® Postepy Hig Med Dosw (online), 2019; 73: 316-324
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 11.09.2018
Accepted: 07.03.2019
Published: 18.06.2019

The role of fecal microbiota transplantation in the therapy of intestinal and extraintestinal diseases: The basics for health professionals

Rola transplantacji mikrobioty jelitowej w terapii chorób jelitowych i pozajelitowych – podstawy dla pracowników ochrony zdrowia

Aleksandra Kwiatkowska[1], Karolina Skonieczna-Żydecka[1], Maria Marlicz[2], Wojciech Marlicz[3]

[1] Department of Human Nutrition and Metabolomics, Pomeranian Medical University, Szczecin, Poland
[2] Students' Collaboration Group at the Department of Gastroenterology, Pomeranian Medical University, Szczecin, Poland
[3] Department of Gastroenterology, Pomeranian Medical University, Szczecin, Poland

Summary

The knowledge of the role of the digestive tract in human physiology and pathology has expanded tremendously in recent years. The human intestine is a habitat for a host complex of bacteria, fungi, viruses and *Acheaea*, all contributing to food digestion, fermentation, metabolism of xenobiotics as well as immune and neuroendocrine functions. Moreover, evidence is mounting that many environmental factors such as diet, drugs, stress and infection may potentially disrupt intestinal microbial milieu. Therefore, methods aimed to modulate gut microbiota are eagerly investigated and applied into daily clinical practice. Fecal microbiota transplantation (FMT) is a transplant of gut bacteria from a healthy donor to a recipent. Usually, the stool bacteria are introduced by means of colonoscopy, gastroduodenoscopy, enema, orogastric tube or orally in the form of a capsule containing freeze-dried material. The effectivness of FMT in the treatment of recurrent *Clostridioides difficile* infection (CDI) has been confirmed in a numer of high quality studies and is currently recommended as evidence-based therapy in clinical settings. However, FMT is promising in the treatment of other diseases, as it has proven to be an effective method of treating ulcerative colitis (UC) and is of promise in treating Crohn's disease (CD), metabolic and neuropsychiatric disorders. Many questions related to FMT remain unanswered. A better understanding of fecal and mucosal microbial composition is needed, followed by the optimisation of regulatory issues and selection of best possible donor. Novel protocols based on a new class of probiotics as emerging alternatives to FMT in CDI are also briefly disscussed.

Keywords: **gut microbiota • fecal microbiota transplantation • FMT • *Clostridium difficile* infection • *Clostridioides difficile* infection • pseudomembranous colitis • probiotics**

GICID 01.3001.0013.2524
DOI: 10.5604/01.3001.0013.2524
Word count: 4700
Tables: –
Figures: –
References: 68

Author's address: Karolina Skonieczna-Żydecka, PhD, Department of Biochemistry and Human Nutrition, Broniewskiego 24, 71-460 Szczecin, Poland; e-mail: karzyd@pum.edu.pl

BACKGROUND

The human intestine is densly populated by a microbial community. Its diversity and function have only recently been discovered [38]. Gut microbiota aid digestion and the fermentation of nutrients, produce short chain fatty acids (SCFAs), synthesize vitamins and regulate the proliferation and differentiation of cells. Moreover, microbiome is involved in the formation of intestinal barrier and protects the body against pathogens [8]. Though the microbiota composition is relatively stable, their persistent disruption might be the cause or consequence of a malfunction in gastrointestinal and extraintestinal tissues. Faecal microbiota transplantation (FMT) is one of the emerging methods of reversing the gut microbial alterations and balancing the immune function. The goal of this review is to present the current knowledge, benefits, challanges and hopes related to FMT as well as to critically assess its efficacy and long-term effects in various diseases.

IS FECAL MICROBIOTA TRANSPLANTATION TRULY AN INNOVATIVE METHOD?

The earliest evidence of feces being used as a potential medicine can be found in the fourth century, when a Chinese medic, living in the times of the Dong-jin Dynasty, reported treating patients suffering from diarrhea or food poisoning with fecal suspentions. The procedure proved successful, which was later described in the first Chinese Emergency Medicine book titled "Zhou Hou Bei Ji Fang" [68].

Subsequently, known instances of using human feces in treatment are dated from the fifteenth century, when Li Shizhen administered fresh, fermented or dried stool orally in order to alleviate symptoms of diarrhea, fever, pain, vomiting or constipation in his patients. It was then referred to as a "yellow soup" for the procedure to appear less unpleasant. In turn, in seventeenth century Italian veterinarians disseminated coprophagia as a popular method of treating diarrhea in horses and conditions affecting cattle. Furthermore, german soldiers stationed in North Africa during World War II consumed fresh cammel feces to recover from bacillary dysentery [8].

The first FMT in humans was described in 1958 and pertained to the treatment of pseudomembranous colitis caused by *Micrococcus pyogenes* [16]. The material was administered to the sick by an enema. Schwan in 1983 first used FMT as a treatment for *Clostridioides difficile* infection (CDI) [55]. Until 1989 enemas had been the most popular method of FMT; however, alternatives such as fecal infusion through a nasogastric tube (used in 1991), *via* gastroscopy (1998) and colonoscopy (2000), as well as self-administration (2010) superseded this technique [9]. Due to its therapeutic potential, FMT was placed on the top 10 innovations list in 2014 [5]; however, it seems to be inaccurate to consider the translocation of intestinal bacteria an innovation as it has been practiced for centuries.

PREPARING THE DONOR AND RECIPIENT FOR THE PROCEDURE

Fecal microbiota transplanation is performed due to replace the bacterial flora of an ill person with a new one, containing commensal bacteria which aid proper function of the colon and the whole human organism in general [37].

According to current medical standards, FMT is recommended for treating recurrent forms of *C. difficile* infection [23]. A patient infected with *C. difficile* is selected for the fecal microbiota transplantation. FMT selection criteria include at least three recurrent episodes of CDI [40]. The process of transferring fecal microbiota involves finding a healthy donor tested for pathogenic bacteria, viruses and parasites with their eggs as well as *C. difficile* toxins, in stool. Test for hepatitis A, B and C viruses, HIV, bacteria causing syphilis, *H. pylori* antigenes, *Sallmonella*, *Shigella*, *Campylobacter* type bacteria, *Escherichia coli* and *Yersinia enterocolitica* spieces as well as for *Rotavirus*, *Cytomegalovirus* and *Epstein- Barr* viruses are recommended.

Equally crucial in donor selection is for a physician to perform a detailed interview in order to collect information about pathogenic microorganisms (not revealed by laboratory tests) or past contagious diseases as well as a history of travels to countries in which various infectious agents might have affected the individual. A person willing to donate their stool must be free from any

gastrointestinal dysfunctions, allergies or autoimmune diseases. Other eliminating factors are the following: I) taking antibiotics up to three months before collecting the stool, II) having a tatoo or III) piercing done during this period of time or IV) sexual intercourse with a member of the same sex or an HIV infected person [29, 40]. Moreover, a potential donor should be in overall good health and consume easily digestible meals for three months prior to the procedure. Furthermore, the donor is also obliged to sign a formal, written consent for performing control tests and collecting a stool sample. Donor's obesity is a disqualifying factor [46]. As per experience, the proper criteria of donor selection should not only include contagious diseases, but also those associated with alterations of the microbiome, such as diabetes, previously diagnosed cardiovascular diseases, cancer and mental disorders. Clinical exposure to various treatments with potential to alter microbiome might disqualify the donor until more knowledge in gained to find the causative links [66]. Given the delicate nature of the procedure, the donor is usually related to and chosen by the recipent; most commonly a friend or a family member. As shown in numerous studies, this strategy produced better results than when collecting material from an unrelated individual. According to a study performed ina group of 317 patients with pseudomembranous colitis, 84% treatment efficacy was observed in a group using stools from unrelated donors, contrasting with 93% efficacy of stool donation from relatives [8].

Meanwhile, a recipent with confirmed *C. difficile* diarrhea is selected for a procedure and treated with a combination of antibiotic therapy: metronidazole, vancomycin or fidaxomicin. The last dose is administered to the patient no later than three days before the procedure and depends on the protocol followed by the physicians. An intestinal lavage is recommended as it has been proven to decrease the number of *C. difficile* spores and toxins. It has also been observed that due to intestinal lavage and removal of stool remnants, the whole procedure is more effective. As mentioned previously, the recipent is obliged to sign a written consent [29].

In reality, finding the right donor for a person qualified for the FMT procedure is a challenge for the health service. Accuracy in interviewing the patient and performing a wide range of tests which may potentially disqualify an individual is needed. However, all this effort seems justified in the face of promising results which emerge from scientific studies conducted among affected populations.

FMT AS AN EFFECTIVE METHOD OF TREATING *C. DIFFICILE*

C. difficile are Gram positive, toxin-producing bacteria. In 1978 they were recognised as the main cause of antibiotic related infections [8]. The bacteria enter the organism *via* faecal-oral route. The main source of bacteria are hands of the medical staff who have contact with infected patients or their enviroment. In order for the disease to develop, toxinogenic strains of *C. difficile* or it's vegetative form, which usually dies already in the stomach, have to colonize in the organizm or in persistent spores capable of surviving in a low pH environment. Although these stages are necessary, they are not always sufficient for the disease to expand. In practice, three factors are crucial for its development: 1) dysbiosis caused by broad-spectrum antibiotics use, 2) colonization of the colon by a toxinogenic *C. difficile* strain, 3) growth of the toxin-producing bacteria population [8, 21].

The symptoms of CDI include stomach pain, fever and weight loss; over time, a life-threatening pseudomembranous colitis may occur. At risk are mainly the elderly, hospitalized and immunodeficient individuals [40]. However, as some sources demonstrate, women in peripartuirent period might also be affected, which until recently had not been considered a risk factor. The incidence increases among people who have not been hospitalized, but have had even limited contact with a health service institution [46].

Undoubtely, FMT is a promising opportunity to obtain healthy colonic microbiota, especially in *C. difficile* infections which are the cause of 250.000 hospitalizations and 14.000 deaths annually in the United States only [38]. In years 2001–2005, incidence of CDI both in Europe and the US increased by 100%. This contributes to immense costs, reaching even 5 billion dollars annually in the US only. In Poland, morbidity increased from 2000 incidents in 2009 to 10.000 in 2013 [40]. Fecal microbiota transplant has officialy been classified by the European Society for Microbiology and Infectious Disease and the American College of Gastroenterology as a recommended method of CDI treatment [3]. Furthermore, in 2013 Food and Drugs Administration (FDA) classified stool modified for FMT as a biological substance and considered fecal material as a medicine for various maladies [66]. In addition, in 2012 Grzesiowski and Herman launched in Poland the Fecal Microbiota Transplantation Program. In 2014 Center for Research and Transplantation of Intestinal Microbiome at the Center for Preventive Medicine and Rehabilitation in Warsaw was created. Due to these investments, more than 150 patients underwent the FMT procedure with an estimated 90% treatment efficiency [46]. A study conducted in Amsterdam in years 2010-2016 involved 39 adult patients diagnosed with recurrent CDI episodes in which antibiotic treatment had proved unsuccessful. After the FMT procedure, 37 patients were monitored for over 6 months. In 7 patients, early relapses of CDI were observed. Serious side-effects were observed in 9 patients up to 12 weeks after the procedure, 5 of these were linked to the procedure. In 4 patients symptoms as nausea or vomiting appeared; however, none of the patients experienced further complications. In one of them the disease reocurred, which was however effectively eliminated after 10 days of antibiotic treatment [64]. Almost 82% efficiency of this study shows a very high level of sensitivity for the treatment method in patients with

recurrent CDI. Lack of symptoms in many patients or minor side-effects (vomiting, nausea) raises great hopes and is an opportunity to use FMT as a basic therapeutic method in CDI treatment. A study conducted in Finland in 2007-2014 involved 84 patients infected by *C. difficile*. Forty-five people underwent the FMT procedure and the remaining 39 were traditionally administered antibiotics, such as vancomycin or metronidazole. Patients were then observed for 3.8 years on average. Individuals with serious, health-threatening *C. difficile* infections where qualified for the FMT treatment. In both groups the disease relapsed at least twice in 6 months time. At the end of the experiment it was observed that all patients had been cured effectively, regardless of the treatment method. As much as 97.6% participants who underwent the FMT procedure claimed that in the future they would choose this method over antibiotic therapy as an initial treatment. It was also observed that 77.8% of this group's members recovered from all CDI symptoms in three days or less. Among patients treated with antibiotics only 23.1% individuals have reported such a recovery. Moreover, FMT patients experienced a significant improvement of the intestinal function and reported fewer gastrointestinal symptoms than the other group [25]. As the authors have noticed, this may suggest that retrieving healthy intestinal microbiotic ecosystem plays a greater role for the host than the antibiotic use only [25]. This study does not only show the efficiency of FMT, but also its advantage over antibiotic treatment. There are noticeably fewer side-effects and better overall well-being of patients. The fact that patients would be eager to undergo such a procedure again if necessary is another interesting aspect of introducing it as a standard of CDI treatment. Studies involving groups of elderly people (≥65 years) at risk of developing CDI showed FMT's efficacy comparable to that observed in the general population [11]. In a review article based on 10 different studies, the authors deduced that FMT is safe and gives permanent results. The rate of remission marker (89.6%) was higher than in a traditional therapy with vancomycin (80.8%). The effects of recovery lasted for 5 years, regardless of age and chronic or coexisting diseases [10]. Although the precise mechanism of FMT is not known yet, it is increasingly often claimed to be an effective CDI treatment method.

The aim of FMT is to improve one's immune function. However, further studies are necessary to clarify the mechanisms of this procedure as well as describe factors responsible for FMT's efficiency. Until 2017 there have been no reported FMT-related deaths [29]. However, the therapeutic interference resulting in a change of microbial composition in other clinical entities does not necessarily prove its efficacy [3].

FMT USE IN OTHER INTESTINAL DISORDERS

Inflammatory bowel disease (IBD) is a chronic, idiopathic state affecting mainly young adults. IBD includes several different disease entities, such as ulcerative colitis (UC) or Crohn's disease (CD). Both disorders are characterized by chronic and recurring intestinal inflammation, with slightly different pathophysiology and clinical manifestation. UC usually affects the colon and is limited to the mucosa (*epithelium*). Meanwhile, CD can affect the whole gastrointestinal tract and mucosa, submucosa and muscular layers. Both conditions have been linked to the intestinal dysbiosis, although it is not clear to what extent these alterations are linked to the causes and consequences. IBD is a complex disease which is also influenced by genetic, dietary and immunological factors. It is likely that the interactions between the intestinal *epithelium*, genetic make-up and the mucosa play a greater role in the disease's pathogenesis than changes in microbiota composition and function. However, there is mounting evidence suggesting that intestinal bacteria are able to independently prompt IBD symptoms [3]. A report about treating IBD with FMT was published for the first time in 1989 [6]. Despite the positive effects observed in the week after a self-administered enema, studies on FMT's role in IBD were rarely conducted during the following 20 years. From the available information, until 2012, 9 retrospective reports were found, they were deemed by the authors as insufficient to conduct a metanalysis [39]. The authors of this paper and others found only a few reports in the literature [24].

Information about the FMT treatment in paediatric patients with IBD is limited and precise treatment guidelines are lacking. Results of a study involving 10 individuals aged 10-17 diagnosed with UC (8 patients) and CD located in the colon (2 patients) immune to standard treatment seem to be highly promising. Clinical response was observed in 9 patients; 3 UC patients and all CD patients experienced remission. It was also reported over 2 weeks time that FMT was safe and the reported symptoms were limited to vomiting after the first FMT dose and nausea in one of the patients. FMT was well tolerated by all individuals. These results confirmed efficacy of the treatment in most children and adolescents with IBD [31].

Meanwhile, in a study conducted on a group of persons aged 7–21 years (9 patients) with UC, it was shown that 78% (7 patients) of the respondents experienced a clinical improvment in the week after transplantation and 67% (6 patients) mantained this state for up to a month after the procedure. As many as 3 individuals (33%) found themselves in remission just a week after FMT, which lasted for 4 weeks. All of the observed adverse symptoms resultuing from FMT procedure (e.g. fever) did not require medical intervention and resolved spontaneously. The results showed that the use of FMT in the form of a fecal enema was feasible, well tolerated and safe among children suffering from UC [32].

In the first randomized, placebo-controlled group involving 75 patients, conducted by Moayyedi et al., 37 patients received placebo and the rest fresh or frozen

stool. The FMT method proved to be significantly more effective compared to placebo. In 24% of the patients (9 out of 38) full remissions were observed after FMT, in comparison to 5% (2 out of 37) of those receiving placebo, consisting of water given as retention enema. Importantly, 8 out of 9 patients from the FMT group did not relapse for 52 weeks after the follow-up. What is more important, no significant discrepancies in the side effects in both groups were observed. Histological samples of intestinal biopsies of patients in remission were examined 7 weeks after the FMT procedure. None of the patients exhibited active inflammatory states, two respondents developed indetermine proctitis. What is interesting, patients diagnosed with UC during their first years of life were more sensitve to FMT (75%) compared to patients with the chronic disease diagnosed later in life (18%). The results of the study suggest that the use of FMT turns out to be the most effective therapeutic method in patients diagnosed early following the symptoms. At the same time, it is biologically plausible that the reversal of micriobiome alterations is easier in the early stages of a disease [48].

Anderson et al. and Brandt et al. demonstrated in their studies the long-term positive therapeutic effects of FMT in patients with IBD. The clinical effect was not immediately visible after the procedure; however, it turned out that over the months or even years after fecal microbiota transplantation, mucosal inflammation decreased, as confirmed by histopathology [29]. In Paramsothy et al.'s metanalysis of 53 FMT studies, 52% of patients with Crohn's disease and 33% with UC responded to treatment [51]. Similar results were achieved in a metanalysis prepared by Colman et al. based on 18 various studies, in which in 45% (54 out of 119) of patients with IBD the FMT proved effective [12].

FMT appears to be an effective method of treating UC and is claimed to be a safe procedure [12, 51]. However, due to the low number of identified studies with low quality of evidence as well as uncertainty about the rate of serious adverse events, FMT still awaits its formal aproval in the treatment of UC in a clinical settings [24]. Similarly, the quality of available studies on FMT for Crohn's disease is low, with a predominance of cohort studies on very small groups of patients; thus, further studies and observations are necessary. Available studies are hetergoenous, differing in methodology, which makes agreeing on a a unitary FMT procedure difficult. In order to introduce standarization of the protocols for FMT as a treatment for patients with IBD, in spite of already available and well-conducted studies, future prospective large scale trials assessing protocols utilizing pooled stool samples from various donors are critical and eagerly awaited. [17, 24, 27, 39].

CAN INTERFERING WITH INTESTINAL MICROBIOTA THROUGH FMT AFFECT BODY MASS?

Obesity is an increasingly common health problem in the twenty-first century. Excessive consumption of high-energy products seems to be the main cause of the phenomenon; however, genetics, endocrine disorders or drug use might also be as decisive [36, 53]. Such a lifestyle affects the intestinal microbiota compostion, leading to dysbiosis, which can result in or promote decreased immunity, endocrine disorders or altered lipid metabolism [13]. In an attempt to understand the cause of obesity, the link between microbiota composition and body mass was hypothesized. The hypothesis turned out to be real, as studies in mice, revelead the excessive body mass linked to *Firmicutes* abundance and diminished *Bifidobacteria* as compared to the lean rodents [54].

It has been calculated that a 20% prevalence of *Firmicutes* over *Bacteroidetes* increases energy intake by 150 kcal. In addition, a link between the increase in the number of *Bacteroides* and lost of body weight measured in kilograms has been shown [53]. Moreover, such species as *Escherischia coli*, *Staphylococcus aureus* or *Faecalibacterium prausnitzii* were more often found in obese individuals [4]. Transplanting fecal microbiota to germ-free mice induced obesity and insulin resistance [7]. Another study conducted on germ-free mice established the link between an obese donor and later body mass growth as compared to mice that had received content from lean individuals [63]. As studies on obese donors' microbiota transplantation have shown, such a transplant cured the recurrent *C. difficile* infection, but resulted in obesity [1].

Vrieze et al. conducted a double-blind randomized controlled FMT trial on 18 males diagnosed with metabolic syndrome. Nine participants received stool from lean same-sex donors, while the control group received autologous fecal transplants. Results showed increased insulin sensitivity and increase in butyrates-producing intestinal bacteria (*Roseburia intestinalis* i *Eubacterium hallii*) after 6 weeks of enemas; no alterations were observed in the control group [65]. Results of said studies demonstrate how crucial intestinal bacteria can be in the pathogenesis of obesity and for that reason they appeal to the medical community. Future analysis and observations seem to be in perspective; however, currently most of the studies are conducted on mice due to which we cannot determine precise course and effects of FMT in people and if in reality the procedure leads to weight loss.

ONGOING FMT STUDIES

There is a growing body of evidence linking gut microbiota alterations to extraintestinal diseases, among them neuropsychiatric ones [58]. In autism spectrum disorder (ASD) Strati et al. [61] found a significant elevation in the *Firmicutes/Bacteroidetes* ratio. The abundance of *Alistipes, Bilophila, Dialister, Parabacteroides*, and *Veillonella* was diminished and *Collinsella, Corynebacterium, Dorea*, and *Lactobacillus* counts significantly increased. Kushak et al. [33] evaluated the microbiome of the small bowel in ASD subjects and found elevated *Burkholderia* and lowered *Neisseria* counts. *Bacteroides* species and *Escherichia coli* concentration increased. These observations and

common gastrointestinal symptoms in ASD [14] confirm the usefulness of microbiota modulation in this disorder [35]. In ASD, a modified protocol of FMT – microbiota transfer therapy (MTT) has only begun to be implemented [30]. MTT utilizes 14 days of vancomycin administration orally and is followed by 12–24h fasting and bowel cleansing. Afterwards, a high dose of human gut microbiota is transferred orally or rectally along with a 7–8 weeks long stomach acid suppressant supply. The improvement of digestive health as well as core ASD symptoms lasted for at least 8 weeks post intervention. In all, the studies describing the FMT approach as a support for neuropsychiatric disorders are limited to individual patients and no exact conclusions can be drawn, especially as the effectiveness and safety of the method have not yet been adequately established, eg. giant obesity in a woman treated for recurrent *Clostridioides difficile* infection [1] or microscopic bowel disease in a patient with ulcerative colitis [62]. Despite promising results, it is necessary to conduct more studies in order to establish the efficiacy and adverse events of this intervention. Potential future clinical application of FMT include [19, 26, 47, 49, 50, 67]:

- Arthritis
- Asthma
- Atopy
- Autism spectrum disorders
- Breast cancer
- Cardiovascular diseases
- Chronic fatigue syndrome
- *Clostridioides difficile* infection
- Crohn's disease
- Functional constipation
- Hashimoto's thyroiditis
- Hepatocellular carcinoma
- Lymphoma
- Idiopathic thrombocytopenic purpura
- Insulin resistance/Type 2 diabetes
- Irritable bowel syndrome
- Metabolic syndrome
- Multiple sclerosis
- Myoclonus dystonia
- Non-alcoholic fatty liver disease
- Obesity
- Parkinson's disease
- Systemic lupus ertyhematosus
- Type 1 diabetes
- Ulcerative colitis

PROBIOTICS AS AN ALTERNATIVE TO FMT THERAPY

Probiotics are live microorganisms which positively impact gut microbiota and human health [22]. Probiotics could be viewed as an attractive alternative to FMT. Several clinically tested probiotic strains have already been recommended as an aid to the treatment or prophylaxis of selected gastrointestinal and extraintestinal diseases. The World Gastroenterology Organisation (WGO) in 2017 issued the probiotic guidelines, which include the statetement concering probiotic use in symptomatic patients infected with CDI. The following strains were listed: *Lactobacillus acidophilus* CL1285, *L. casei* LBC80R, *Lactobacillus casei* DN114, *Saccharomyces boulardii* CNCM I-745, *Lactobacillus rhamnosus* HN001 + *L. acidophilus* NCFM and *Lactobacillus acidophilus* + *Bifidobacterium bifidum* [20, 34, 52].

Moreover, recent data presented in metaanalyses indicate that timely co-administration of probiotics and antibiotics lowers the risk for CDI vs placebo or no treatment [23, 30, 57]. Goldenberg et al. in their recent systematic review conducted a complete case analysis of 31 trials investigating *Clostridioides difficile* associated diarrhea (CDAD) in 86.72 patients and suggested that probiotics reduced the risk of CDAD by 60%. The incidence of CDAD was 1.5% (70/4525) in the probiotic group compared to 4% (164/4147) in the placebo or no treatment control group (RR 0.40, 95% CI 0.30 to 0.52; GRADE = moderate) [20]. In addition, co-administration of probiotics with antibiotics was associated with a lower risk of adverse events, including abdominal cramping and nausea vs placebo or no treatment (620/4329 [14.3%] vs 677/3976 [17%]; RR, 0.83 [95% CI, 0.71 to 0.97], P =.02; GRADE: very low-quality evidence; NNT = 37) [21].

To evaluate the role of probiotics in CDI prevention and to draw conclusions from the available studies, which could aid clinicians in diagnostic and therapeutic workouts, other epidemiological factors are worth discussing. First, recent CDI guidelines issued the statement that the results of trails with an abnormally high baseline incidence of CDI should be evaluated with caution and concluded that the current data was insufficient to recommend probiotics for primary prevention of CDI, save their use in randomized trials [44]. Similar conclusions should concern studies with low baseline incidence of CDI [2] Second, the efficacy of probiotics is strain dependent and varies across clinical areas of their application, thus extrapolating data from one study to another is not feasible [60]. Third, the duration and time of probiotics administration could be the most detrimental factor when assessing their efficacy in prophylaxis of CDI. For example, long-term administration of probiotics to high-risk population of patients might prove beneficial as shown in an intriguing study conducted by Dudzicz et al. [15]. The authors retrospectively analysed three twelve-months periods, when all patients hospitalized in the Department of Nephrology, Transplantation and Internal Medicine and under antibiotic and immunosuppressive therapies received *Lactobacillus plantarum* 299V as part of CDI prophylaxis. Surprisingly, after starting prophylactic measure with probiotic, the CDI incidence significantly declined from 10.3 to 1.1 per 1.000 patients hospitalized (RR 0.11; CI 0.03–0.47; p = 0.0003). After the cessation of prophylaxis, the incidence of CDI significantly increased from 1.1 to 7.7 per 1.000 hospitalized patients (RR 6.93; CI 1.58–30.47; p = 0.0028) [15]. The retrospective analysis of this study limits its implementation into clinical guidelines; however, the results are intriguing and warrant further investigations.

It is likely that vulnerability to CDI infection strongly depends on the host immune and gut microbiota status of the whole community [45]. For example, Fredberg et al. assessed whether administration of antibiotics to a prior occupant of a hospital bed was associated with increased risk for CDI in a subsequent patient who occupied the same bed [18]. In their retrospective cohort study, the authors observed that receipt of antibiotics by prior bed occupant was associated with an increased risk for CDI in subsequent patients and concluded that antibiotics directly affected the risk for CDI in patients who did not themselves receive antibiotics [18]. The discussion on the role of probiotics in other GI and non-GI diseases is beyond the scope of this paper and has been addressed in other publications [43, 44, 58, 60].

CONCLUSION

The fecal microbiota transplantation, although known for almost 1.700 years, has only recently gained interest and medical attention, as FMT offers hope in the search of a cure for many contemporary diseases. Further studies and observations to clarify the mechanisms of FMT and find clinical correlations are needed. Establishing FMT protocols due to classification of stool as a medical substance is currently of challange. The selection of donors is also challenging as requires great accuracy in collecting medical history and conducting a series of medical tests.

Although clinical efficacy of FMT in CDI management has already been proven, treatment of other diseases (e.g., IBD) needs more evidence in well-designed prospective large-scale studies. As for now, the evidence is scarce and insuffiecient to recommend FMT to treat obesity. So far, most of the studies have been conducted on rodents and the results, although promising, do not fully reflect its effectivness in people. FMT shows efficacy in individuals with CDI and promise in those diagnosed with IBD. Selected strains of high quality probiotics delivered to individuals based on novel trials and clinically proven protocols could be viewed as promissing alternatives to FMT therapy.

In conclusion, it is anticipated that the standarization of the FMT protocols will soon be accepted, enabling FMT to become a promising method of treating many extraintestinal disorders related to the intestinal microbiota. New strains of probiotics identified along the course of FMT research are also eagerly awaited.

Conflict of interest: W.M. is a foundation shareholder in Sanprobi, a probiotic manufacturer and distributor. K.S.Ż received remuneration from this company. The content of this study was neither restricted nor constrained by this fact. Other authors have no conflict of interest to declare.

REFERENCES

[1] Alang N., Kelly C.R.: Weight gain after fecal microbiota transplantation. Open Forum Infect. Dis., 2015; 2: ofv004

[2] Allen S.J., Wareham K., Wang D., Bradley C., Hutchings H., Harris W., Dhar A., Brown H., Foden A., Gravenor M.B., Mack D.: Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet, 2013; 382(9900): 1249–57

[3] Bakker G.J., Nieuwdorp M.: Fecal microbiota transplantation: Therapeutic potential for a multitude of diseases beyond *Clostridium difficile*. Microbiol. Spectr., 2017; 5: doi: 10.1128/microbiolspec.BAD-0008-2017

[4] Balamurugan R., George G., Kabeerdoss J., Hepsiba J., Chandragunasekaran A.M., Ramakrishna B.S.: Quantitative differences in intestinal *Faecalibacterium prausnitzii* in obese Indian children. Br. J. Nutr., 2010; 103(3): 335–8

[5] Bartnicka A., Szachta P., Gałecka M.: Faecal microbiota transplant - prospects and safety. Pomeranian J. Life Sci., 2015; 61(3): 282–6

[6] Bennet J., Brinkman M.: Treatment of ulcerative colitis by implantation of normal colonic flora. Lancet, 1989; 333: 164

[7] Blaut M., Klaus S.: Intestinal microbiota and obesity. In: Appetite Control. Handbook of Experimental Pharmacology, vol. 209. Ed.: H.G. Joost. Springer, Berlin, Heidelberg 2012, 251–273

[8] Borgia G., Maraolo A.E., Foggia M., Buonomo A.R., Gentile I.: Fecal microbiota transplantation for *Clostridium difficile* infection: back to the future. Expert Opin. Biol. Ther., 2015; 15(7): 1001–14

[9] Brandt L.J., Aroniadis O.C.: An overview of fecal microbiota transplantation: techniques, indications, and outcomes. Gastrointest. Endosc., 2013; 78(2): 240–9

[10] Burke K.E., Lamont J.T.: Fecal transplantation for recurrent *Clostridium difficile* infection in older adults: A review. J. Am. Geriatr. Soc., 2013; 61(8): 1394–8

[11] Cheng Y.W., Fischer M.: The present status of fecal microbiota transplantation and its value in the elderly. Curr. Treat. Options Gastroenterol., 2017; 15(3): 349–62

[12] Colman R.J., Rubin D.T.: Fecal microbiota transplantation as therapy for inflammatory bowel disease: A systematic review and meta-analysis. J. Crohns Colitis, 2014; 8(12): 1569–81

[13] Conroy K.P., Davidson I.M., Warnock M.: Pathogenic obesity and nutraceuticals. Proc. Nutr. Soc., 2011; 70(4): 426–38

[14] De Angelis M., Francavilla R., Piccolo M., De Giacomo A., Gobbetti M.: Autism spectrum disorders and intestinal microbiota. Gut Microbes, 2015; 6(3): 207–13

[15] Dudzicz S., Kujawa-Szewieczek A., Kwiecień K., Więcek A., Adamczak M.: *Lactobacillus plantarum* 299v reduces the incidence of *Clostridium difficile* infection in nephrology and transplantation ward-results of one year extended study. Nutrients, 2018; 10: E1574

[16] Eiseman B., Silen W., Bascom G.S., Kauvar A.J.: Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. Surgery, 1958; 44(5): 854–9

[17] Fang H., Fu L., Wang J.: Protocol for fecal microbiota transplantation in inflammatory bowel disease: A systematic review and meta-analysis. Biomed. Res. Int., 2018; 2018: 8941340

[18] Freedberg D.E., Salmasian H., Cohen B., Abrams J.A., Larson E.L.: Receipt of antibiotics in hospitalized patients and risk for *Clostridium difficile* infection in subsequent patients who occupy the same bed. JAMA Intern. Med., 2016; 176(12): 1801–8

[19] Gagliardi A., Totino V., Cacciotti F., Iebba V., Neroni B., Bonfiglio G., Trancassini M., Passariello C., Pantanella F., Schippa S.: Re-

building the gut microbiota ecosystem. Int. J. Environ. Res. Public Health, 2018; 15(8): E1679

[20] Goldenberg J.Z., Yap C., Lytvyn L., Lo C.K., Beardsley J., Mertz D., Johnston B.C.: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst. Rev., 2017; 12: CD006095

[21] Goldenberg J.Z., Mertz D., Johnston B.C.: Probiotics to prevent *Clostridium difficile* infection in patients receiving antibiotics. JAMA, 2018; 320(5): 499–500

[22] Hill C., Guarner F., Reid G., Gibson G.R., Merenstein D.J., Pot B., Morelli L., Canani R.B., Flint H.J., Salminen S., Calder P.C., Sanders M.E.: Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat. Rev. Gastroenterol. Hepatol., 2014; 11(8): 506–14

[23] Hota S.S., Poutanen S.M.: Is a single fecal microbiota transplant a promising treatment for recurrent *Clostridium difficile* infection? Open Forum Infect. Dis., 2018; 5(3): ofy045

[24] Imdad A., Nicholson M.R., Tanner-Smith E.E., Zackular J.P., Gomez-Duarte O.G., Beaulieu D.B., Acra S.: Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database Syst. Rev., 2018; 11: CD012774

[25] Jalanka J., Hillamaa A., Satokari R., Mattila E., Anttila V.J., Arkkila P.: The long-term effects of faecal microbiota transplantation for gastrointestinal symptoms and general health in patients with recurrent *Clostridium difficile* infection. Aliment. Pharmacol. Ther., 2018; 47(3): 371–9

[26] Jeon S.R., Chai J., Kim C., Lee C.H.: Current evidence for the management of inflammatory bowel diseases using fecal microbiota transplantation. Curr. Infect. Dis. Rep., 2018; 20(8): 21

[27] Jitsumura M., Cunningham A.L., Hitchings M.D., Islam S., Davies A.P., Row P.E., Riddell A.D., Kinross J., Wilkinson T.S., Jenkins G.J., Williams J.G., Harris D.A.: Protocol for faecal microbiota transplantation in ulcerative colitis (FMTUC): a randomised feasibility study. BMJ Open, 2018; 8: e021987

[28] Johnston B.C., Lytvyn L., Lo C.K., Allen S.J., Wang D., Szajewska H., Miller M., Ehrhardt S., Sampalis J., Duman D.G., Pozzoni P., Colli A., Lönnermark E., Selinger C.P., Wong S., et al.: Microbial preparations (probiotics) for the prevention of *Clostridium difficile* infection in adults and children: An individual patient data meta-analysis of 6,851 participants. Infect. Control. Hosp. Epidemiol., 2018; 39(7): 771–81

[29] Juszczuk K., Grudlewska K., Mikucka A., Gospodarek E.: Fecal microbiota transplantation - methods of treatment of recurrent *Clostridium difficile* infections and other diseases. Postępy Hig. Med. Dośw., 2017; 71(0): 220–6

[30] 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., et al.: Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: An open-label study. Microbiome, 2017; 5: 10

[31] Karolewska-Bochenek K., Grzesiowski P., Banaszkiewicz A., Gawronska A., Kotowska M., Dziekiewicz M., Albrecht P., Radzikowski A., Lazowska-Przeorek I.: A two-week fecal microbiota transplantation course in pediatric patients with inflammatory bowel disease. In: Clinical Investigation. Advances in Experimental Medicine and Biology, vol. 1047. Ed.: M. Pokorski. Springer, Cham 2017, 81–7

[32] Kunde S., Pham A., Bonczyk S., Crumb T., Duba M., Conrad H.Jr., Cloney D., Kugathasan S.: Safety, tolerability, and clinical response after fecal transplantation in children and young adults with ulcerative colitis. J. Pediatr. Gastroenterol. Nutr., 2013; 56(6): 597–601

[33] Kushak R.I., Winter H.S., Buie T.M., Cox S.B., Phillips C.D., Ward N.L.: Analysis of the duodenal microbiome in autistic individuals: Association with carbohydrate digestion. J. Pediatr. Gastroenterol. Nutr., 2017; 64(5): e110–e116

[34] Lahtinen S.J., Forssten S., Aakko J., Granlund L., Rautonen N., Salminen S., Viitanen M., Ouwehand A.C.: Probiotic cheese containing *Lactobacillus rhamnosus* HN001 and *Lactobacillus acidophilus* NCFM® modifies subpopulations of fecal lactobacilli and *Clostridium difficile* in the elderly. Age, 2012; 34(1): 133–43

[35] Li Q., Han Y., Dy A.B., Hagerman R.J.: The gut microbiota and autism spectrum disorders. Front. Cell. Neurosci., 2017; 11: 120

[36] Ludwig D.S., Ebbeling C.B.: The carbohydrate-insulin model of obesity: Beyond „calories in, calories out". JAMA Intern. Med., 2018; 178(8): 1098–1103

[37] Lynch S.V., Pedersen O.: The human intestinal microbiome in health and disease. N. Engl. J. Med., 2016; 375(24): 2369–79

[38] Ma Y., Liu J., Rhodes C., Nie Y., Zhang F.: Ethical issues in fecal microbiota transplantation in practice. Am. J. Bioeth., 2017; 17(5): 34–45

[39] Maida M., Mcilroy J., Ianiro G., Cammarota G.: Faecal microbiota transplantation as emerging treatment in European countries. In: Updates on Clostridium difficile in Europe. Advances in Experimental Medicine and Biology, vol. 1050. Ed.: P. Mastrantonio, M. Rupnik. Springer, Cham 2018, 177–95

[40] Małopolska M., Fol M.: Intestinal microbiota transplantation for the treatment of Clostridium difficile infection. Med. Dosw. Mikrobiol., 2015; 67(3–4): 207–19

[41] Marlicz W., Wunsch E., Mydlowska M., Milkiewicz M., Serwin K., Mularczyk M., Milkiewicz P., Raszeja-Wyszomirska J.: The effect of short term treatment with probiotic VSL#3 on various clinical and biochemical parameters in patients with liver cirrhosis. J. Physiol. Pharmacol., 2016; 67(6): 867–77

[42] Marlicz W., Yung D.E., Skonieczna-Żydecka K., Loniewski I., van Hemert S., Loniewska B., Koulaouzidis A.: From clinical uncertainties to precision medicine: the emerging role of the gut barrier and microbiome in small bowel functional diseases. Expert Rev. Gastroenterol. Hepatol., 2017; 11(10): 961–78

[43] Martirosian G., Hryniewicz W., Ozorowski T., Pawlik K., Deptuła A.: Zakażenia *Clostridioides (Clostridium) difficile*: epidemiologia, diagnostyka, terapia, profilaktyka. Narodowy Instytut Leków, Warszawa 2018

[44] McDonald L.C., Gerding D.N., Johnson S., Bakken J.S., Carroll K.C., Coffin S.E., Dubberke E.R., Garey K.W., Gould C.V., Kelly C., Loo V., Shaklee Sammons J., Sandora T.J., Wilcox M.H.: Clinical Practice Guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin. Infect. Dis., 2018; 66(7): e1–e48[45] McLure A., Clements A.C., Kirk M., Glass K.: Healthcare-associated *Clostridium difficile* infections are sustained by disease from the community. Bull. Math. Biol., 2017; 79(10): 2242–57[46] Michalska M., Bienias R., Wojciechowska Z.: Przeszczep mikrobiomu jelitowego jako metoda leczenia nawrotowych zakażeń Clostridium difficile. Pielęg Op. Długoter., 2017; 2017: 64–70

[47] Moayyedi P.: Update on fecal microbiota transplantation in patients with inflammatory bowel disease. Gastroenterol. Hepatol., 2018; 14(5): 319–22

[48] Moayyedi P., Surette M.G., Kim P.T., Libertucci J., Wolfe M., Onischi C., Armstrong D., Marshall J.K., Kassam Z., Reinisch W., Lee C.H.: Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. Gastroenterology, 2015; 149(1): 102–9.e6

[49] Moayyedi P., Yuan Y., Baharith H., Ford A.C.: Faecal microbiota transplantation for *Clostridium difficile*-associated diarrhoea: a systematic review of randomised controlled trials. Med. J. Aust., 2017; 207(4): 166–72[50] Narula N., Kassam Z., Yuan Y., Colombel J.F., Ponsioen C., Reinisch W., Moayyedi P.: Systematic review and meta-analysis: Fecal microbiota transplantation for treatment of active ulcerative colitis. Inflamm. Bowel Dis., 2017; 23(10): 1702–9

[51] Paramsothy S., Paramsothy R., Rubin D.T., Kamm M.A., Kaakoush N.O., Mitchell H.M., Castaño-Rodríguez N.: Faecal microbiota trans-

plantation for inflammatory bowel disease: A systematic review and meta-analysis. J. Crohns Colitis, 2017; 11(10): 1180–99

[52] Plummer S., Weaver M.A., Harris J.C., Dee P., Hunter J.: *Clostridium difficile* pilot study: effects of probiotic supplementation on the incidence of *C. difficile* diarrhoea. Int. Microbiol., 2004; 7(1): 59–62

[53] Pokrzywnicka P., Gumprecht J.: Intestinal microbiota and its relationship with diabetes and obesity. Clin. Diabetol., 2016; 5: 164–72[54] Sanz Y., Santacruz A., Gauffin P.: Gut microbiota in obesity and metabolic disorders. Proc. Nutr. Soc., 2010; 69(3): 434–41

[55] Schwan A., Sjölin S., Trottestam U., Aronsson B.: Relapsing Clostridium difficile enterocolitis cured by rectal infusion of homologous faeces. Lancet, 1983; 2(8354): 845

[56] Shen N.T., Maw A., Tmanova L.L., Pino A., Ancy K., Crawford C.V., Simon M.S., Evans A.T.: Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: A systematic review with meta-regression analysis. Gastroenterology, 2017; 152(8): 1889–1900.e9

[57] Skonieczna-Żydecka K., Kaczmarczyk M., Łoniewski I., Lara L.F., Koulaouzidis A., Misera A., Maciejewska D., Marlicz W.: A systematic review, meta-analysis, and meta-regression evaluating the efficacy and mechanisms of action of probiotics and synbiotics in the prevention of surgical site infections and surgery-related complications. J. Clin. Med., 2018; 7(12): E556

[58] Skonieczna-Żydecka K., Łoniewski I., Maciejewska D., Marlicz W.: Mikrobiota jelitowa i składniki pokarmowe jako determinanty funkcji układu nerwowego. Część I. Mikrobiota przewodu pokarmowego. Aktualn. Neurol., 2017; 17(4): 181–8

[59] Skonieczna-Żydecka K., Marlicz W., Misera A., Koulaouzidis A., Łoniewski I.: Microbiome - the missing link in the gut-brain axis: Focus on its role in gastrointestinal and mental health. J. Clin. Med., 2018; 7(12): E521

[60] Sniffen J.C., McFarland L.V., Evans C.T., Goldstein E.J.: Choosing an appropriate probiotic product for your patient: An evidence-based practical guide. PLoS One, 2018; 13(12): e0209205

[61] Strati F., Cavalieri D., Albanese D., De Felice C., Donati C., Hayek J., Jousson O., Leoncini S., Renzi D., Calabrò A., De Filippo C.: New evidences on the altered gut microbiota in autism spectrum disorders. Microbiome, 2017; 5(1): 24

[62] Tariq R., Smyrk T., Pardi D.S., Tremaine W.J., Khanna S.: New-onset microscopic colitis in an ulcerative colitis patient after fecal microbiota transplantation. Am. J. Gastroenterol., 2016; 111(5): 751–2

[63] Turnbaugh P.J., Ley R.E., Mahowald M.A., Magrini V., Mardis E.R., Gordon J.I.: An obesity-associated gut microbiome with increased capacity for energy harvest. Nature, 2006; 444(7122): 1027–31

[64] van Beurden Y.H., de Groot P.F., van Nood E., Nieuwdorp M., Keller J.J., Goorhuis A.: Complications, effectiveness, and long term follow-up of fecal microbiota transfer by nasoduodenal tube for treatment of recurrent *Clostridium difficile* infection. United European Gastroenterol. J., 2017; 5(6): 868–79

[65] 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., et al.: Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology, 2012; 143(4): 913–6.e7

[66] Woodworth M.H., Carpentieri C., Sitchenko K.L., Kraft C.S.: Challenges in fecal donor selection and screening for fecal microbiota transplantation: A review. Gut Microbes, 2017; 8(3): 225–37

[67] 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 J. Gastroenterol., 2015; 21(1): 102–11

[68] Zhang F., Luo W., Shi Y., Fan Z., Ji G.: Should we standardize the 1,700-year-old fecal microbiota transplantation? Am. J. Gastroenterol., 2012; 107(11): 1755

The authors have no potential conflicts of interest to declare.