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The application of fecal microbiota transplantation in patients with oncologic diseases

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Abstract: Oncologic patients often undergo a long-term hospitalization and exhaustive treatment. For this reason they often suffer from intestinal microbiota violations and dysbiosis, which results in *C. difficle* colonization and infection. Disorders in the composition of microbiota also can predispose to the development of some cancers. There are more than 2,000 bacterial species in the human intestine, with the composition of microbiota changing during a life. These microorganisms, often called "colonization resistance factor" are an important barrier for infections, caused by intestinal pathogens. Fecal microbiota transplantation (FMT, also referred as stool transplantation, fecal transplantation, fecal flora reconstitution, or fecal bacteriotherapy) is a procedure involving the transfer of a specially prepared stool sample from a healthy donor to the recipient, suffering from intestinal dysbacteriosis. The purpose of FMT is to rebuild and restore the normal bacterial microflora, especially the population of anaerobic bacteria. Currently, FMT is used for treatment of the recurrent *C. difficile* infection (rCDI), as well as other diseases related to the gastrointestinal tract, such as Inflammatory Bowel Disease, neurological, hematological and functional disorders. The stool donor may be related or not with the recipient, but most importantly, each donor should undergo many examinations similar to those for organ donors. Besides these, the presence of multi-resistant bacteria in the feces as well as a number of etiological agents of intestinal infections (bacteria, viruses and parasites) should be excluded from donatation. On the other hand, the FMT procedure as an application of biologically-alien material seems to be quite risky, especially in patients who are undergoing anticancer and immmunosuppressive therapy. However, in most cases, when FMT has been used, positive therapeutic effects for eradication of CDI have been described. Moreover a protective action against acute graft-versus-host disease has been observed.
In this review, we will focus on the problem of FMT usage in oncologic patients, in the light of recent publications.

1. Introduction

FMT (fecal microbiota transplantation, but also referred to as stool transplantation, fecal transplantation, fecal microbiota reconstitution, or fecal bacteriotherapy); is a procedure involving the transfer of a stool sample from a healthy person, to the recipient who has disturbed composition of the intestinal microbiota. These disorders also are called bacterial or intestinal dysbiosis which are abnormalities in quantitative and qualitative composition of commensal microbiota (Hill, Hoffman et al. 2010). Dysbiosis may lead to the development of inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), diabetes, obesity, cancer, cardiovascular and central nervous system disorders (Belizário, Faintuch 2018). The purpose of FMT is to rebuild and restore normal bacterial population of the recipient's intestinal microbiota. Currently, FMT is used for the treatment of recurrent *Clostridioides difficile* infection (rCDI). Besides rCDI treatment, FMT is also used in other gastrointestinal (GI) inflammatory diseases, such as Inflammatory Bowel Disease and non-gastrointestinal diseases (n-GI). There are attempts made to use FMT in the treatment of: autism, chronic fatigue syndrome, fibromyalgia, idiopathic thrombocytopenic purpura, multiple sclerosis, myoclonus dystonia, and Parkinson disease. However lack of randomized trials makes it impossible to develop strict guidelines for the treatment of these diseases (Vindigni, Surawicz 2017).

The number of microorganisms inhabiting the human intestine is up to 10^{14}/ml of feces. Based on the bacterial analysis of 16S rRNA, 2172 bacterial species were identified, of which 386 were classified as obligate anaerobes. Anaerobes are classified in 12 different phyla, of which 93.5% belonged to *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Bacteroidetes* (Thursby, Juge 2017, Hill, Hoffman et al. 2010). The composition of the physiological mirobiota inhabiting the intestine changes over the course of life. The intestine of newborns after delivery is quickly settled with bacteria. Type of bacteria depends on the type of delivery and the method of feeding. The intestine of newborns with natural delivery is quickly settled mainly with *Lactobacillus* spp., while those after Caesarean section is mainly colonized by *Bacteroides* spp. and *Clostridium* spp. During the first year of life the diversity of intestinal microbial species increases, so that after the child re-

aches 2.5 years, it has a microbiota characteristic for an adult. The composition of this microbiota may also vary depending on diet, accompanying diseases or medication. Subsequent changes occur after the age of 65, when again the number of *Clostridium* and *Bacteroides* genus increases. With the aging of the body, rearrangement in the intestinal microbiota, leads to an increase in butyric acids production and a decrease in short-chain fatty acids production as well as the decrease efficiency of the process amylolysis (Thursby, Juge 2017, Quigley 2017, Arumugam, Raes et al. 2011, Bhatt, Redinbo et al. 2017). Intestinal microbiota is responsible for a large variety of important functions and processes in human life, such as:

– induction of synthesis of antimicrobial particles increasing of mucin gene expression, increasing of IgA secretion

– stimulation of intestinal macrophages to produce IL1β. IL1β is a highly pro-inflammatory cytokine, responsible during infection for neutrophil recruitment to the site of inflammation and others

– differentiation and activation of Th17 lymphocytes (killing of extracellular pathogens)

– production of bacteriocines and short-chain fatty acid (SCFA) inhibitions the growth of *C. difficile*

– the restriction of substances facilitating the germination of spores and the development of vegetative cells of *C. difficile* (taurocholate, mannitol, fructose, sorbitol)

– limitation of carbohydrate and sialic acid, which facilitate the growth of *C. difficile* (El Feghaly, Bangar et al. 2015).

2. Search strategy and selection criteria

The aim this study was to find an answer to the question whether the FMT procedure applies in the course of treatment of oncological patients? In order to achieve this goal, the literature was reviewed in the PubMed, Google Scholar, and Medline databases by entering: Fecal microbiota transfer, Fecal microbiota transplantation and cancer, Fecal microbiota transplantation and oncology, *Clostridium difficile* infection and cancer, *Clostridium difficile* infection and oncology. Particular attention was paid to English-language articles from recent years. The search revealed a large number of publications on the FMT procedure and its use in the treatment of intestinal diseases, while information on the use of FMT in patients undergoing oncological treatment is scarce.

3. State of the Art

FMT History

An intestinal microbiota transplantation is not an invention of our time. In ancient China, in the fourth century, attempts were made to treat food poisoning and severe diarrhea by using stool administered to the patient's mouth. The Chinese manual "Handy Therapy for emergencies" said that this therapy is wonderful and brings patient back from the edge of death. In the 16th century, various fecal preparations (fermented fecal solution, fresh fecal suspension, dried feces, feces from infants) were named by the doctors of alternative medicine "yellow soup" or "golden syrup". Li Shizhen described their use in the treatment of severe diarrhea, fever, pain, vomiting and constipation. In the seventeenth century, the Italian doctor Acquapendente tried to apply sick animals an intestinal microbiota transplant from healthy animals basing on the observed coprophagia in animals. In the nineteenth century there was a breakthrough when Antonie van Leeuwenhoek discovered bacteria in the stool. Another scientist was Russian zoologist Ilja Miecznikow, who observed among poor Bulgarian farmers maintaining good health, thanks to drinking fermented milk, and then linked the occurrence of *Lactobacillus bulgaricus* in milk, as a protective and health-improving bacterium. German physician and bacteriologist Alfred Nissle isolated *Escherichia coli* and noted that *Escherichia coli* competes with *Shigella* spp. for growth factors. During World War II, German soldiers in Africa used a Bedouin way against dysentery - eating fresh, warm camels stool. Nazi scientists isolated from this stool *Bacillus subtilis*, which was later used as a treatment against dysentery (Sbahi, Di Palma 2016, de Groot, Frissen 2017).

3.2. FMT in XXI century

FMT standards are regulated by EUTCD guidelines (The European Union Tissue and Cells Directives). The consensus was elaborated in 2016 at the European conference, and in 2017 a guide with a set of recommendations was published. FMT guide developed by the European Working Group, set standards for the selection of stool donors, the method of material preparation and the route of FMT administration (Cammarota, Ianiro et al. 2017). A group of researchers from Denmark very precisely developed the FMT transplant procedure. It is a good idea to look for

fecal donors among blood donors who already have some of the diagnostic tests done; such as complete blood counts or serological blood tests for HIV, cytomegalovirus (CMV), hepatitis B and C (HBV, HCV), Epstein-Barr (EBV) and syphilis. Donors are recruited among people aged 25-50, in general healthy, without obesity but also without malnutrition (BMI Body Max Index 18-28 kg/m^2). The excluding factor is permanent drug usage, the use of antibiotics in the last 6 months, risky behaviors (sexual relations with unknown partners, tattoos, piercing body parts, trips to countries with low hygiene standards), intestinal diseases and other chronic diseases, including depression. In additional, blood tests are performed to evaluate the functions of specific organs: pancreas (amylase), kidneys (creatinine), liver (ALT, AST, bilirubin, INR, albumin) and the level of electrolytes, CRP, immunoglobulins and glycated hemoglobin. Besides the DNA of the parasites *Strongyloides stercoralis* and *Entamoeba histolytica*, *Cryptosporidium* spp. is also sought. Fecal sample are also tested for presence of enteropathogenic bacteria such as *C. difficile* (toxinogenic and ribotype 027), EPEC, *Salmonella* spp., *Shigella* spp., *C. jejuni*, *Y. enterocolitica*, multi-drug resistant bacteria and several viruses (adenovirus, enterovirus, parechovirus) (Jørgensen, Hansen et al. 2017).

Currently, FMT is mainly used to treat rCDI and IBD. The FMT may be administrated by nasogastric tube, nasoduodenal tube, esophagoduodenoscopy (EGD), colonoscopy, or enema (Khanna, Pardi 2012, Rohlke, Stollman 2012, Landy, Al-Hassi et al. 2011).The volume of material for FMT may also vary, depending on the route of administration. When using a nasogastric tube, 25-50 ml is given, and 200 to 500 ml when during colonoscopy. There are also differences regarding the administration of a fresh or frozen sample, the time that elapses from donating feces to the preparation of FMT (6-24h). Researchers also suggest bowel lavage before FMT and loperamide after colonoscopy to stop diarrhea or probiotics use (Kim, Gadani et al. 2018, Rohlke, Stollman 2012). In a study of 35 patients infected with *C. difficle* and subjected to the FMT procedure, it was confirmed that 30 patients (85,7%), achieved improvement and there was no recurrence of CDI. Patients had previously undergone conventional treatment with metronidazole, vancomycin or fidaxomycin, but this did not work. Among group of 5 patients infected with hypervirulent strain 027, 60% efficacy was achieved, suggesting that the *C. difficile* strain 027 is not easily treated by the FMT (Kim, Gadani et al. 2018). This procedure, however, seems to be very evaluative and gives hope for the treatment of other diseases, e.g. it can be used against multi-resistant microorganisms, such as rod-shaped Gram-negative bacteria possesing New Dehli metalobetalactamase (NDM), extended-spectrum beta-lactamases (ESBL), *Klebsiella pneumoniae* carbapenemase (KPC), OXA 48. Biliński et al. described the case of treating oncology patient colonized by multi-resistant bacteria, including *K. pnemoniae* NDM (+) and *E. coli* ESBL (+) with FMT. The patient with hematologic disease was undergoing neoplastic therapy in strong neutropenia. There was a high risk of systemic multi-drug resistant (MDR) infection. Antibiotic therapy did not work, but after the use of a FMT, MDR strains were not found in the control cultures (Biliński, Grzesiowski et al. 2016).

3.3. FMT in oncology

There are indications that bacterial dysbiosis, and in particular the presence of specific groups of bacteria may lead to carcinogenesis. The processes that promote tumor formation are chronic inflammation and damage to the host's DNA. Dysbiosis leads to a decrease in the production of short-chain fatty acids and activation of inflammation through TLRs. Some bacteria produce proteins that promote the separation of β-catenin from E-cadherin, activating β-catenin signal pathway involved in carcinogenesis (Chen, Wu et al. 2018). β-catenin regulates cell proliferation and differentiation by regulating transcription factors, controls the adhesion and migration of cells, while in the complex with E-cadherin, it builds intercellular connections (Tian, Liu et al. 2011). Intercellular junctions provide the integrity of tissues, their development and proper maturation. They enable interaction and transmission of signals between neighboring cells and between them and the extracellular matrix. Weakening of cell adhesion may lead to disturbance of cell cycle control (Kwiatkowski, Godlewski et al. 2009). Changes in the composition of the intestinal microbiota may lead to the development of cancer: colorectal cancer (CRC), hepatocellular carcinoma (HCC), pancreatic cancer, breast cancer, and melanoma. Although the impact of long-term antibiotic therapy on cancerogenesis is debatable. *Helicobacter pylori*, *Bacteroides fragilis*, *Streptococcus gallolyticus*, pathogenic *Escherichia coli*, *Fusobacterium nucleatum*, are species that have been proven in cancerogenesis. *H. pylori* is classified by the World Health Organization (WHO) as a class I carcinogen and results in gastric adenocarcinoma and mucos-associated lymphoid tissue (MALT lymphoma). *H. pylori* virulence factors stimulate the signal path leading to tumor development (Wang, Meng et al. 2014). Chronic inflammation and oxidative stress, which leads to

damage of the host DNA are main causes of carcinogenesis. Very important is *H. pylori* cytotoxin (CagA) and its other virulence factors such as VacA, urease and NapA2 (Ajagopala, Vashee et al. 2017). The bacterium uses a type IV secretion system to translocate CagA to gastric epithelial cells, activating β-catenin signaling pathway (Müller 2012). *B. fragilis* toxin causes inflammation and DNA damage in host cells, leading to the development of colorectal cancer (CRC). In the CRC tissue, *S. gallolyticus* is also present, additionally activating β-catenin signaling pathways in mice. The pathogenic strains of *E. coli* can produce calmodulin, leading to the development of a tumor. *F. nucleatum* promotes proliferation and the ability to adhere tumor cells to tissue (Chen, Wu et al. 2018, Cammarota, Ianiro et al. 2017).

In CRC patients, changes in the composition of the intestinal microbiota were noted - a decrease in the number of *Lactobacillus* and *Bifidobacterium* genus, and an increased number of the *Staphylococcus*, *Fusobacterium* genus, and the *Peptostreptococcus anaerobius* species. On the basis of experiments carried out on mice, it was found that buttyric acid producers such as *Clostridium butyricum* and *Bacillus subtilis* may promote the development of CRC tumor, while the probiotic bacteria *Lactobacillus casei* strain BL23 counteracts. It was also noticed that in germ-free mice after transplantation of the intestinal microbiota from patients with CRC, the tumor develops, whereas after transplantation of feces from wild mice this development is stopped (Chen, Wu et al. 2018).

Oncological patients are exposed to long-term hospitalization, the use of anti-cancer drugs, immunosuppressants and antibiotic therapy. These factors also may predispose to the development of the cancer. The type and malignancy of the tumor may affect predisposition to CDI, but there are no clearly defined correlations between the type of cancer and the risk of development of CDI (Garzotto, García et al. 2015, Abughanimeh, Qasrawi et al. 2018). Researchers estimated the prevalence of CDI in the general hospitalized population at 1-2%, while the incidence was 7-14% in adult oncological patients (Scappaticci, Perissinotti et al. 2017). In patients during chemotherapy, CDI is estimated at 7% (Chung, Kim et al. 2016). The prevalence of CDI in patients undergoing bone marrow transplantation (HSCT) is 9 times higher than in general population and 1,4-fold higher than that of other oncology patients (Chopra, Chandrasekar et al. 2011). CDI also occurs 15 times more often in children with cancer compared to the pediatric population without cancer (Tai, Richardson et al. 2011).

At the present time, FMT seems to be a safe procedure. However, considering that it consists of the administration of biological material from the donor, the question arises whether the method of treatment of recurrent CDI is also safe in oncological patients, especially those with immunosuppression and neutropenia. Hefazi et al. Examined 23 patients with various tumors (hematologic and visceral) using the FMT procedure for the treatment of recurrent CDI. The majority of patients improved, CDI recurrence occurred only in 2 patients, but it was cured with standard therapy (metronidazole, vancomycin and fidaxomycin) without any problems. It turned out that this method is also safe for non-immunocompetent patients with multiple comorbitidies (Hefazi, Patnaik et al. 2017).

CDI is one of the main complications in patients undergoing hematopoietic stem cell transplant. Long-term hospitalization, antibiotic therapy, chemotherapy and radiotherapy damaging the intestinal mucosa and microbiota promote the development of CDI. A higher percentage of CDI is observed among allogeneic compared with autogenous transplant recipients. This can be explained by a higher frequency of hospitalization, a greater impairment of the immune system and longer antibiotic therapy. The development of CDI also predisposes to the development of acute graft-versus-host disease (GI GVHD) (Alonso, Treadway et al. 2012).

The FMT procedure for HSCT recipients in the treatment of CDI, including recurrent cases, is possible. This method is effective regardless of the patient's age and route of administration (gastro-intestinal tube, capsuled feces). There is also evidence that FMT prevents and treats patients with acute graft-versus-host disease GI GVHD, because after administration of FMT in patients' stool the number of bacteria from the genus of *Bacteroides*, *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium* increases and intestinal microenvironment is restored. Increasing the diversity of microorganisms in the feces of HSCT patients leads to a decrease in side effects after transplantation including CDI development (De Filipp, Hohmann et al. 2019).

4. Discussion

FMT is a procedure involving the administration of a specially prepared stool samples from healthy donor to a recipient who has qualitative and quantitative disturbances in the normal intestinal microbiota (Limketkai, Hendler et al. 2019). Bacteria produce different substances (of which the most important are short-chain fatty acids – SCFAs and secondary bile acids, polyamines and vitamins), which may, affect the development of cancer and the effectiveness of anti-cancer therapies (Zitvogel, Daillère et al. 2017).

The FMT procedure was first used in 1958 in 4 patients suffering from pseudomembranous colitis, when Eisman et al. used the enemas from

donor feces (Eisman, Silen et al. 1958). Intestinal microbial disorder can lead to dysbiosis. It was noted that critical patients hospitalized in ICU have a disturbed intestinal microbial composition (Lankelma, van Vught et al. 2017). Dysbiosis is also a predisposing factor for the development of many serious diseases, including cancer and CDI. (Chen D. Wu J. et al. 2018, Cammarota, Ianiro 2017). There is a connection between the composition of the intestinal microbial composition and the development of cancer. Microorganisms as *H. pylori, F. nucleatum,* Epstein-Barr Virus (EBV) and Human Papilloma Virus (HPV) are well known carcinogenesis factors, which may have direct oncogenic effects, by producing toxins, damaging the epithelial barrier, impairing the anticancer immune surveillance, stimulating the production of trophic factors such as growth factors or other proinflammatory cytokines (Zitvogel, Daillère et al. 2017).

In the literature there is a broadly described, close connection between intestinal dysbiosis and the development of colorectal cancer. The composition of the intestinal microbiota of CRC patients differs from the microflora of the control group patients (Helmink, Khan et al. 2019, Sears, Garret 2014, Gao, Guo et al. 2015). In CRC tumor tissues, the presence of *F. nucleatum* was found, moreover this bacterium may also contribute to resistance to anti-cancer chemotherapy (Yu, Guo et al. 2017). Experiments in mice have shown that the use of the FMT procedure may reduce colorectal carcinogenesis (Bel, Elkis et al. 2014).

Recently, an increase in *C. difficile* incidence has been observed. The main factors predisposing to CDI are older age, long-term hospitalization and the use of antibiotics. Important factors contributing to the development of CDI are immunosuppression and achlorhydria (Barlett 2017).

Oncological patients are hospitalized for a long time, undergo immunosuppressive therapy (hematooncological patients undergoing bone marrow transplantation) and preventive antibiotic therapy. All of these increases risk of CDI (by 10%) (Alonso, Treadway et al. 2012). Hematological malignant tumors are an independent risk factor that causing the development of CDI (Dubberke, Reske et al. 2007). The use of fecal transplantation in patients with multiple comorbidities seems to be very risky. Stool is a material containing a large number of microorganisms, including pathogenic ones. Therefore, it is very important to keep all safety procedures during the selection of the donor and during the FMT procedure itself. In oncological patients, the FMT procedure also has positive effects in the treatment of CDI, without causing excessive side effects (Abu- Sbeih, Ali et al. 2019). With all precautions taken, the FMT procedure can be used in cancer patients both for CDI treatment and for the eradication of multiresistant bacteria (Biliński, Grzesiowski. et al. 2016).

5. Short conclusion

For most people FMT seems to be a highly controversial procedure, having features of alternative medicine. Since the first application of FMT in 1958, there has been a significant development of medicine. Research methods have developed (including molecular ones, allowing to evaluate the bacterial microbiom), the approach to the concept of bacterial microbiota inhabiting the human body has also changed. While the XX century enraptured with antibiotics, the XXI century, aware of the growing antibiotic resistance among bacteria and the severity of CDI, reduce this admiration. FMT is a procedure that belongs to non-standard therapies. Based on the observations described above, it can be concluded that it is relatively safe, and above all, effective in the treatment of an increasing number of diseases, including comorbidities of oncological patients.

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