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Przeszczep mikrobioty kałowej – podsumowanie współczesnych możliwości badawczych i terapeutycznych

Faecal microbiota transplant - a summary of contemporary research and therapy possibilities

Abstract

The animals' gastrointestinal tract is a microenvironment colonized by multiple bacterial species. Those organisms perform many important functions, inter alia the digestion aiding, enabling maturation of the colonic epithelium, participating in many metabolic changes. Keeping their stable, appropriate composition aims to protect from an excessive outgrowth of pathogenic bacteria and the development of many diseases. The gut microbiome differs significantly among species and individuals. The most common reasons for its adverse change include improper diet, disease, and certain drugs, especially antibiotics. The method ''faecal microbiota transplant'' - FMT refers to a procedure of transmitting bacterial content of intestines from a healthy donor to a diseased recipient in order to help in the re-colonization of his intestines by the optimal bacteria for this environment. This results in the resolution of the disease caused by non-viable microorganisms. There are many diseases directly connected with the gut microbiota, including *Clostridium difficile* infection, however many studies show remarkable results in treating also many autoimmune and metabolic diseases, behavioural alterations, and neurological problems. Recent years showed directly that dysbiosis is a dangerous condition not only in conjunction with a gastrointestinal problem, but the discoveries of many years in this field may serve as proof of a great connection of all body systems and their interactions with each other and a need of implementation the holistic medical processes in treating many systemic problems.

In this review, the authors summarised the available information regarding the development of a Fecal Microbiota Transplant method, evidence-based efficient methods of its application, and the newest research in this field in both human and animal medicine.

Key words: faecal microbiota transplant, human medicine, veterinary medicine.

Streszczenie

Układ pokarmowy zwierząt to mikrośrodowisko skolonizowane przez wiele gatunków bakterii. Organizmy te pełnią ważne funkcje w zachowaniu homeostazy organizmu, poprzez między innymi wspomaganie trawienia, umożliwienie dojrzewania nabłonka okrężnicy, uczestnictwo w wielu przemianach metabolicznych. Utrzymanie ich stabilnego, odpowiedniego składu ma na celu ochronę przed nadmiernym wzrostem bakterii chorobotwórczych i rozwojem chorób. Mikrobiom jelitowy różni się znacznie zarówno między gatunkami i osobnikami. Najczęstsze przyczyny niekorzystnej zmiany to niewłaściwa dieta, choroby, niektóre leki, zwłaszcza antybiotyki. Metoda „przeszczepu mikrobioty kałowej" – FMT odnosi się do procedury przenoszenia treści bakteryjnej jelit od zdrowego dawcy do chorego biorcy w celu pomocy w ponownej kolonizacji jego jelit przez bakterie optymalne dla tego środowiska. Powoduje to ustąpienie choroby wywołanej przez chorobowe mikroorganizmy. Istnieje wiele schorzeń bezpośrednio związanych z mikroflorą jelitową, w tym zakażenie *Clostridium difficile*. Wiele badań wykazuje również niezwykle pomyślne wyniki w lecze-

STRESZCZENIE
niu tą metodą także chorób autoimmunologicznych i metabolicznych, zmian behawioralnych i problemów neurologicznych. Ostatnie lata pokazały wprost, że dysbioza jest stanem niebezpiecznym nie tylko w połączeniu z problemem żołądkowo-jelitowym ale wieloletnie odkrycia w tej dziedzinie mogą być dowodem na istotność powiązania wszystkich układów organizmu i ich wzajemne oddziaływanie oraz potrzebę wdrażania holistycznych procesów medycznych w leczeniu wielu problemów systemowych.

W niniejszym przeglądzie autorzy podsumowali dostępne informacje dotyczące opracowania metody przeszczepu mikrobioty kałowej, skutecznych metod jej zastosowania opartych na dowodach oraz najnowszych badań w tej dziedzinie zarówno w medycynie ludzi, jak i zwierząt.

Słowa kluczowe: przeszczep mikrobioty kałowej, medycyna ludzka, medycyna weterynaryjna.

THE HISTORY OF FMT DEVELOPMENT

The history of faecal microbiota transplant goes back to ancient times. Originally in the form of a faecal infusion performed in animals, nowadays administered mostly in a modern capsule formula, FMT as a therapeutic method, constantly increases its scope and importance.

The first known records of its use date back to China and the 4th century, when a human doctor Ge Hong was using a human faecal suspension called a ‘’soup’’ administered by mouth to patients suffering from profuse diarrhoea or food poisoning. This therapy had great results and helped many of his patients (Zhang et al., 2012). Later records concerning faecal bacteria treatment were discovered in the Middle ages, among others the Li Shizhen therapy could be highlighted. His innovative ideas included prescriptions of fermented solutions, fresh suspensions, and dry matter made by faeces. He also appreciated the quality of infant faeces and used them in his therapies. In those documents, there can be found an extension of the scope of illnesses treated by this method to include fever, pain, vomiting, or constipation. Unfortunately, since the earliest times, aesthetic considerations were the greatest obstacle to the commercialisation of this method. The solution used by this doctor was labelling this medication as a ‘’yellow soup’’ (Zhang et al., 2018).

A similar procedure was used among indigenous tribes of Arab countries, North Africa, and the Middle East who were struggling with bacterial dysentery. As a remedy, they used faeces of their principal animals - camels (de Groot et al., 2017).

In the middle ages, Europe’s first records of FMT use describe applying it in veterinary medicine. The Italian doctor Fabricius Acquapendente lived in the 16th and at the beginning of the 17th century. The procedure he has been performing is based on transferring the intestinal content from a healthy to a sick animal. Later on, it was called a transfaunation and has greatly spread among veterinary medicine practitioners. In those times, but also nowadays the most abundant reason for FMT is a restoration of ruminal microbes in cattle with ruminal hypomotility disorders. Especially innovative variation was used for centuries in Sweden. Their most common form of sample used was a regurgitated digesta, contrary to the usual contents of the intestines (Brag and Hansen, 1994; de Petters and George, 2014).

At the beginning of the 20th also paediatrics started to pay attention to FMT.

In 1906 Henry Tissier, who worked as a doctor at the Pasteur Institute claimed that children with diarrhoea may become beneficial when treated with *Bifidobacterium bifidum* bacteria. He discovered the presence of lower numbers of such bacteria in patients with such symptoms. He was a strong opponent of the theses that artificial administration of those microbes might supersede the pathogenic ones and treat this condition (Tissier, 1906).

The FMT had also an influence on the course of the second world war. In 1941 the Nazi army suffered huge troubles because of dysentery outbreaks. Doctors after some research found that local nomads seemed to be more defended against those pathogens. They connected this fact with a tradition of eating fresh and warm camel faeces if only someone experienced some diarrhoea condition. They performed some analyses of those animals' stools and revealed them to contain Bacillus subtilis. These bacterias can antagonise the persistence of other bacterias, like the dysentery causative agents. However, due to social stigma they did not decide on a direct FMT for their soldiers. Despite this, they replaced it with the cultivation of this *Bacillus species* in large vats and administered it in a form of a soup or powder as a preventative method (Damman et al., 2012).

The newest history includes many attempts to integrate this therapy into mainstream medicine but the general sense of rejection felt by most of modern society significantly delayed the process. One of them can be described by the history of the bacteriologist Stanley Falkow, who sampled the faecal material from patients during pre- surgery period, then converted it into aesthetic pills and administered it to half of his experimental group, noting positive results. As he did it on his own, when the heads of his department got the information about his experiments, due to the social stigma he got fired and his results have been lost for many years. This history took place in the 1950s (de Groot et al., 2017).

The following year brought a scientific breakthrough. In Colorado scientists officially decided to try this therapy in critically ill patients with pseudomembranous colitis with faecal enemas. No other therapies worked and surprisingly this procedure brought a great alleviation of symptoms and then a complete recovery. After this in the following years more and more interest focused on this method and finally in articles from the 1980s there can be found information about 94% of success in this therapy (Browden et al., 1981; Eiseman et al., 1958).

The rising interest in the FMT caused this method to be also used in non-infectious diseases. The earliest record authors were able to find describes a 45-year-old man suffering due to ulcerative colitis. The results included full recovery without relapse. During this time it was called'' a bowel flora exchange'' (Borody et al., 1989).

The breaking point in FMT history was the decision of the US Food and Drug Administration when this method was officially approved for the therapy of refractory *Clostridium difficile* infections (Edelstein et al., 2015). The same year, Els et al. performed the first randomised official controlled trial, which showed more prominent efficiency in treating recurrent CDI with FMT use than using antibiotics alone. Since then, the interest and amount of experiments and therapies including FMT greatly increased. Currently, this method is considered safe, with only a few adverse effects and long-lasting effects, however, future research on long-term possible adverse consequences is strictly recommended (van Nood et al., 2013).

With medical progress, there is also a growing number of patients both animal and human, suffering from many coexisting disorders and expressing modified progress of diseases and unusual clinical signs as a result of environmental or individual variations. It results in overall growing pressure to use personalised therapies that go beyond the usual treatment regimen that meets their needs. The commercialisation of FMT usage may be considered a step forward in the development of future medicine and a focus on the remarkable healing properties of our bodies and the use of its natural healing sources.

In the recent past, this procedure has gained renewed interest also in the field of farm animals as well as domestic pets not only for therapeutic but also prophylactic use. Some laboratories define FMT as a method that helped them in reducing the number of porcine circoviruses or canine parvovirus, as well as horse colitis, showing great diversity in the range of positive effects in a multitude of mammals species (Niederwerder et al., 2018; Mullen et al., 2018; Pereira et al., 2018).

THE USAGE POTENTIAL

The potential for using this method varies significantly. The most common - therapeutic use is applied predominantly these days, however, there can also be found examples of use in immunogenic - pathogen-specific or prophylactic purposes. The therapeutic goal is represented when the patient already faces the disease in its organism and the aim is to resolve or alleviate its course. Prophylactic use means administration before encountering a dangerous pathogen exposure. The most specific - immunogenic type of usage focuses on specific pathogens to increase the number of immunoglobulins against them. The mechanism of action is then similar to traditional vaccines. Besides the therapy, the last two purposes are nowadays unique to the veterinary specialisation (Niederwerder, 2018).

PREPARATION AND ADMINISTRATION APPROACHES

The FMT procedure inseparably connects with a choice of an appropriate donor. To reduce the risk of side effects and the possibility of infectious disease transmission a strict test and a questionnaire are performed before the procedure. There is also a great advantage if a donor is a close relative of a recipient, especially when the environmental risk factors are similar in both cases. Those tests aim to exclude inter alia the presence of *C. difficile*, parasites like *Giardia*, *Isospora* or *Cryptosporidium*; viruses like rotavirus, hepatitis type A, B and C, HIV and other immunosuppressive states. It is also impossible to become a donor when there was a history of antibiotic therapy in the last 3 months and in the case of a human getting a tattoo, piercing or imprisonment in the last quarter (Bakken et al., 2011; Mattila et al., 2012).

For faeces storage it is important to not freeze the sample, only cooling is possible. The most common forms of administration include a nasogastric tube, nasoenteric tube, gastroduodenoscopy, colonoscopy, flexible sigmoidoscopy, and enema, which can be also omitted or administered by a previously prepared capsule (Allegretti et al., 2018, Kao et al., 2017). A previous preparation of a patient including a diet and medications is highly recommended and depends on specific cases. Solutions used as solvents usually include normal saline, milk or tap water. After that, mixing is performed by a hand or a blender and filtration by gauze.

Adverse effects of this procedure are not often, but if they appear, usually are mild and short-term. Most commonly documented ones include abdominal discomfort, borborygmus, bloat, diarrhoea or constipation, vomiting and short-term fever. The average time of their lasting is maximally 2 days (Wang et al., 2014). Most serious hazards are related not directly to the medical material biohazardous threats but to the procedure itself and a human's mistakes like the endoscopy complications, including possible perforation or adverse effects related to sedation. The greatest concerns include transmission of potential diseases carried by the donor, so the proper selection and preparation of the procedure is exceedingly important (Quera et al., 2014; Brandt et al., 2012, Rossen et al., 2015).

In the following paragraphs, the authors will present the current analysis and innovative experiments performed during the last few years on both human and non-human animal patients.

THE ANIMALS' RESEARCH

Intestinal microbiota plays a crucial function in the general health of the host. The balance of harmful and beneficial bacteria existing in the gut is vital for maintaining the health of animals and the body's homeostasis. The intestinal bacterias participate in the metabolism and absorption of food (Ridaura et al., 2013; Turnbaugh and Gordon, 2009), regulate intestinal barrier homeostasis as well as gut motility (Backhed et al., 2004; Bercik et al., 2012; Wayman, 2016). Fermentation of dietary fibre and resistant starch by microbiota leads to the formation of short-chain fatty acids particularly acetate, propionate, and butyrate. Those fatty acids influence the activity of digestive enzymes and play a significant role in regulating energy equilibrium.

Additionally, microbial metabolites can intercommunicate with the gastrointestinal mucus system by taking part in the intestinal processes and neurological disorders (Hu et al., 2018; Herath et al., 2020). The metabolites assist also in the cross-talk between the gut epithelium and immune cells and regulate and fine-tune the immune system by suppressing unnecessary inflammatory responses. Negative alteration in gut microbiota can lead to dysregulation in immune responses and consequently inflammation, insulin resistance, and oxidative stress (Yoo et al., 2020; Chen et al., 2022).

Communication exists between gut microbiota and the central nervous system known as the microbiota-gut-brain axis influencing the behaviour of animals, including investigation, aggression, and depressive, anxiety-like behaviours (Azeem, 2013; Vuong, 2017; Goodfellow, 2019). The absence of gut microbiota in Japanese quails reduces social activity that is related to fear and social commotion. Moreover, social contact among animals could shape bacterial transmission and influence the microbiota of the host, which lead to alterations in host phenotypes (Kraimi et al., 2018).

Most likely there is also interdependence between gut microbiota influence on behaviour and the influence of behaviour on gut microbiota through direct (eg., nervus vagus) and indirect (eh., cytokines, hormones) mechanisms. However, this field of study is still not fully understood and needs more research to discover the mechanism behind the connection between gut microbiota and the central nervous system (Chen et al., 2022).

The microbiota-gut-brain axis plays a vital role in the process of the stress response. Stress acting via the brain can result in an alteration of the microbial composition in the gut (Scott et al., 2013; Molina-Torres et al., 2019). The hypothalamus-pituitary-adrenal axis regulates corticosterone and cortisol secretion. Those hormones modulate the immune circulating cytokine secretion in the gut, which can further affect the intestinal barrier and the composition of gut microbiota (Cryan and Dinan, 2012; Lima-Ojeda et al., 2020). The specific composition and interaction of bacteria present in the intestines influence many pathways that together affect the overall health of the animal.

Faecal microbiota transplant (FMT) known also as faecal bacteriotherapy is used for the repair, replacement, and restoration of primary gut microbiota of a host with healthy faecal microbiota and it is administered via an enema, nasogastric tube, endoscopy, or by indigestion peroral capsules (Borody and Khoruts, 2012). In veterinary medicine, this tool is utilised mainly therapeutically, prophylactically, or for the stimulation of pathogen-specific immunity (Niederwerder, 2018).

LARGE ANIMALS

The use of FMT in animals dates back to the 17th century in Italy, where transfaunation as a restoration of microbes to the ruminal contents in cattle was used mostly for the treatment of metabolic or digestive disorders to restore normal rumination (Borody et al., 2004). In Sweden, regurgitated digesta or cud was used for microbial transplantation as a method to cure ruminal indigestion and was cultivated for centuries (Brag and Hansen, 1994).

The FMT is also a method that is applied to farm animals nowadays. Disturbances in the homogeneity of gastrointestinal microbiota have severe effects on the digestive system and various organs of dairy cows. Dysbiosis causes various metabolic disorders, including bloat, ruminal acidosis, hypoglycemia, diarrhoea, ulcers in the GI tract, reticuloperitonitis (Xu et al., 2021) and ketosis. Disharmony in commensal bacteria is also observed in infections conducting to severe conditions, such as Johne's Disease (Khalil et al., 2022). Alteration in microbiota composition caused by the application of antibiotics has been associated with a vast number of health problems. Supporting a healthy composition of gastrointestinal microbiota in the rumen and lower intestines where fermentation and energy production occurs in ruminants is essential for maintaining the productivity and general health of those animals. However common infections occurring on farms exposes ruminants to frequent antibiotic administration during their lifetime. This can disturb the original microbiota and contribute to an expansion in antibiotic-resistant genes in dairy cows (Wichmann et al., 2014; Chambers et al., 2015; Liu et al., 2016).

Ji et al. investigated the microbiota shift in the foregut and hindgut of lactating cows after antibiotics administration and after antibiotics withdrawal with or without microbiota transplantation. Their study demonstrated that after 3-14 days of antibiotics exposure microbiota in both parts of the gut significantly changed and this condition persisted for an extended period (more than 18 days) after the termination of antibiotics administration. Further results indicated that in both foregut and hindgut after FMT application restoration of the microbiota occurred faster compared to the control group. The microbiota in the foregut mainly profited from FMT by restoration of the alpha diversity and microbiota in the hindgut predominantly benefited from FMT by reestablishing the co-occurrence network. Together the results indicated that FMT might be a valuable treatment for delayed microbiota restoration caused by antibiotics in cows (Ji et al., 2018).

In healthy cattle, the digestive system microbiota consists of bacteria (the most abundant group), archaea, protozoa, fungi and bacteriophages (Xu et al., 2021) and varies a lot depending on the compartment. The rumen naturally dominate Bacteroidetes (with genus Prevotella being 90% of them), followed by Firmicutes. Within the small intestine *Enterobacteriaceae*, *Firmicutes* and *Proteobacteria* are highly abundant. Among the large intestine microbiome, Firmicutes are dominant, followed by Bacterioidetes. Other significant phyla in cattle gastrointestinal (GI) tract are *Actinobacteria*, *Tenericutes*, *Spirochetes* and *Fibrobacteres* (Khalil et al., 2022).

A study made by Ma et al. explored the modifications in the composition of microbiota caused by weaning stress, and if the early-life application of FMT might decrease the stress by the modification in the intestinal microbiota in weaned piglets. On the same farm, both diarrheal and healthy weaned piglets were observed and nine litters of newborn piglets were selected and distributed to three groups: sucking normally, weaned at day 21, and weaned at day 21 but with the administration of early-life FMT. The results of the study showed that there is a difference in the composition of gut microbiota in the diarrheal and healthy piglets and early-life FMT notably decreases diarrheal occurrence in weaned piglets. Furthermore, intestinal integrity, as well as morphology, were ameliorated in the group with FMT administration. Additionally, early-life FMT modified intestinal bacterial composition where an increase in some beneficial bacteria like Akkermansia, Spirochaetes, and Alistipes was observed. The changes were also noted in the lipid biosynthesis and aminoacyl-tRNA biosynthesis and were enriched in a group with the application of early-life FMT (Ma et al., 2021).

In the other research, Xiang and his team analysed whether early administration of FMT from gestation sows combined with *Clostridium butyricum* and *Saccharomyces boulardii* (FMT-CS) would be beneficial for the maturation of both gut microbiota and immune system in piglets. The results showed that early-life intervention with FMT-CS could be helpful for the development of both adaptive and innate immune systems and vaccine efficacy. Moreover, it led to the alleviation of weaning stress by promoting the maturation of gut microbiota in piglets (Xiang et al., 2020).

The predominant phyla in the natural faecal microbiota of pigs are Firmicutes and Bacteroidetes, followed by Proteobacteria and Spirochaetes. *Prevotella, Streptococcus, Lactobacillus*, and *Clostridium* are the most abundant genera (Maltecca et al., 2021).

The faecal microbiota transplant appears to be a promising tool for decreasing the susceptibility of domestic pigs to the African swine fever virus (ASFV). African warthog is a natural reservoir for ASFV but apart from the genetic differences also environmental factors could be involved in the differential susceptibility to ASF of Eurasian suids compared to African warthogs. Domestic pigs that were raised on the pathogen-free farm were extremely susceptible to even highly attenuated ASFV strains that were harmless to genetically identical domestic pigs kept on conventional farms. The research focused on the transplantation of warthog faecal microbiota to domestic pigs to examine any changes in the host's susceptibility to ASFV. The results showed that FMT from warthog to domestic pigs provided partial protection against attenuated ASFV strains (Zhang et al., 2020).

FMT is a tool also commonly implemented in the therapy of acute and chronic diarrhoea and inflammatory bowel disease (IBD) in horses (Mullen et al., 2016).

Colitis is one of the examples where the administration of FMT contributes to a great overall reduction of diarrhoea score and greater normalisation of microbiome compared to untreated horses (McKinney et al., 2021). A healthy gut microbiome is essential for digestion and its restoration in horses with colitis is expected to contribute to the potentiation of an effective immune system and counteraction of infection. The observed relative increase in the quantity of mucus-dwelling Verrucomicrobia in FMT-treated patients promotes the production of mucus that contributes to the barrier against pathogens and prevents its attachment to the intestinal tract (Watanabe et al., 2021). FMT promotes the establishment of a more diverse microbiome in the GIT of horses with colitis and may represent a cost-effective and easy-to-perform as well as widely available therapy to promote restoration of gut function in horses with colitis or dysbiosis.

Although regardless of positive clinical outcomes still little is known about the effect of FMT on the recipient's faecal microbiota as well as on the mechanism behind this improvement (McKinney et al., 2020).

Domestic small animals

Although the use of FMT has many advantages, it is not a common tool in the ordinary practice in small animal medicine and there aren't many studies depicting the beneficial effects of this method in the treatment of acute and chronic diarrhoea in small animals (Takáčová et al., 2022).

In both dogs and cats, gastrointestinal dysfunction is mainly associated with intestinal dysbiosis and the composition of gut microbiota is usually affected during both acute and chronic conditions.

Results of a case report with an 8-month-old French bulldog suffering from chronic colitis and positive *C. difficile* faecal culture that received a single oral dose of FMT showed significant improvement in the consistency of faeces and frequency of defecation after 2 to 3 days. Moreover, the relapse was not observed for at least half a year (Pereira et al., 2018).

Another case report described a toy poodle with refractory inflammatory bowel disease. The patient received nine FMTs within six months and after the end of the treatment, the faecal microbiome normalised and resembled that of the healthy donor's faecal microbiome. Furthermore, the clinical symptoms significantly improved and no side effects were observed during the FMT treatment. The results indicate that FMT is both a safe and beneficial tool in long-term periodic FMT for a case of canine IBD and it could be a treatment option in the future (Niina et al., 2019).

A different study characterised the effect of FMT on a nine-year-old dog that suffered from chronic enteropathy for the last three years. The treatment included a two-cycle oral treatment of FMT after which the dog's vitality, appetite, and body weight increased together with a complete disappearance of systemic and gastrointestinal signs. The clinical parameters and gut microbiome gradually were restored to that resembling the ones observed in healthy dogs. Chronic enteropathies are diseases that affect about one in five dogs in Europe therefore it is important to develop a treatment that is not associated with negative side effects and is highly effective. FMT seems to be a promising tool in the treatment of this group of diseases and future studies should be done regarding this topic (Berlanda et al., 2021).

In the domestic cat, Furmanski and More documented a case report of usage of FMT in a female spayed Abyssinian cat diagnosed with ulcerative colitis. The patient did not show any improvement in conventional treatment and FMT was performed via enema as the last therapeutic option before euthanasia. After two FMT the cat gradually improved and during the three months started passing normal faeces leading to long-term resolution of clinical symptoms (Furmanski and Mor, 2017).

There are also few studies with no observed advantages of the use of FMT. In one study the FMT did not prevent post-weaning diarrhoea in puppies by oral application of the faecal inoculum. Additionally, no clinical improvement was observed (Burton et al., 2016). Pereira et al. tried to improve the survival of puppies infected with parvovirus by a combination of FMT and standard treatment. The FMT does not significantly enhance survival, but the team noted the resolution of diarrhoea within two days, and the hospitalisation time was shorter (Pereira et al., 2018).

Additionally, there is no universally accepted protocol regarding any specific indication as well as preparation and administration of FMT in small animal medicine. The factors including the geographical variation of infectious and non-infectious gastrointestinal diseases will contribute to the grand variation in the selection of both donor and recipient. Small animal veterinarians currently do not use FMT as a frequent treatment option and the awareness regarding the administration of FMT is particularly inconsistent among small animal practitioners. FMT is not only cheap but also an easy-to-perform method and there is no need for any special equipment (Schmitz, 2022).

It appears to be a very promising tool for the treatment of gastrointestinal diseases, especially as a supportive treatment or when there is no response to conventional medication.

Future studies and case reports are needed to enhance our wisdom about the gut microbiota in animals and the mechanism behind the efficacy of FMT. There are also needed commonly-accepted standardised protocols for administration and donor selection in all groups of animals (Niederwerder, 2018).

Wildlife

The FMT in conservative biology is still preliminary but appears to be significantly important in the introduction of captive breeding animals into the wild which is one of the main approaches that are used for both protection and improving the population size in nature. Nonetheless, habitats, diet, and artificial feeding are one of the main aspects that influence the gut microbiota which leads to a significant difference in the composition of gut microbiota of wild and captive breed animals (Kleiman, 1989; Schmidt et al., 2019). The gut microbiota contributed to better adaptation of wildlife to specific habitats, and diets and enhance the resistance to infections. (Michael, 2016; Rosshart et al., 2017; Ceja-Navarro et al., 2019). In comparison, the animals that live in captivity have altered gut microbiota and more vulnerable digestive and immune systems (Mckenzie et al., 2017).

Unfortunately, after the release of captive animals, the modified gut microbiota often needs a long period to resemble the composition of the gut microbiota of that of wildlife (Tang et al., 2020; Yao et al., 2019).

Moreover, the differences in the gut microbiotas may lead to a decreased probability of survival of reintroduced individuals into the wild (Allan et al., 2018; Redford et al., 2012). In reintroduced captive-born herbivores the altered gut bacterial community is assumed to be one of the factors that decrease the ability to obtain nutrition from the native diet (Allan et al., 2018; Guo et al., 2019; Mckenzie et al., 2017). Consequently, the improvement in the gut microbiota through the diet and environment should increase the health and survival rate of candidates for reintroduction and FMT is one of the recommended tools for the reconstruction of gut microbiota. (Allan et al., 2018). Moreover, FMT was documented to heal the diarrhoea of infant kangaroos with almost 100% effectiveness (Milliken, 2018).

FMT is a new research field in conservative biology therefore more investigations regarding the standardisation of application, preparation, selection of donors, and evaluation of the safety of FMT are needed as well as more case reports including wildlife. Nevertheless, the FMT appears to be a promising method, which can be utilised to save endangered wild animals (Blyton et al., 2019).

HUMANS RESEARCH

Composition of human gut microbiota, its variations in the same individual and between individuals.

The human gastrointestinal microbiota contains approximately $3.9x10^{13}$ organisms - an amount similar to the number of human cells in the body (Sender et al., 2016). It consists of bacteria, fungi, protozoa, archaea and viruses, including phage viruses that infect bacteria (Almeida et al., 2019). The density of bacterial cells in the colon has been estimated at 10^{11} to 10^{12} per millilitre which makes it one of the most densely populated microbial habitats known on earth (Ley et. al., 2006).

The gut microbiota is mainly composed of *Bacteroidetes, Firmicutes, Proteobacteria, Verrucomicrobia, Actinobacteria* and *Fusobacteria.* Two main phyla - *Firmicutes* and *Bacteroidetes* - represent 90% of gut microbiota (Arumugam et al., 2011; Almeida et al., 2019). The *Firmicutes* phylum is represented by different genera such as *Lactobacillus, Bacillus, Clostridium, Enterococcus* and *Ruminococcus*, with *Clostridium genera* accounting for 95% of the Firmicutes phyla. *Bacteroidetes* consist of predominant genera such as *Bacteroides* and *Prevotella.* The Actinobacteria phylum is proportionally less abundant and mainly represented by the *Bifidobacterium genus* (Arumugam et al., 2011).

VARIATIONS IN THE SAME INDIVIDUAL

Human gut microbiota differs taxonomically and functionally in each part of the gastrointestinal tract varies in terms of physiology, pH, O_2

tension, digesta flow rates, substrate availability, and host secretions. Due to these factors, a small intestine is mainly occupied by *Lactobacillus* and *Enterobacteriaceae*, whereas in a colon dominate *Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae* and *Ruminococcaceae* (Flint et al., 2012).

There are differences in microbiota composition depending on birth gestational age - preterm infants show low diversity with increased colonisation of potentially pathogenic bacteria from the *Enterobacteriaceae* family (Arboleya et al., 2012) and reduced levels of strict anaerobes such as *Bifidobacterium* (Butel et al., 2007), *Bacteroides* and *Atopobium* (Arboleya et al., 2012), the type of delivery - the intestinal microbiota of neonates delivered by caesarean section are less diverse in terms of bacteria species than the microbiota of vaginally delivered infants (Biasucci et al., 2008) and manner of milk feeding - breastfed infants have more beneficial gut microbiota, with higher richness and diversity of *Bifidobacterium spp.* and a lower number of *Clostridium difficile* and *Escherichia coli* than formula-fed infants (Penders et al., 2006).

After the termination of milk feeding, the intestinal microbiota changes a lot. The introduction of high-fibre and carbohydrate foods (traditional foods) causes an increase in *Firmicutes* and *Prevotella*, whereas the introduction of high-fibre and animal protein foods causes an increase in *Bacteroidetes* (Tanaka and Nakayama, 2017).

Gut microbiota changes with age. From the dominance of *Akkermansia muciniphila, Bacteroides, Veillonella, Clostridium coccoides spp.*, and *Clostridium botulinum spp.* at age one, through the characteristic of humans abundance of three bacterial phyla: Firmicutes (*Lachnospiraceae* and *Ruminococcaceae*), Bacteroidetes (*Bacteroidaceae, Prevotellaceae,* and *Rikenellaceae*), and Actinobacteria (*Bifidobacteriaceae* and *Coriobacteriaceae*) since age three-four for the majority of a lifetime (Tidjani et al.,2016), to a decrease amount of anaerobic bacteria such as *Bifidobacterium spp.* and an increase in *Clostridium* and *Proteobacteria* in people over the age of 70 (Toshitaka et al., 2016).

Variations between individuals happen due to enterotypes, body mass index (BMI) level, and external factors such as lifestyle, training frequency, ethnicity, and dietary and cultural habits (Rinninella et al., 2019).

ANTIBIOTICS - IMPACT

Broad-spectrum antibiotics conduct an imbalance between Firmicutes and Bacteroidetes. The bacterial diversity decreases and so does the abundance of these bacteria during the treatments. The alteration of microbiome composition depends on the antibiotic class, dose, period of exposure, pharmacological action, and target bacteria (Iizumi et al., 2017). The impact of antibiotic disturbance on the resilience of microbiota during future antibiotic treatments can thus also vary considerably across individuals (Lozupone et al., 2012). For instance, macrolides like clarithromycin decrease the level of Actinobacteria, Firmicutes and Proteobacteria while increasing the amount of Bacteroidetes; vancomycin lowers the quantity of *Lactobacillus* and *Clostridium genera*, ciprofloxacin reduces the abundance of Bifidobacterium, Alistipes, Bacteroides, Faecalibacterium, Oscillospira, Ruminococcus as well as Dialister genera and clindamycin lowers *Bifidobacteriaceae* and *Lactobacillus* amount. All of these antibiotics decrease intestinal bacteria diversity (Yatsunenko et al., 2012).

FMT IN HUMAN TREATMENT

Today, faecal microbiota transplantation is predominantly utilised for the treatment of multiple, recurrent *Clostridium difficile* infections (CDI) (Soo et al., 2020; Baunwall et al., 2021). Evidence also supports the use of FMT following severe *C. difficile* infection which has resulted in shock or supportive care, as well as in cases of disease refractory to antibiotic therapy (Trubiano et al., 2016; McDonald et al., 2018; Costello et al., 2019). The repeated use of FMT in recurrent CDI is superior to vancomycin. Baunwall et al. gathered 4 studies comparing the use of vancomycin and a single FMT in the 8th week of *Clostridium difficile*-associated diarrhoea, with the anticipated absolute effect of 35% for vancomycin and 72% for FMT, and 3 studies comparing use of vancomycin and a repeat FMT, with the anticipated absolute effect of 27% for vancomycin and 93%

for FMT. The clinical effect 8 weeks after FMT, preceded by antibiotics treatment of varying duration, was 91% following repeat FMT and 84% following a single FMT (Baunwall et al., 2020).

FMT in CDI treatment can be performed using lower GI endoscopy, upper administration, capsules or enema. Delivery by lower GI endoscopy is the most effective method (in the 8th week of *Clostridium difficile*-associated diarrhoea anticipated effect of single administration: 88%; repeated administrations: 96%). However, capsule (anticipated effect of single administration: 81%; repeated administrations: 92%) and enema (anticipated effect of single administration: 50%; repeated administrations: 88%) FMT have practical benefits that make FMT easily applicable and capsule may eventually be the better first choice. In this context, delivery by lower GI endoscopy may be reserved for patients who fail their initial FMT (Baunwall et al., 2020).

There is also significant concern regarding the selection of an appropriate donor for this procedure. To meet those demands, nowadays there are multiple FMT centres across Europe. Such places provide high safety and hygiene standards and provide easier accessibility of material when needed. The European estimation suggests at least a 10 times increase in carrying out this procedure to fill the needs gap (Baunwall et al., 2021).

CURRENT RESEARCH FIELD IN HUMAN MEDICINE

The primary reason for use of faecal transplant among human patients is the treatment of primary infection of *Clostridium difficile*. There were several studies performed in this field but its effectiveness was not established for now (Allegretti et al., 2019). Nevertheless, those researches are also important in the field of intestinal carriage of multidrug-resistant organisms. Recurrent *C. difficile* infection successfully treated with FMT is related to a notable reduction in antibiotic-resistance genes within the patient's intestinal microbiota. There could be a role for FMT in the decolonisation of multidrug-resistant organisms in the human gut, even in patients struggling with immunosuppression (Allegretti et al., 2019).

There was also much research done in the field of ulcerative colitis treatment.

The evidence of increased rates of clinical remission of ulcerative colitis in patients treated with FMT compared to those receiving a placebo is unquestionable. Nonetheless, before more data are supporting these results, FMT can not be recommended as a usual therapy in ulcerative colitis (Allegretti et al., 2019; Costello et al., 2017; Costello et al., 2018; Paramsothy et al., 2017; Haifer et al., 2020).

Crohn's disease - a type of inflammatory bowel disease is another example of an illness with many clinical trials in FMT usage. The rate of clinical remission of Crohn's disease was found to be about 50%, and few serious adverse effects due to the FMT occurred (Paramsothy et al., 2017). Research estimating the efficacy of FMT in patients with Crohn's disease is continued now (Allegretti et al., 2019).

FMT via colonoscopy or nasojejunal tube may be beneficial in IBS (irritable bowel syndrome). However, studies were providing diverse consequences. Larger and more rigorously conducted trials are necessary to understand if FMT will be efficacious in this condition (Ianiro et al., 2019; Allegretti et al., 2019).

There are also many non-GI tract-connected diseases, in which FMT is a useful support. An example can be hepatic insufficiency, in which the described method significantly lowers the number of hepatic encephalopathy episodes and improves the results of cognitive testing in comparison to controls. The benefits of FMT last for up to 12 months and no serious adverse events distinctly related to FMT were currently noted (Allegretti et al., 2019; Bajaj et al., 2019).

There was also performed a pilot clinical trial on ten patients suffering because of primary sclerosing cholangitis and in three of them a 50% decrease in alkaline phosphatase concentration by 6 months after the FMT occurred. This could be a good prognosis and improve the understanding of the role of faecal microbiota in the pathogenesis of primary sclerosing cholangitis. Larger research on this topic is planned. (Allegretti et al., 2019).

There is nowadays a great interest in the connection between bacterial microflora and the neuroendocrine human system. This is why currently more and more scientists focus on the connection of FMT with neuro-hormonal ailments. It is known that gut microbiota has an assigned role in host metabolic rates, and those were investigated in anorexia nervosa patients with underweight. In de Clercq et al. case study of a patient with recurrent underweight following clinical recovery from anorexia nervosa, FMT resulted in a 13.8% weight gain over 36 weeks. In this patient, a reduction of the resting energy metabolism after FMT was noticed, perhaps making the gain in body weight possible. This was the first study showing FMT as a probable treatment for underweight AN patients (de Clercq et al., 2019).

There can be also found studies in which administering allo-FMT to patients with metabolic syndrome, obesity, insulin resistance, and type 2 diabetes (T2D) to prevent weight regain showed a significant result, as well as trials showing significant improvements in peripheral insulin sensitivity. However, there were also studies resulting in no significant weight loss or increased insulin sensitivity, even while it proved a change in microbiota composition (Fuhri Snethlage et al., 2021; Allegretti et al., 2019).

Type 1 diabetes (TID) was also investigated in mouse models, as well as observational human studies, indicating variations in gut microbiota between healthy patients and those with T1D. Moreover, hopeful results in retaining residual pancreatic function in T1D cases due to FMT were observed. As in the majority of FMT-related trials, more research is needed also to investigate if the microbiome certainly plays a role in the persistence of pancreatic beta cell function. Nevertheless, there is a potential role for FMT in the future treatment of T1D (Fuhri Snethlage et al., 2021).

FMT could be considered as the additive treatment for allogeneic-hematopoietic stem-cell transplant recipients. These transplants in many cases require antibiotics, which cause a reduction in gut microbial diversity. It may lead to increased mortality in these patients. Autologous FMT was shown to restore intestinal microbiota composition and diversity to that before the transplant. Serious adverse effects related to FMT were not observed (Allegretti et al., 2019).

It is known that the gut-brain axis plays an important role in psychical and psychological conditions and part of world research focuses on the use of FMT in such cases. Collyer et al. observed three patients with both depression and IBS, who received FMT. This treatment resulted in an improvement in both mood, symptoms and/or medication (Collyer et al., 2020). Koppenol et al. study showed that recovery of multiple recurrent *C. difficile* infections due to FMT resulted in improved self-rated health. They also observed that the intensity of depressive symptoms decreased up to 26 weeks post-FMT (Koppenol et al., 2022). In at least one trial, autistic spectrum disorder behaviour had markedly improved by FMT administration. These improved results were maintained until at least ten weeks after the FMT treatment (Kang et al., 2017). Subsequent studies should concentrate on defining the part that gut microbiota changes play in psychological welfare.

Other ongoing research on FMT as a new therapy covers for instance bipolar disorder, malnutrition, Parkinson's disease and psoriatic arthritis (Allegretti et al., 2019).

SUMMARY

The microbiome diversity is extraordinarily huge and tills now not fully recognized. Dysbiosis is a great risk for the general health of humans and animals. This severity of the condition can be alleviated or completely treated by faecal microbiota transplantation. FMT is a process during which the faecal bacteria are transferred from a healthy donor to a diseased individual to restore the normal intestinal flora. There are several methods of administration of FMT but nowadays the most efficient appears to be a direct transmission of faecal bacteria to the intestines. Many studies show remarkable results in treating diseases with the gastrointestinal tract. Moreover many autoimmune and metabolic diseases, neurological problems, and behavioural alterations can be also alleviated by restoration of the healthy intestinal microbiota. The advantages include also its natural character and almost no side effects when the adherence to hygienic protocols is maintained and careful selection of appropriate donors preserves from spreading additional diseases. The possible limitation includes a need for a strict examination of a possible donor which can be costly and time-

consuming. The disadvantage is also a procedure of administration which can be unpleasant in the matter of direct approach or more expensive if the form of administration is the pill. The above article includes mostly clinical cases but also more advanced research studies to summarise the current state of knowledge of this therapy. FMT is nowadays known as an underutilized but inexpensive and efficient method with not many side effects and future research in this field is needed.

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Praca wpłynęła do redakcji: 01.07.2022r.
Zrecenzowano: 09.09.2022r.
Przyjęto do druku: 25.09.2022r.