated by Ilya Mechnikov. A microbiota, or microbiome, is a population of microorganisms (overwhelmingly of bacteria) that coexist symbiotically with humans. The human intestinal microbiota includes about 10^{14} microorganisms of almost 1000 different species, most of which are representatives of two phyla: *Bacteroidetes* and *Firmicutes* [1].

Today, there are numerous data that indicate the role of one or another dysbiotic disorders in the microbiome of the gastrointestinal tract in the development of obesity, Crohn's disease, ulcerative colitis, multiple sclerosis, and diabetes mellitus [2–5]. Poor efficacy and overuse of antibacterial drugs contribute to the search for new treatments. Therefore, there is a growing interest in fecal microbiota transplantation. The essence is to transfer the microbiota of a healthy person feces to the gastrointestinal tract of a sick recipient in order to restore the normal microbiota [6, 7].

Prerequisites for the development of fecal microbiota transplantation. Although the FMT use is a little-known practice, it is not an innovative technology. It is first mentioned in medical treatises of the IV century AD, found in China, which described a case of successful treatment of food poisoning. This technique was also used in veterinary medicine (treatment of colitis accompanied by diarrhea in horses).

The first publication on the FMT use to treat pseudomembranous colitis was published in 1958. Then Ben Eisman described a case of successful enema transplantation of suspended feces to four patients with pseudomembranous colitis. The *Clostridium difficile* role in the development of this disease was discovered

only in 1978 [8].

Currently, there are many publications on the FMT effectiveness, which are confirmed by evidence-based medicine. Thus, according to data obtained from the official register of clinical trials (ClinicalTrials.gov) for the term "Fecal Microbiota Transplantation", it can be found 353 clinical investigations, 29 of which are active. Studies are being conducted in Canada, India, the United States, Hong Kong, Denmark, Finland, France, South Africa, and Israel.

To date, the results of studies confirming the high effectiveness of FMT in the treatment of chronic pseudomembranous colitis caused by *C. difficile* are recognized [9–11].

Practical guidelines for the FMT use. Practical recommendations for the FMT use have been published by several reputable international societies: the American Board of Gastroenterologists, the European Society of Clinical Microbiology and Infectious Diseases, the American Society of Infectious Diseases (IDSA) in conjunction with the American Society of Health Epidemiology (SHEA), World Society of Emergency Surgery (WSES). Experts of these societies recognize FMT as an effective and appropriate way to treat recurrent infections caused by *C. difficile* [12].

We consider the features of FMT obtained from the European consensus on FMT in clinical practice [13].

Donor selection. The provisions of the European consensus provide for thorough screening of fecal material donors. To reduce possible risks, the age of the donor should not exceed 60 years. Healthy donors are usually selected from family members.

At the beginning of the process, potential donors should undergo a medical interview to rule out possible risk factors.

Key diseases / conditions to be tested in the selection of potential donors for pre-screening:

◆ Infectious diseases:

• a history of HIV, hepatitis B virus or hepatitis C virus, syphilis, human T-lymphotropic virus type I or II, malaria, trypanosomiasis, tuberculosis presence;

• known systemic infection not controlled at the time of donation;

• use of illicit drugs;

• incomprehensible sexual behavior (anonymous sexual intercourse; presence of a history of sexually transmitted diseases);

• previously undergone organ / tissue transplantation as a recipient;

• taking blood products (<12 months);

• tattooing, piercing, acupuncture (<6 months);

• recent treatment in unsatisfactory hygienic conditions;

• risk of transmitting diseases caused by prions;

• recent parasitosis or infectious diseases caused by rotavirus, *Giardia lamblia* and other microorganisms that affect the gastrointestinal tract;

• recent stay in tropical countries, countries at high risk of infectious diseases or travelers' diarrhea (<6 months);

• recent vaccination with alive attenuated virus if there is a risk of transmission (<6 months);

• healthcare professionals (to eliminate the risk of transmission of multidrug-resistant organisms);

• individual work with animals (to eliminate the risk of zoonotic infections transmission).

◆ Diseases of the gastrointestinal tract, metabolic and neurological diseases:

• history of irritable bowel syndrome, inflammatory bowel disease, functional chronic constipation, celiac disease, other chronic diseases of the gastrointestinal tract;

• history of chronic systemic autoimmune diseases associated with the gastrointestinal tract;

• history or high risk of gastrointestinal cancer or polyposis;

• recent diarrhea or hematochezia;

• history of neurological or neurodegenerative diseases;

• history of mental disorders;

• overweight or obesity (body mass index> 25 kg/m^2).

◆ Drugs that may affect the composition of the intestinal microbiota:

• Recent use of antibiotics, immunosuppressants, chemotherapy (<3 months);

• Prolonged therapy with proton pump inhibitors.

Selected donors for FMT must pass the analysis of blood and feces no later than 4 weeks before the donation of fecal material (Table 1).

Preparation of material. The European consensus on the transplantation of fecal microbiota clearly regulates the amount of fecal material, the optimal time of delivery to the laboratory, the requirements for the premises in which feces are treated. A suspension of feces which can be prepared from fresh or frozen feces is used for FMT. The optimal method of fecal material preparation is uncertain. Randomized trials indicate that fresh and frozen material are

The range of required laboratory tests of fecal material donors (according to Cammarota G. et al. [13])

General blood test	*Infectious disease*
	• Cytomegalovirus; • Hepatitis A, hepatitis B, hepatitis C and hepatitis E viruses; • Syphilis; • HIV-1 and HIV-2; • *Entamoeba histolytica*
	Biochemical research
	• Complete clinical blood test; • C-reactive protein and ESR; • Albumin, creatine and electrolyte; • Aminotransferase, bilirubin, γ-glutamyltranspeptidase, alkaline • phosphatase.
Blood tests in specific cases	• Antibodies to human T-lymphotropic virus type I and II; • *Strongyloides stercoralis.*
General analysis of feces	• *Clostridium difficile*; • Intestinal pathogens, in particular *Salmonella* and *Shigella*; • *Campylobacter, Escherichia coli O157 H7, Yersinia,* vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, gram-negative multidrug-resistant bacteria; • Novovirus; • Antigens and / or acid-resistant staining on *Giardia lamblia* and *Cryptosporidium parvum;* • The simplest (including *Blastocystis hominis*) and helminths; • Analysis of feces on occult blood.
Analysis of feces in specific cases	• *Vibrio cholera* and *Listeria monocytogenes*; • Antigens and / or acid staining for *Isospora* and *Microsporidia*; • Calprotectin; • Fecal antigen *Helicobacter pylori*; • Rotavirus

equally effective in the treatment of *C. difficile* infections [14, 15].

There is considerable heterogeneity in studies on the material for FMT preparation, which makes it difficult to draw a firm conclusion. However, it has been shown that infusions with water are more effective than with physiological saline (98.5% vs. 86%) [16].

Fresh fecal material must be processed within 6 hours of receipt. Approximately 50 g of donor fecal material is mixed with 150 ml of sterile sodium chloride solution. The mixture is filtered to remove large particles which may hinder the administration [13, 17].

The use of frozen material contributes to the standardization of the FMT process and the development of fecal sample banks. Frozen fecal material should be stored at –80 °C. When using the material in FMT, fecal suspension is thawed in a water bath at 37 °C, mixed with physiological saline. The infusion should be performed within 6 hours after thawing [13].

Means of fecal material delivery. The means of fecal material delivery used today are conventionally divided into upper (oral capsules), middle (by esophagogastroduodenoscopy or nasogastric, nasojejunal, nasoduodenal catheter) and lower (by colonoscopy or retention enema). The literature discusses the effectiveness of different methods of fecal suspensions administration.

The main advantages of colonoscopy are the ability to visualize the process [18; 19], reliable delivery to the affected parts of the intestine [20], providing a larger volume of material, which will increase the success rate of the procedure [16]. But colonoscopy is an expensive, relatively risky invasive procedure.

The use of enemas is less invasive, relatively cheaper and easier way to perform. However, there is a problem of material retention, which may require multiple infusions to achieve clinical efficacy [21].

The use of medium means of delivery is a faster and cheaper way, better tolerated than colonoscopy [22]. However, smaller volumes of material are used, which is associated with lower clinical efficacy of this method. Wang and coauthors [7] note that the frequency of side effects was higher when using medium delivery methods compared to the lower ones (43.6% vs. 17.7%).

The capsules are minimally invasive and convenient. In addition, the capsules are more

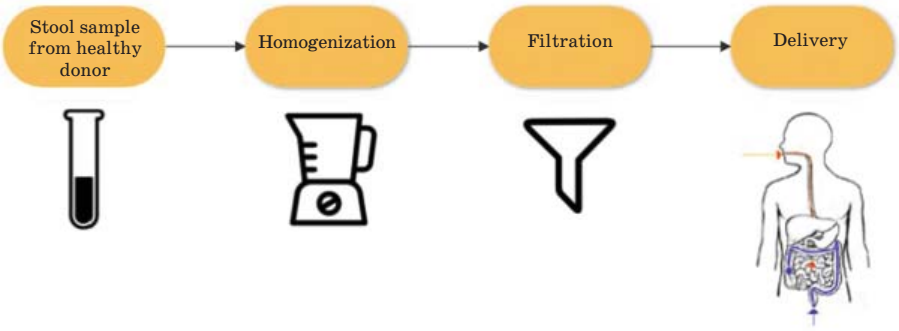

Fig. 1. **Schematic diagram of the FMT process**

aesthetically pleasing because patients prefer this method of delivery over others [23].

To date, in clinical practice there is no strong evidence of the most optimal means of fecal material delivery. The decision to choose a method should depend on the individual clinical situation. Schematic diagram of the FMT process is shown in Fig. 1.

Monitoring. After FMT performing, experts recommend careful monitoring of patients. The length of the period during which the patient should be monitored has not been established. If FMT procedure is successful and the clinical symptoms of the disease begin to decrease progressively, European experts do not recommend retesting *C. difficile* in the feces, as toxins of this bacterium can be stored in the feces for several weeks [12, 24].

Fecal microbiota transplantation in the treatment of infections caused by C. difficile. At present, the idea of the FMT effectiveness in the treatment of recurrent infection caused by *C. difficile* has been established. The efficiency indicator of treatment when using FMT is approximately 90%. At the same time, the efficiency indicator of long-term antimicrobial therapy is 20–30% [25]. Numerous studies also demonstrate the FMT efficiency in the treatment of recurrent *C. difficile* infection in elderly patients, patients with comorbidities or weakened immunity [26–28].

So, van Nood and coauthors [29] conducted a randomized open-labelled controlled clinical trial in which patients with recurrent *C. difficile* infection were randomly assigned to one of three groups: 1) initial treatment with vancomycin (orally, by 500 mg 4 times a day for 4 days) followed by bowel lavage and infusion of donor suspended feces solution through a catheter; 2) standard course of therapy with vancomycin (orally, by 500 mg 4 times a day for 14 days); 3) standard course of therapy with vancomycin with bowel lavage. The endpoint was initially identified — the persistent disappearance of diarrhea (within 10 weeks of follow-up) caused by the bacterial infection.

In 13 of 16 patients in the first group there was a disappearance of diarrhea after the first administration of the drug. Three patients in this group were re-infused (from another donor), in these circumstances, diarrhea disappeared in two of them. Disappearance of diarrhea was observed only in 4 of 13 patients of the second group, in 3 of 13 — in the third group.

Thus, FMT was more effective than the vancomycin use in the treatment of recurrent *C. difficile* infection.

Ethan Gough and coauthors in the review [16] showed that in 317 patients in the 27 studies reviewed, FMT showed efficacy in treating the disease in 92% of cases. Efficacy varied depending on the route of administration, the volume of drug administered, and the treatment before infusion.

Therefore, FMT is now the recommended treatment for the third recurrence of *C. difficile* infection. The acute form of the infection and the first recurrence are still treated with antibiotics. However, given the effectiveness and low frequency of complications, more FMT is predicted to be used in the first recurrences of the disease in the future [30].

Fecal microbiota transplantation in the treatment of inflammatory bowel disease. In addition to the treatment of *C. difficile* infections, FMT is considered a potential method of treating inflammatory bowel disease.

Encouraging results have been obtained with the use of FMT for the treatment of ulcerative colitis. In their study Ahmet Uygun and coauthors [31] demonstrated the FMT effectiveness in the treatment of ulcerative colitis. After the procedure, 21 of 30 patients

showed a clinical response to treatment, 13 of 30 patients achieved remission by the twelfth week, 9 patients had no clinical response by the twelfth week. In 2012, a retrospective review of 62 patients with ulcerative colitis who underwent FMT over a 24-year period was conducted. In this study, the frequency of a positive FMT result was reported to be 91.9%, with 67.7% achieving complete clinical remission after FMT; 24.2% achieved partial remission, and only 8% did not have a positive response to FMT [32].

Available data on the FMT use in the Crohn's disease treatment are limited to descriptions of a series of studies on small groups or an isolated cases description. Vermeire and coauthors [33] reported no significant clinical or endoscopic improvement after 8 weeks in four Crohn's disease patients who underwent FMT through a nasojejunal catheter three times over a 2-day period. Temporary changes in the recipient's microbiota were observed in all patients (weeks 2–4), but the microbial composition of the intestine returned to baseline after eight weeks. These results, along with other studies, suggest that Crohn's disease has increased resistance to FMT compared with ulcerative colitis [34].

Fecal microbiota transplantation in the treatment of irritable bowel syndrome. FMT is also considered as a possible method of treating irritable bowel syndrome.

Many studies have shown that microbial changes in the intestine (reduced biodiversity and increased numbers of *Bacteroidetes*) are associated with the development of irritable bowel syndrome [35, 36]. If the pathogenicity model of *C. difficile* infections is applied to irritable bowel syndrome, FMT may also be effective in this group of patients. Indeed, positive results have been reported in the treatment of irritable bowel syndrome with a predominance of diarrhea. Pinn and coauthors [37] informed of 13 patients with refractory irritable bowel syndrome, 70% of whom showed improvement in symptoms after FMT, including symptoms such as abdominal pain (72%), dyspepsia (67%), and bloating (50%). A randomized, double-blind, placebo-controlled study [38] showed that FMT alters the composition of the intestinal microbiota in patients with irritable bowel syndrome. However, placebo-treated patients had greater symptom relief compared with the FMT group. Therefore, more research is needed to better understand the effects of FMT on the patients with irritable bowel syndrome health and the subsequent wider use of FMT in treatment.

Fecal microbiota transplantation in the treatment of autoimmune diseases. There are publications that indicate a link between the functioning of the immune system and the microbiota [39, 40], between changes in the intestinal microbiota and the development of autoimmune disorders, including idiopathic thrombocytopenic purpura, systemic lupus erythematosus, arthritis, Sjögren's syndrome, and Hashimoto's thyroiditis [41].

Borody and coauthors [42] reported the sudden disappearance of idiopathic thrombocytopenic purpura in a patient with prolonged ulcerative colitis who underwent FMT, which led to prolonged normalization of platelet counts and decreased ulcerative colitis activity.

There are also examples of treatment for multiple sclerosis. Thus, a clinical case is indicative — a 30-year-old man was observed for multiple sclerosis and trigeminal neuralgia. To treat constipation, the patient underwent five FMT procedures by rectal infusion, which resulted in the complete disappearance of the problem. At the same time, there was a decrease in the severity of neurological deficits caused by multiple sclerosis, including the restoration of the ability to walk independently. Initially, this was considered remission, but 15 years after FMT, the patient did not have periods of exacerbation [43].

In addition, FMT is trying to be used in the complex treatment of metabolic syndrome [44–46], as well as for the correction of autism in children with complex therapy [47]. The evidence base for the treatment of these pathologies is still insufficient, but there are encouraging results.

Regulatory aspects. In July 2013, the US Food and Drug Administration (FDA) officially confirmed that it would regulate the use of human fecal-derived drugs in clinical practice. Due to the growing interest to FMT, the question of such a need has been raised in the United States and other countries for the past few years [48]. The European Medicines Agency does not currently regulate intestinal microbiota transplantation. The only conditions that the doctor must follow are to obtain the informed patient consent and to follow the donor selection protocol. Similar requirements are set in Australia [49].

Consider in more detail the regulation in the United States. A fecal microbiota transplantate used to treat, alleviate, or prevent a disease falls within the United States acting drug definition. In the United States, a requirement was introduced in

2013 that physicians using FMTs must submit to the FDA an application for a new investigational drug (Investigative New Drug (IND) application), which is equivalent to filing an application for a clinical trial, with a detailed clinical research protocol. The IND submitted to the FDA, in addition to standard information, should include information on procedures restricting the transmission of pathogens to the subjects involved; intestinal microbiota donors screening procedures; description of pharmaceutical and biological testing methods of the fecal transplantate properties; description of the procedure for fecal microbiota introduction; the amount of administered product (dose) and frequency of administration; a description of the donor material obtaining process and its storage (e.g., fresh / frozen); description of the method of fecal transplantate preparation; characteristics of physicochemical and biological properties of the pharmaceutical substance [50].

Canada has made great strides in the development of FMT, so it is worth considering the position of the Canadian regulator on this new technology. Health Canada has classified FMT materials as "new biological drugs". As part of the documents submission for consideration to this agency, FMT protocols are considered by the Directorate of Biological and Gene Therapy. Examination of documents is fairly standard, including an on-site inspection to determine whether the rules and guidelines of good manufacturing practice are followed at the production site. In addition, Health Canada requires that donors should be screened for infections included in organ transplant screening protocols, as well as intestinal infections. Validated bacterial mixtures extracted from human fecal material should be monitored for contamination and cultural stability [6].

Economic aspects. C. difficile infection has a significant financial burden on the health care system and requires the development and implementation of more cost-effective treatments [51, 52]. In the United States, the financial cost of hospital treatment of patients with *C. difficile* infection in 2015 was 6.3 billion US dollars [52]. In Europe, financial costs are estimated at about 3 billion euros [53].

Economic analyzes comparing treatment with FMT and antibiotics showed the potential cost-effectiveness of FMT in the treatment of recurrent infection caused by *C. difficile*.

So, in their work G. Konijeti and coauthors [54] compared four strategies for treating the recurrent infection caused by *C. difficile*: treatment with metronidazole; using vancomycin; using fidaxomicin; FMT. According to their estimates, the use of FMT by colonoscopy was the most cost-effective treatment strategy with an incremental cost-effectiveness ratio (ICER) of $17.016.

Lauren Lapointe-Shaw and coauthors [55] analyzed the cost-effectiveness of six treatment strategies for recurrent *C. difficile* infection: metronidazole treatment; vancomycin treatment; fidaxomicin treatment; FMT with an enema treatment; FMT using a nasogastric catheter treatment; FMT by colonoscopy treatment. It should be noted that FMT by means of a colonoscopy showed the greatest efficiency and was less expensive, in comparison with the considered alternatives. According to all model parameters, an 87 % probability was determined that FMT by colonoscopy is the most profitable strategy.

Zainab I Abdali and coauthors [56] conducted an analysis using a decision model that represents the cost for an additional year of life adjusted for its quality (QALY). This analysis showed that the FMT use is a less expensive and more effective treatment compared to fidaxomicin and vancomycin. The incremental cost-effectiveness ratio was 242.514 pounds sterling / QALY.

Therefore, based on economic analyzes, it can be argued that FMT is a more cost-effective way to treat recurrent *C. difficile* infection compared to antibiotic therapy.

Bioethical aspects of FMT use. Ethical aspects in the field of FMT can be summarized as follows [57]:

1. Problems related to donor selection.
2. Safety issues and the risk-benefit balance of the procedure.
3. Problems of informed consent.
4. Problems of commercialization.

Problems with donor's selection. To date, a number of different donors screening protocols for FMT have been published. However, there are some inconsistencies between the protocols regarding the requirements for certain tests or the frequency of their conduct. In addition to the uncertainties associated with the screening procedure, there are uncertainties related to the donor's profile — it has not been established whether children and pregnant women can become donors, or whether the donor's religious background related to a special diet should be taken into account. From the donor's point of view, the issues of

confidentiality, information on the duration of screening and the possibility of refusal are also important [57]. In 2019, two cases of infection with multidrug-resistant organisms were registered, one of which resulted in the patient's death. These cases have led the FDA to revise its recommendations by introducing additional screening for multidrug-resistant organisms. Modern protocols are insufficient and do not take into account the possibility of microbiota perturbation by currently unknown mechanisms [58].

Safety issues and the risk-benefit balance of the procedure. Modern research, in most cases, demonstrates the safety of FMT. However, some patients have side effects — constipation, fever, increased levels of C-reactive protein. Risks should also include exacerbation of an existing disease, known and unknown infections, and so on. The follow-up period for patients who have undergone FMT is not long enough to identify long-term side effects. Another risk is the use of FMT in children. There is a critical period in infancy and early childhood, during which manipulations with the intestinal microbiota have the greatest impact on health and the brain, which can affect the overall development of the child [59, 60]. The possibility of such side effects also raises ethical questions about patients' informed consent regarding the possibility of side effects in the future.

Problems of informed consent. From the recipient's point of view, the informed consent process should fully inform him of the main objectives, possible benefits and risks of the study. This aspect is the most ethically complex in the case of a child's treatment, as legal decisions are made by guardians who must consider both the risks and the benefits to the other person. From the donor's point of view, it is important to provide complete information on the procedure [58].

Problems of commercialization. The problem of FMT commercialization raises questions of ownership of the material, availability of data and biological material, as well as the consequences of the direct sale of material to the consumer [61]. The commercialized and widespread use of FMT raises the question of the risk-benefit balance, as unpredictable long-term side effects of FMT use are possible.

Some authors also highlight such a possible ethical issue as family relationships, as family members may become potential secondary recipients of the altered microbiota [57].

To date, the FMT effectiveness in the treatment of recurrent *C. difficile*-associated infections has been proven. The FMT use is also considered as a possible treatment for inflammatory bowel disease, irritable bowel syndrome, autoimmune and metabolic diseases. However, data on the FMT efficacy in these conditions are limited to isolated clinical cases and small studies, so further randomized controlled trials are needed. It is also important to regulate organizational, legal, technical and economic issues related to the widespread use of FMT. A necessary priority is to develop effective regulation that will protect patients and donors, prevent abuse of treatment. In addition, the issue of FMT use safety is important, so it is necessary to further determine the consequences of FMT long-term use.

This study did not receive any financial support from a government, community or commercial organization.

The authors state that they have no conflict of interest.

REFERENCES

1. *Neish A. S.* Microbes in gastrointestinal health and disease. *Gastroenterology*. 2009, 136(1), 65–80. https://doi.org/10.1053/j.gastro.2008.10.080.
2. *Evdokimova N.V., Chernen'kaja T.V.* Fecal Microbiota Transplantation: Past, Present and Future. *Zhurnal im. N.V. Sklifosovskogo Neotlozhnaya medicinskaya pomoshch*. 2019, 8(2), 160–165. (In Russian).
3. *Clemente J. C., Manasson J., Scher J. U.* The role of the gut microbiome in systemic inflammatory disease. *BMJ (Clinical research ed.)*. 2018, 360. https://doi.org/10.1136/bmj.j5145.
4. *Mohajeri M. H., Brummer R., Rastall R. A., Weersma R. K., Harmsen H., Faas M., Eggersdorfer M.* The role of the microbiome for human health: from basic science to clinical applications. *European journal of nutrition*. 2018, 57(Suppl 1), 1–14. https://doi.org/10.1007/s00394-018-1703-4.
5. *Tseng CH, Wu CY.* The gut microbiome in obesity. *J Formos Med Assoc*. 2019, 118 Suppl 1:S3-S9. https://doi.org/10.1016/j.jfma.2018.07.009.
6. *Vasil'ev A. N., Gorjachev D. V., Gavrishina E. V., Nijazov R. R., Seliverstov Ju. A., & Digtjar' A. V.* Fecal microbiota transplantation: possible

therapeutic approaches and regulatory issues. *Biopreparaty. Profilaktika, diagnostika, lechenie*. 2015, 2 (54), 15-23. (In Russian).
7. *Wang S., Xu M., Wang W., Cao X., Piao M., Khan S., Yan F., Cao H., Wang B.* Systematic Review: Adverse Events of Fecal Microbiota Transplantation. *PLoS One*. 2016, 11(8). https://doi.org/10.1371/journal.pone.0161174.
8. *de Groot P.F., Frissen M. N., de Clercq N. C., Nieuwdorp M.* Fecal microbiota transplantation in metabolic syndrome: History, present and future. *Gut Microbes*. 2017, 8(3), 253-267. https://doi.org/10.1080/19490976.2017.1293224.
9. *Rubin T. A., Gessert C. E., Aas J., Bakken J. S.* Fecal microbiome transplantation for recurrent Clostridium difficile infection: report on a case series. *Anaerobe*. 2013, 19, 22–26. https://doi.org/10.1016/j.anaerobe.2012.11.004.
10. *Kelly B. J., Tebas P.* Clinical Practice and Infrastructure Review of Fecal Microbiota Transplantation for Clostridium difficile Infection. *Chest*. 2018, 153(1), 266–277. https://doi.org/10.1016/j.chest.2017.09.002.
11. *Czepiel J., Dróżdż M., Pituch H., Kuijper E. J., Perucki W., Mielimonka A., Goldman S., Wultańska D., Garlicki A., Biesiada G.* Clostridium difficile infection: review. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology*. 2019, 38(7), 1211–1221. https://doi.org/10.1007/s10096-019-03539-6.
12. *Hubska O. Yu., Hridniev O. Ye.* . Fecal microbiota transplantation: a modern, effective and safe method of treating *Clostridium difficile* infection. *Suchasna Hastroenterolohiia*. 2019, 3, 66–78. (In Ukrainian).
13. *Cammarota G., Ianiro G., Tilg H., et al.* European consensus conference on faecal microbiota transplantation in clinical practice. *Gut*. 2017, 66(4), 569-580. https://doi.org/10.1136/gutjnl-2016-313017.
14. *Tang G., Yin W., Liu W.* Is frozen fecal microbiota transplantation as effective as fresh fecal microbiota transplantation in patients with recurrent or refractory Clostridium difficile infection: A meta-analysis? *Diagn Microbiol Infect Dis*. 2017, 88(4), 322-329. https://doi.org/10.1016/j.diagmicrobio.2017.05.007.
15. *Lee C. H., Steiner T., Petrof E. O., Smieja M., Roscoe D., Nematallah A., Weese J. S., Collins S., Moayyedi P., Crowther M., Ropeleski M. J., Jayaratne P., Higgins D., Li Y., Rau N. V., Kim P. T.* Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. *JAMA*. 2016, 315(2), 142-149. https://doi.org/10.1001/jama.2015.18098.
16. *Gough E., Shaikh H., Manges A.R.* Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. *Clin Infect Dis*. 2011, 53(10), 994-1002. https://doi.org/10.1093/cid/cir632.
17. *Vindigni S.M, Surawicz C.M.* Fecal Microbiota Transplantation. *Gastroenterol. Clin. North. Am*. 2017, 46(1), 171-185. https://doi.org/10.1016/j.gtc.2016.09.012.
18. *Mattila E., Uusitalo-Seppälä R., Wuorela M., Lehtola L., Nurmi H., Ristikankare M., Moilanen V., Salminen K., Seppälä M., Mattila P. S., Anttila V. J., Arkkila P.* Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. *Gastroenterology*. 2012, 142(3), 490–496. https://doi.org/10.1053/j.gastro.2011.11.037.
19. *Kelly C. R., de Leon L., Jasutkar N.* Fecal microbiota transplantation for relapsing Clostridium difficile infection in 26 patients: methodology and results. *Journal of clinical gastroenterology*. 2012, 46(2), 145–149. https://doi.org/10.1097/MCG.0b013e318234570b.
20. *Yoon S. S., Brandt L. J.* Treatment of refractory/recurrent C. difficile-associated disease by donated stool transplanted via colonoscopy: a case series of 12 patients. *Journal of clinical gastroenterology*. 2010, 44(8), 562–566. https://doi.org/10.1097/MCG.0b013e3181dac035.
21. *Kassam Z., Hundal R., Marshall J. K., Lee C. H.* Fecal transplant via retention enema for refractory or recurrent Clostridium difficile infection. *Arch. Intern. Med*. 2012, 172(2), 191–193. https://doi.org/10.1001/archinte.172.2.191.
22. *Gweon T. G., Kim J., Lim C. H., Park J. M., Lee D. G., Lee I. S., Cho Y. S., Kim S. W., Choi M. G.* Fecal Microbiota Transplantation Using Upper Gastrointestinal Tract for the Treatment of Refractory or Severe Complicated Clostridium difficile Infection in Elderly Patients in Poor Medical Condition: The First Study in an Asian Country. *Gastroenterology research and practice*. 2016. https://doi.org/10.1155/2016/2687605.
23. *Kao D., Roach B., Silva M., Beck P., Rioux K., Kaplan G. G., Chang H. J., Coward S., Goodman K. J., Xu H., Madsen K., Mason A., Wong G. K., Jovel J., Patterson J., Louie T.* Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. *JAMA*.

2017, 318(20), 1985–1993. https://doi.org/10.1001/jama.2017.17077.
24. *Smits L. P., Bouter K. E., de Vos W. M., Borody T. J., Nieuwdorp M.* Therapeutic potential of fecal microbiota transplantation. *Gastroenterology*. 2013 Nov, 145(5), 946-53. https://doi.org/10.1053/j.gastro.2013.08.058.
25. *Kassam Z., Lee C. H., Yuan Y., Hunt R. H.* Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. *The American journal of gastroenterology*. 2013, 108(4), 500–508. https://doi.org/10.1038/ajg.2013.59.
26. *Agrawal M., Aroniadis O. C., Brandt L. J., Kelly C., Freeman S., Surawicz C., Broussard E., Stollman N., Giovanelli A., Smith B., Yen E., Trivedi A., Hubble L., Kao D., Borody T., Finlayson S., Ray A., Smith R.* 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*. 2016, 50(5), 403–407. https://doi.org/10.1097/MCG.0000000000000410.
27. *Girotra M., Garg S., Anand R., Song Y., Dutta S. K.* Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection in the Elderly: Long-Term Outcomes and Microbiota Changes. *Digestive diseases and sciences*. 2016, 61(10), 3007–3015. https://doi.org/10.1007/s10620-016-4229-8.
28. *Khoruts A., Rank K. M., Newman K. M., Viskocil K., Vaughn B. P., Hamilton M. J., Sadowsky M. J.* Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2016, 14(10), 1433–1438. https://doi.org/10.1016/j.cgh.2016.02.018.
29. *Van Nood E., Vrieze A., Nieuwdorp M., Fuentes S., Zoetendal E. G., de Vos W. M., Visser C. E., Kuijper E. J., Bartelsman J. F., Tijssen J. G., Speelman P., Dijkgraaf M. G., Keller J. J.* Duodenal infusion of donor feces for recurrent Clostridium difficile. *N. Engl. J. Med*. 2013 Jan 31, 368(5), 407-15. https://doi.org/10.1056/NEJMoa1205037.
30. *Borody T. J., Brandt L. J., Paramsothy S.* Therapeutic faecal microbiota transplantation: current status and future developments. *Curr Opin Gastroenterol*. 2014, 30(1), 97-105. https://doi.org/10.1097/MOG.0000000000000027.
31. *Uygun A., Ozturk K., Demirci H., Oger C., Avci I. Y., Turker T., Gulsen M.* Fecal microbiota transplantation is a rescue treatment modality for refractory ulcerative colitis. *Medicine*. 2017, 96(16). https://doi.org/10.1097/MD.0000000000006479.
32. *Borody T., Wettstein A., Campbell J. et al.* Fecal microbiota transplantation in ulcerative colitis: review of 24 years experience [abstract]. *Am. J. Gastroenterol*. 2012, 107. https://doi.org/10.14309/00000434-201210001-01644.
33. *Vermeire S., Joossens M., Verbeke K. et al.* Pilot study on the safety and efficacy of fecal microbiota transplantation in refractory Crohn's disease. *Gastroenterology*. 2012, 142, 360. https://doi.org/10.1016/S0016-5085(12)61356-0.
34. *Green J. E., Davis J. A., Berk M., Hair C., Loughman A., Castle D., Athan E., Nierenberg A. A., Cryan J. F., Jacka F., Marx W.* Efficacy and safety of fecal microbiota transplantation for the treatment of diseases other than *Clostridium difficile* infection: a systematic review and meta-analysis. *Gut microbes*. 2020, 12(1), 1–25. https://doi.org/10.1080/19490976.2020.1854640.
35. *Johnsen P. H., Hilpüsch F., Cavanagh J. P., Leikanger I. S., Kolstad C., Valle P. C., Goll R.* Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial. *The lancet. Gastroenterol. hepatol*. 2018, 3(1), 17–24. https://doi.org/10.1016/S2468-1253(17)30338-2.
36. *Ianiro G., Eusebi L. H., Black C. J., Gasbarrini A., Cammarota G., Ford A. C.* Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics*. 2019, 50(3), 240–248. https://doi.org/10.1111/apt.15330.
37. *Pinn D. M., Aroniadis O. C., Brandt L. J.* Follow-up study of fecal microbiota transplantation (FMT) for the treatment of refractory irritable bowel syndrome (IBS) [abstract]. *ACG 2013 Annual Scientific Meeting and Postgraduate Course*; 11–16 October 2013 San Diego, CA: San Diego Convention Center.
38. *Halkjær S. I., Christensen A. H., Lo B., Browne P. D., Günther S., Hansen L. H., Petersen A. M.* Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: results from a randomised, double-blind placebo-controlled study. *Gut*. 2018, 67(12), 2107–2115. https://doi.org/10.1136/gutjnl-2018-316434.
39. *Chen F., Stappenbeck T. S.* Microbiome control of innate reactivity. *Current opinion in immunology*. 2019, *56*, 107–113. https://doi.org/10.1016/j.coi.2018.12.003.

40. *McCoy K. D., Ignacio A., Geuking M. B.* Microbiota and Type 2 immune responses. *Current opinion in immunology*. 2019, 54, 20–27. https://doi.org/10.1016/j.coi.2018.05.009.
41. *Xu M. Q., Cao H. L., Wang W. Q., Wang S., Cao X. C., Yan F., Wang B. M.* Fecal microbiota transplantation broadening its application beyond intestinal disorders. *World journal of gastroenterology*. 2015, 21(1), 102–111. https://doi.org/10.3748/wjg.v21.i1.102.
42. *Borody T. J., Campbell J., Torres M. et al.* Reversal of idiopathic thrombocytopenic purpura (ITP) with fecal microbiota transplantation (FMT) [abstract]. *Am J Gastroenterol*. 2011, 106, 352.
43. *Borody T. J., Leis S. M., Campbell J., Torres M., Nowak A.* Fecal microbiota transplantation (FMT) in multiple sclerosis (MS). *Am J Gastroenterol*. 2011, 106, 352.
44. *Ridaura V. K., Faith J. J., Rey F. E., Cheng J., Duncan A. E., Kau A. L., Griffin N. W., Lombard V., Henrissat B., Bain J. R., Muehlbauer M. J., Ilkayeva O., Semenkovich C. F., Funai K., Hayashi D. K., Lyle B. J., Martini M. C., Ursell L. K., Clemente J. C., Van Treuren W., Gordon J. I.* Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science*. 2013, 341(6150). https://doi.org/10.1126/science.1241214.
45. *Vrieze A., Van Nood E., Holleman F., Salojärvi J., Kootte R. S., Bartelsman J. F., Dallinga-Thie G. M., Ackermans M. T., Serlie M. J., Oozeer R., Derrien M., Druesne A., Van Hylckama Vlieg J. E., Bloks V. W., Groen A. K., Heilig H. G., Zoetendal E. G., Stroes E. S., de Vos W. M., Hoekstra J. B., Nieuwdorp M.* Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. 2012, 143(4), 913–6.e7. https://doi.org/10.1053/j.gastro.2012.06.031.
46. *Fischer M., Sipe B., Torbeck M., Xu H., Kassam Z., Allegretti J. R.* Does fecal microbiota transplantation from an obese donor lead to weight gain? a case series of 70 recipients. *Gastroenterology*. 2017, 152(5), p. S1004. https://doi.org/10.1016/S0016-5085(17)33408-X.
47. *Kang D. W., Adams J. B., Gregory A. C., Borody T., Chittick L., Fasano A., Khoruts A., Geis E., Maldonado J., McDonough-Means S., Pollard E. L., Roux S., Sadowsky M. J., Lipson K. S., Sullivan M. B., Caporaso J. G., Krajmalnik-Brown R.* Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome*. 2017, 5(1), 10. https://doi.org/10.1186/s40168-016-0225-7.
48. *Mole B.* FDA gets to grips with faeces. *Nature*. 2013, 498(7453), 147–148. https://doi.org/10.1038/498147a.
49. *De Vrieze J.* Medical research. The promise of poop. *Science (New York, N.Y.)*. 2013, 341(6149), 954–957. https://doi.org/10.1126/science.341.6149.954.
50. U.S. Food and Drug Administration: FDA's Public Workshop; Fecal Microbiota for Transplantation — Presentations. Available at: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm352636.htm (accessed 20 January 2021).
51. *Roldan G. A., Cui A. X., Pollock N. R.* Assessing the Burden of Clostridium difficile Infection in Low– and Middle-Income Countries. *Journal of clinical microbiology*. 2018, 56(3), e01747-17. https://doi.org/10.1128/JCM.01747-17.
52. *Zhang S., Palazuelos-Munoz S., Balsells E. M., Nair H., Chit A., Kyaw M. H.* Cost of hospital management of Clostridium difficile infection in United States-a meta-analysis and modelling study. *BMC infectious diseases*. 2016, 16(1), 447. https://doi.org/10.1186/s12879-016-1786-6.
53. *Reigadas Ramírez E., Bouza E. S.* Economic Burden of Clostridium difficile Infection in European Countries. *Advances in experimental medicine and biology*. 2018, 1050, 1–12. https://doi.org/10.1007/978-3-319-72799-8_1.
54. *Konijeti G. G., Sauk J., Shrime M. G., Gupta M., Ananthakrishnan A. N.* Cost-effectiveness of competing strategies for management of recurrent Clostridium difficile infection: a decision analysis. *Clin. Infect. Dis.* 2014 Jun, 58(11), 1507-14. https://doi.org/10.1093/cid/ciu128.
55. *Lapointe-Shaw L., Tran K. L., Coyte P. C., Hancock-Howard R. L., Powis J., Poutanen S. M., Hota S.* Cost-Effectiveness Analysis of Six Strategies to Treat Recurrent Clostridium difficile Infection. *PLoS One*. 2016 Feb 22, 11(2). https://doi.org/10.1371/journal.pone.0149521.
56. *Zainab I. Abdali, Tracy E. Roberts, Pelham Barton, Peter M. Hawkey.* Economic evaluation of Faecal microbiota transplantation compared to antibiotics for the treatment of recurrent Clostridioides difficile infection. *EClinicalMedicine*. 2020. https://doi.org/10.1016/j.eclinm.2020.100420 .
57. *Ma Yonghui, Liu Jiayu, Rhodes Catherine, Nie Yongzhan, Zhang Faming.* Ethical Issues in Fecal Microbiota Transplantation in Practice. *The American Journal of Bioethics*. 2017, 17, 34-45. https://doi.org/10.1080/15265161.2017.1299240.

58. *Zoya Grigoryan, Michael J. Shen, Shaina W. Twardus, Marc M. Beuttler, Lea Ann Chen, Alison Bateman-House*. Fecal microbiota transplantation: Uses, questions, and ethics. *Medicine in Microecology*. 2020, 6. https://doi.org/10.1016/j.medmic.2020.100027.
59. *Bokulich N. A., Chung J., Battaglia T., Henderson N., Jay M., Li H., D Lieber A., Wu F., Perez-Perez G. I., Chen Y., Schweizer W., Zheng X., Contreras M., Dominguez-Bello M. G., Blaser M. J.* Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Science translational medicine*. 2016, 8(343), 343ra82. https://doi.org/10.1126/scitranslmed.aad7121.
60. *Fujimura K. E., Sitarik A. R., Havstad S., Lin D. L., Levan S., Fadrosh D., Panzer A. R., LaMere B., Rackaityte E., Lukacs N. W., Wegienka G., Boushey H. A., Ownby D. R., Zoratti E. M., Levin A. M., Johnson C. C., Lynch S. V.* Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nature medicine*. 2016, 22(10), 1187–1191. https://doi.org/10.1038/nm.4176.
61. *Zhang F., Zhang T., Zhu H., Borody T. J.* Evolution of fecal microbiota transplantation in methodology and ethical issues. *Current opinion in pharmacology*. 2019, 49, 11–16. https://doi.org/10.1016/j.coph.2019.04.004.

ТЕХНОЛОГІЇ ТРАНСПЛАНТАЦІЇ ФЕКАЛЬНОЇ МІКРОБІОТИ: МЕДИЧНІ, БІОТЕХНОЛОГІЧНІ ТА РЕГУЛЯТОРНІ АСПЕКТИ

М. М. Бакальчук
О. Б. Бесараб

Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського»

E-mail: bakalchukmaria@gmail.com

Метою огляду є узагальнення інформації щодо медичного застосування трансплантація фекальної мікробіоти (ТФМ), регуляторних аспектів його застосування. ТФМ — метод лікування шляхом введення розчину фекалій донора у шлунково-кишковий тракт пацієнта. ТФМ ефективно застосовують у лікуванні рецидивної інфекції, спричиненої *Clostridium difficile*. Дедалі зростає інтерес у терапевтичному застосуванні методу для лікування метаболічних, автоімунних та інших розладів, що їх раніше не асоціювали з кишковою мікробіотою. Проте попри багатообіцяльні результати використання ТФМ, в європейській та українській медичній спільноті ще й досі не вирішено організаційно-правові питання та питання безпеки застосування ТФМ. Здійснено аналіз практичних настанов з проведення ТФМ у клінічній практиці, розглянуто біоетичні проблеми, пов'язані з використанням ТФМ.

Ключові слова: кишкова мікробіота, трансплантація фекальної мікробіоти, *Clostridium difficile*, запальні захворювання кишечника.

ТЕХНОЛОГИИ ТРАНСПЛАНТАЦИИ ФЕКАЛЬНОЙ МИКРОБИОТЫ: МЕДИЦИНСКИЕ, БИОТЕХНОЛОГИЧЕСКИЕ И РЕГУЛЯТОРНЫЕ АСПЕКТЫ

Н. Н. Бакальчук
О. Б. Бесараб

Национальный технический университет Украины «Киевский политехнический институт имени Игоря Сикорского»

E-mail: bakalchukmaria@gmail.com

Целью обзора является обобщение информации по применению трансплантации фекальной микробиоты (ТФМ), регуляторных аспектов его применения. ТФМ — метод лечения путем введения раствора фекалий донора в желудочно-кишечный тракт пациента. ТФМ эффективно применяется в лечении рецидивирующей инфекции, вызванной *Clostridium difficile*. Возрастает интерес в терапевтическом применении метода для лечения метаболических, аутоиммунных и других расстройств, которые ранее не ассоциировались с кишечной микробиотой. Однако, несмотря на многообещающие результаты использования ТФМ, в европейском и украинском медицинском сообществе до сих пор не решены организационно-правовые вопросы и вопросы безопасности применения ТФМ. Осуществлен анализ положений практических инструкций по проведению ТФМ в клинической практике, рассмотрены биоэтические проблемы, связанные с использованием ТФМ.

Ключевые слова: кишечная микорбиота, трансплантация фекальной микробиоты, *Clostridium difficile*, воспалительные заболевания кишечника.