Faecal Transplantation and Clostridioides difficile Infection

Darija A Knežević,1 Miroslav Petković2

Abstract

Faecal microbiota transplantation (FMT), known equally well as faecal transplantation or faecal bacteriotherapy, is the process of implanting the faecal suspension containing balanced microbiota from a healthy donor to the colon of a recipient patient. Excessive growth of Clostridioides difficile (C difficile) in the intestinal microbiota resulting from antibiotic consumption is currently a rising threat to public health. FMT is one of the most important, newer approaches to treating C difficile infections. Since C difficile is regarded as an opportunistic bacterium triggering disease in conditions of disturbed homeostasis of the intestinal microbiota, restoration of healthy intestinal microflora facilitates suppression of toxic strain of C difficile by anaerobic bacteria of normal intestinal microflora with concomitant cure. Nurses have important role in caring for patients after faecal transplantation.

Key words: Faecal microbiota transplantation; Clostridioides difficile infection; Microbiota.

Introduction

Faecal microbiota transplantation (FMT), also called faecal transplantation or faecal bacteriotherapy, is the transfer of a faecal suspension from a healthy donor into the colon of a recipient patient. The goal of FMT is to achieve the restoration of the intestinal flora of an infected person by transmitting the intestinal flora bacteria of a healthy donor. FMT is one of the more important, newer approaches for the treatment of Clostridioides difficile (C difficile) infections (CDI).1-3 As a method of treatment, FMT was used long before modern medicine. Ancient civilisations did not know the concept of microbiota but talked about the healing effect of faeces. The first recorded case of ingestion of faecal material for medical reasons dates from the traditional Chinese medicine that in the 4th century used this procedure for the treatment of gastrointestinal diseases as a “yellow soup”.4, 5 In modern medicine, the first published study in English literature of the use of FMT dated from 1958 and talked about the use of faecal enema, as an additional procedure for pseudomembranous colitis caused by antibiotics. It is rarely mentioned later, until in 2010 when FMT has been increasingly recognised as a successful therapeutic procedure for recurrent cases of CDI, but also the treatment of ulcerative colitis, Crohn’s disease, irritable bowel syndrome, metabolic syndrome, and even chronic fatigue syndrome.6-9

Microbiota and microbiome

More than 100 billion symbiotic microorganisms are found in and on humans, which is on average
The physiological microbiota of an individual is rapidly formed during the first months of life. By the end of the second year, it achieves a composition that remains stable throughout life. Interaction with the intestinal microbiota in infancy plays an essential role in health and disease in later life, creating immune and metabolic pathways. During birth and after birth, the newborn’s body is being quickly inhabited by microorganisms with which it comes into contact. Data from epidemiological studies have shown that caesarean section, preterm birth, early exposure to antibiotics, and supplementation with adapted milk harm the development of the intestinal microbiota and contribute to some diseases later in life, for example obesity, asthma and inflammatory bowel disease.

Although no two humans with the same microbiota exist, there are more remarkable similarities in their composition among members of the same race, ethnic groups and related individuals. The type and function of the human microbiota differ depending on the anatomical localisation, age, sex, race and diet of the host. Bacteria are primarily present in a healthy human microbiota. However, in addition to them, some viruses (primarily bacteriophages), fungi, archaea (mainly of the genus Methanobrevibacter) and some eukaryotes are also present. The most significant number of microorganisms of the human microbiota is found in the intestines, greatly influencing the formation of the metabolic phenotype, the epithelium’s development, and innate immunity. Bacteria that predominate in the colon are Bacteroidetes (including the genus Bacteroides) and Firmicutes (including the genera Clostridioides and Eubacterium). Actinobacteria, Verrucomicrobia, Proteobacteria and Fusobacteria appear as well in smaller numbers. Intestinal commensals prevent colonisation by pathogenic microorganisms by occupying living space and utilising food and in several indirect ways, such as stimulating a local immune response or producing various compounds with an antimicrobial role. Thus, for example, lactic acid produced by the species of the genus Lactobacillus participates in the degradation of the bacterial wall, and the constitution of bile acids, which reflects the overall metabolism of the intestinal microbiota, significantly affects the intergrowth of C difficile spores.

Bacteria, human symbiotes, aid in the metabolism of difficult-to-digest compounds by providing the host with essential nutrients, prevent expansion of opportunistic microorganisms and add to the creation of intestinal architectures. Foods that are difficult to digest, such as dietary fibre xyloglucan, usually found in vegetables, can be broken down by bacteria from the genus Bacteroides. Bacteria from the genera Lactobacillus and Bifidobacterium enable the digestion of difficult-to-digest fibres, for instance fructooligosaccharides. The gut flora alters the metabolism of carbohydrates, proteins and lipids. With its enzymes, it affects the host enzymes by fermentation. Around 50-100 mmol/L of the short chain fatty acids (SCFA), notably acetic, propionic and butyric acid, are produced daily by intestinal microbiota, thus providing the source of energy for the intestinal epithelium.

The microbiota carries an indispensable role in the synthesis of folate, vitamin K and some B vitamins, such as biotin (B1), riboflavin (B2) and cobalamin (B12). It also participates in the metabolism of bile acids, polyphenols, xenobiotics and drugs. In addition, bacteria that colonise the intestine promote the proper development of the mucosal immune system. Alterations in the intestinal microbiota have been observed in obesity, irritable bowel syndrome, ulcerative colitis, Crohn’s disease, inflammatory bowel disease, colorectal cancer, non-alcoholic fatty liver, and some other diseases. Since most primary bacterial pathogens have been successfully brought under control by vaccination or improved living conditions, today, the onset of bacterial disease is more associated with disruption of a complex human ecosystem than with the pathogenic power of a single microorganism. Given the high variability of the human microbiota, it is difficult to deter-
mine what a normal or healthy microbiota is. The ability to treat or prevent disease by altering an individual’s microbiota is a significant challenge in many areas of medicine.23

**Intestinal microbiota and infectious diseases**

The intestinal microbiota is made up of microorganisms, which inhabit various regions of the gastrointestinal tract. The number of bacteria increases towards the end of the digestive tract. The stomach and duodenum are settled by a small number of microorganisms, less than 10³ colony-forming units (CFU) per gram of intestinal contents. Infectious disease is most often the result of microbiota dysbiosis. Then again, infection and its treatment directly influence the intestinal microbiota, which determines the outcome of infection in the human population. The spread of some opportunistic (Enterococcus faecalis, Enterococcus faecium, and bacteria of the Enterobacteriaceae family) and pathogenic bacteria (Salmonella enterica, C difficile) results in a robust inflammatory response, followed by a change in the intestinal microbiota.34-36 Numerous studies have demonstrated an association between infection and microbiota dysbiosis. The intestinal microbiota of patients with CDI was significantly altered.37, 38 Also, microbiota disorders lead to the advancement of infection with viruses such as hepatitis B virus (HBV) or human immunodeficiency virus (HIV).39-41

**Clostridioides difficile infection**

Excessive growth of C difficile bacterium in the intestinal microbiota gives rise to diarrhoea. It is one of the most common complications that occur after the administration of antibiotics, currently presenting the rising threat to public health. Antibiotics disrupt the homeostasis of the intestinal mucosa, thus reducing resistance to the effect of C difficile toxin and leading to the progression of CDI. The higher incidence of these infections in recent years has been closely related to the development of highly virulent strains, such as those with ribotype 027 (NAP1 / 027 / BI).32, 42 C difficile is an anaerobic, sporogenic, rod-shaped, Gram-positive bacterium. It was discovered in 1935 in newborns and was named *Bacillus difficilis* (lat. *Difficilis* - heavy) due to its difficult cultivation. Later, due to the phenotypic similarity with bacteria from the genus *Clostridium*, it was named *Clostridium difficile*. Since 2016, based on the sequence analysis of 16S rRNA gene, it has been called *Clostridioides difficile*.44-46 It is omnipresent in nature, inhabiting the intestines of humans and animals as well. The proliferation of toxigenic strains of this bacterium leads to various clinical conditions, from asymptomatic carriers, through diarrhoea and self-limiting colitis to serious situations just as fulminant colitis and toxic megacolon.47 CDI transmission is horizontal, faecal-oral. In healthcare facilities, it is usually transmitted by contaminated hands (healthcare workers, patients and their families) and objects from the environment (stethoscopes, thermometers, surfaces and space near the patient).48 Although it can be found in meat and meat products, seafood, and fresh vegetables and fruits, no food-borne epidemic disease is directly related to *C difficile*.49, 50 Thanks to the resistance of its spores (they tolerate most antiseptics), C difficile can persist for a long time in the external environment, which allows it to stay in the patient’s vicinity for a long time. It can be found on various surfaces in the hospital with which patients come into contact and on the hands, clothes, and shoes of medical staff, which according to research, has one of the essential roles in the spread of infection.51 Risk factors for the occurrence of the disease are old age, severe chronic diseases, long-term hospitalisation, as well as staying in institutions for the elderly and the chronically ill. However, the most critical factor of risk contributing to the expansion of infection is the change in the intestinal microbiota due to antibiotic therapy. The highest risk is therapy with clindamycin, cephalosporins, penicillins and fluoroquinolones. Moderate risk involves therapy with macrolides and sulphonamides, while treatment with tetracyclines carries no risk.52

*C difficile* is ubiquitous and is statistically present in 15-70 % of neonates and in 2-5 % of the adult population, who are mostly colonised by its community. For example, in most neonates colonisation with *C difficile* is temporarily, and colitis does not develop.53 The observed transient asymptomatic colonisation might result from *C difficile* toxin-binding receptors, a disorder of antibody production against *C difficile* toxins, and the development of protective mechanisms associated with breastfeeding or intestinal bile acid me-
Patients with recurrent CDI have a deficiency of bacteria prevalent in the colon, leading to multiple relapses. When repeated CDI is diagnosed, it is recommended to treat the first CDI relapse with the same therapy as the one used for the initial case of infection (metronidazole or vancomycin). Nevertheless, many authors suggest vancomycin for the treatment of the first relapse after initial infection with CDI was treated with metronidazole. If the first case of CDI was treated orally with vancomycin, fidaxomicin is the next choice of therapy for the first relapse, although it is often budget limited. Since there are concerns about the occurrence of neurotoxic effects with long-term use, metronidazole is not recommended as a therapy for the second relapse. Moreover, the effect of metronidazole is reduced after repeated infections. Thus, for any subsequent relapse, the therapy with antibiotics for a more extended period, even longer than four weeks, often with reduced or increased doses of vancomycin, is considered. Due to the limited possibilities of medical treatment of recurrent cases of CDI, the pursuit of other possible treatments has intensified over the last years. FMT is one of the potential therapies, which has been used quite often since 2010, primarily due to its good efficacy (in some studies, it has been successful in over 90% of cases).

FMT as a therapy for CDI

The concept of FMT implies the restoration of the altered microbiota in the intestines (dysbiosis) of the diseased person to a healthy microbiome (symbiosis). This regeneration is performed by transmitting the intestinal flora of a healthy donor to the intestine of an infected person. As an opportunistic pathogen, *C. difficile* promotes disease when microbiota homeostasis is disrupted. Thus, restoration of balanced intestinal microflora enables suppression of toxic strain of *C. difficile* by anaerobic bacteria of normal intestinal microflora with accompanying cure.

There are three primary indications for FMT in the case of CDI: (1) CDI that reoccurs repeatedly, (2) restrained CDI resistant to standard antibiotic therapy (vancomycin or fidaxomicin) during minimum one week, and (3) serious form of ulcerative colitis (fulminant CDI) not responding to standard antibiotic therapy during 48 hours. In some cases of CDI, antibiotic therapy is unsuccessful due to increased formation of *C. difficile* toxins, delayed response of immune system or conditions such as ileus or diverticulum, preventing the antibiotic from reaching the colon. FMT can be used as a therapeutic option in these cases, especially if the patient is not a candidate for surgery. In addition to CDI, this method is used as a therapy for metabolic syndrome, irritable bowel syndrome and inflammatory bowel disease. Research on FMT use in some other diseases, such as Parkinson's disease, multiple sclerosis, autism and obesity, is underway. FMT leads to a more robust immune response, faster healing but also improves the overall quality of life and the FMT procedure is straightforward.

To perform FMT, it is necessary to provide a healthy donor, the equipment of the laboratory required for processing and storage of faeces and medical equipment for the transfer of faeces into the small or large intestine of the patient. Research has shown that donor selection, processing and storage of faeces differ somewhat, but standardized procedures already exist. FMT providers can be older than 18 years, known to the patient (family members or friends) or unknown, ie those who want to give faeces (volunteers). Family members, especially immediate family, share the most significant amount and content of microorganisms with the recipient. While family members share the risk...
Processing of donor faeces for FMT

The faecal sample must be properly taken from an appropriate donor, must not encounter contaminated water, urine or blood, has to be in the amount of at least 50 grams and delivered to the laboratory at shortest convenience. The faeces are homogenised in the laboratory by centrifugation in sterile 0.9 % saline, filtered and resuspended.

How FMT will be performed depends on the clinical presentation but also on the patient’s requirements. The methods of faecal transplantation currently used are: 1) endoscopy, via a nasoduodenal probe or by swallowing a gelatine capsule, for the upper part of the gastrointestinal tract, 2) colonoscopy, for the initial part of the colon, 3) sigmoidoscopy, rectal probe or enema, for the final part of the colon. The combined route of administration is preferred for more complex conditions, as for example ileus or anatomical disorders of the gastrointestinal tract.

Factors for infection diseases as well, the factors of risk are minimised with unknown donors, as they go through the same procedure as blood donors. In any case, all faecal donors for FMT must undergo rigorous screening to reduce the possibility of transmitting infectious diseases. Current FMT guidelines advise employing a donor questionnaire analogous to the one required for voluntary blood donors, serological testing, or faecal examination for infectious agents. The donor cannot be a person if he has any of the gastrointestinal diseases (inflammatory bowel disease, irritable bowel syndrome, constipation, chronic diarrhoea, history of major gastrointestinal surgery, gastrointestinal cancer or polypsis) or conditions that may influence the intestinal microbiota setup (metabolic syndrome, systemic autoimmune diseases, atopic diseases). Also, donors should not use antibiotics and immunosuppressive drugs for three months before faecal administration.

After answering the questions from the questionnaire, serological testing for syphilis, hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and human T lymphotropic virus (HTLV) I and II is performed. Donor faeces should be tested for bacteria, viruses, protozoa, and parasites: *C difficile*, *Helicobacter pylori*, *Listeria spp*, *Salmonella spp*, *Shigella spp*, *Vibrio spp*, *Yersinia spp*, *Campylobacter spp*, *Escherichia coli* (*E coli*) 0157 H7, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and Gram-negative bacteria producing extended-spectrum β-lactamases and carbapenemases (ESBL), rotavirus, norovirus, adenovirus. Some authors recommend a short screening protocol for the donor that is a close relative or intimate partner. In contrast, others suggest that all tests should be performed regardless of the donor’s choice. The faecal sample for transplantation can be prepared as fresh, frozen or in the form of gelatine capsules. If it is fresh faeces, it is recommended to be transplanted within six hours of defecation. To preserve anaerobic bacteria, some research also suggests automated preparation of faeces, so that the time of preparation itself is reduced to one hour. Faeces can also be stored at - 80 °C. Before the application, the stool suspension should be heated to 37 °C in a water bath, and the transfer should be performed within six hours.

Although, in general, the FMT procedure is considered safe, possible complications have not been well studied as large cohort studies are still missing. After colonoscopic faecal transplantation, stomach pain, diarrhoea, distension with nausea and vomiting, obstipation and mild fever may occur. Such symptoms are usually temporal and subside after several hours. Complications of FMT are associated with risks associated with FMT itself, eg exposure to pathogens. Although the overall risk of exposure to pathogens is considered low, pathogens that can be transmitted include *E coli* and norovirus.
The role of the nurse

Nurses play an essential role in caring for patients with CDI, after they have been subjected to FMT, primarily if those patients are housed in an intensive care unit. Enteric preventive measures and proper isolation of patients with CDI are crucial care procedures. According to the CDI prevention guidelines, contact isolation must be applied for the duration of the disease. The prescribed protective equipment is used: gloves, surgical mask, protective coat during care, PVC apron during other minor interventions. Protective equipment should also be used by those visiting the patient. Hygienic handwashing with soap after each direct contact with the patient is essential, and disinfectants with alcohol must not be used because they do not have a sporicidal effect. Equipment used to access a patient with suspected CDI or confirmed infection should be disposable or intended for these patients only (stethoscopes, thermometers, sphygmomanometer cuffs). The patient area is thoroughly cleaned and disinfected. Nurses should inform the patient about CDI, and his family and visitors about the importance of implementing prescribed hygiene measures.

Patients prone to developing CDI have often used antimicrobial drugs in the recent past (e.g., as a surgical prophylaxis, due to hospitalisation caused by long-term infection, following immunosuppressive therapy or older age). In case the antibiotic therapy is necessary even after FMT, it will again cause a change in the patient’s intestinal microbiota. After FMT procedure, nurses should monitor patients who use antibiotics for possible recurrent CDI. Patients who have undergone FMT are often bedridden and need special care. Since the patient’s environment is most likely contaminated with Clostridium difficile spores, the patient’s room must be thoroughly cleaned with a chlorine-containing agent immediately before performing FMT. If technically feasible, the patient should be placed in a new or thoroughly cleaned bed with clean bedding. Reducing the number of C difficile spores improves the success of FMT administration in patients with CDI. The patient should be asked not to defecate for at least 4 hours, if he can endure, after performing FMT, and if he can go for longer, he must be placed in a semi-sitting position for 24 hours and given diarrhoea medication.

Conclusion

By modulating an individual microbiome, many diseases can be prevented and treated. One of the latest approaches to treating recurrent CDI cases is the FMT method. It is a simple method during which the faeces of a healthy donor is being transplanted to a patient. Several faecal transplant procedures are used, and the most important thing is to perform safe preparation. Nurses apply specific prevention measures during the care of patients who have undergone FMT. In order to improve the effectiveness of FMT in patients with CDI, it is necessary to ask them not to defecate by placing them in a semi-sitting position.

Acknowledgements

None.

Conflict of interest

None.

References


46. Lawson PA, Citron DM, Tyrrell KL, Finegold SM. Reclas-


64. Bobo L. Fecal microbial transplantation: highly effective treatment for severe Clostridium difficile infection. JID Week 2013;281-4.


