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PROBIOTICS AND FECAL BACTERIOTHERAPY: THE LINE BETWEEN DECEPTION AND TREATING

PROBIOTIČI I FEKALNA BAKTERIOTERAPIJA: LINIJA IZMEĐU OBMANE I LEČENJA

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Abstract

The microflora of the gastrointestinal tract is essential for mucosal protection, immune education, and for metabolism of humans. Disturbances of these processes results in various diseases. Regarding these processes, there is a clinical interest in the utility of microbial therapy – the feeding of non-pathogenic bacteria, originally derived from the alimentary tract. Considering the commercial success of probiotics, there is still a difficulty for consumers as well as for physicians when choosing the specific product. Since they are classified as food supplements, and not subject to drug regulations, there is ongoing skepticism about the benefits they offer.

Fecal bacteriotherapy is reported as highly effective in the treatment of various diseases, including those of the digestive tract. The treatment itself consists of feces infusion from a healthy human donor to the gastrointestinal tract of patient. According to current data, fecal bacteriotherapy represents an emerging and promising low-cost solution for diseases with which antibiotic and probiotic products have been struggling for years.

Key words: probiotics, fecal bacteriotherapy, enteric microflora, fecal microbial transplantation.

Apstrakt

Gastrointestinalna mikroflora je od suštinskog značaja za zaštitu crevne sluznice, razvoj imunog odgovora i metabolizma ljudi. Poremećaji gastrointestinalne flore manifestuju se različitim bolestima. U skladu s time, sve je šire interesovanje za implementaciju mikrobne terapije, tj. aplikaciju nepatogenih bakterija, poreklom iz gastrointestinalnog trakta. Iako su probiotici doživeli komercijalni uspeh, prisutne su poteškoće kako za pacijente, tako i za lekare kada treba da odaberu određeni proizvod. Pošto su klasifikovani kao dodaci hrani i ne podležu propisima o lekovima, postoji stalna sumnja u njihov efekat.

Fekalna bakterioterapija je prijavljena kao visoko efikasna u lečenju oboljenja povezanih i nepovezanih sa gastrointestinalnim sistemom. Sam tretman sastoji se od infuzije izmeta zdravog čoveka (davaoca) u gastrointestinalni trakt pacijenta (primaoca). Uzimajući u obzir
Probiotics are a living microbial food supplement that favorably affects the host by improving the intestinal microflora, as well as live microorganisms, which by ingestion cause significant improvement of health when compared to a regular diet. Initially, they were applied as an alternative therapy or simply a health food. However, their reputation in medicine had problems due to the extravagant claims of the producers of the probiotics. While in reality, the consumption of these various strains of bacteria (many of which have not shown any probiotic activity or survival ability) has shown to be inconclusive. The amount of clinical data supporting the use of proven probiotic organisms in the prevention or treatment of many disorders is lacking.

Thus, in recent years another approach has gained considerable attention. Fecal bacteriotherapy (FBT) represents a method that consists of feces infusion from a healthy human donor to the gastrointestinal tract of a patient, with the goal of treatment of disease that is related to gut microbiota alteration. Reports of FBT effect in Western literature started to appear in previous 60 years, first as a treatment for antibiotic related diarrhea, although the first use of this treatment was recorded 1700 years ago. Today, the admirable effect of this approach is reported in various conditions, thus it is still classified as investigational treatment, therefore requires further standardization and developing.

Gastrointestinal flora
Co-evolution led to a symbiotic bond between eukaryotes and prokaryotes with the development of a sophisticated two-way signaling system in mucous epithelium and the immune system, as well integration of gut microflora with various signaling pathways in the central nervous system. It has been clearly established that gastrointestinal flora is of utmost importance for the mucosal protection of the immune function. Laboratory animals
without microbiota (germ-free animals) are sensitive, and with a reduced mucous immune function. The reintroduction of the flora to germ-free animals restores intestinal function, mucosal proliferation, immunity development, animal growth, and normal behavioral development.9–12

This complex microbial world is different in composition throughout the length of the intestine with an increased inclination of the host microbe number and diversity from the stomach to the colon13–17. The gastrointestinal flora is described as the most adjuvant and renewable metabolic organ in the body whose composition and activity can affect both the intestines and the physiology of the individual6, 7, 9, 18, 19. Such an effect is not surprising since dietary byproducts, intestinal secretion of the epithelial cells within the lumen, form the basis for microbial transformations. Compared to other regions of the intestine, the colon contains the most complex microbial population showing a certain level of metabolic activity that cannot be compared to those in the liver17, 20.

Gram positive species, above all Lactobacillus, are most common isolates since they have tolerance to stomach acids. Below the ileocaecal valve, the number of bacteria grows. Of these, we can more easily study specific Clostridium, Bifidobacteria, Bacteroides and Peptostreptococcus. Despite a large number of differences between individuals in the intestinal flora, the composition of the main groups of bacteria within the individual appears to be relatively constant16. The importance of intestinal microflora is reflected in the creation of a barrier against any transient potential pathogens. Examples of proliferation of pathogen are: pseudomembranous colitis caused by the action of Clostridium difficile and Enterococcus faecium toxins, intra-abdominal abscesses for which Bacteroides fragilis can be responsible.

Depending on the genetic and other host-related factors, intestinal flora can contribute to pathogenic processes as indicated by growth and bacterial displacement in the establishment of an immune or microvascular compromise, mobility disorder, irritable bowel syndrome (IBS) or blind loop syndrome. In addition, initiation and maintenance of intestinal disturbances, such as ulcerative colitis and Crohn's disease can occur in persons with genetic predisposition21–23.

During and after childbirth, the fetus is exposed to microbial contamination. The level of contamination impact is related to the duration and type of the delivery process. For example, initial contacts with cesarean-born neonate microbes are related to air, medical
staff and neonatal care\textsuperscript{24}. After giving birth (either natural or through the cesarean section), infants are continuously exposed to food-derived microorganisms, both to those useful and to those which are not. Healthy breast milk contains a significant number of bacteria. These transient bacteria include Streptococci, Lactobacilli, Micrococci, propionic bacteria and special Bifidobacteria\textsuperscript{25,26}.

For breastfed babies, Bifidobacteria are bacterial species that is dominated microbial flora, and significantly less Escherichia coli, Streptococci, Bacteroides and Clostridium species. In contrast, newborns on artificial nutrition have a much more complex composition of microflora, and Bifidobacteria and potentially pathogenic anaerobes are predominant\textsuperscript{25}. This has in recent times influenced the development of artificial baby foods by formulas with bifidogenic properties similar to mother's milk in an attempt to reduce the development of enterocolitis. After 12-24 months after birth, independently on diet, or probiotic intake, children's flora becomes much more complex and more similar to that of adults\textsuperscript{27}.

**Probiotic products – the world of “arranged chaos”**

Lactobacilli and Bifidobacteria are most commonly associated with probiotic activities. Although, other organisms are used, such as the certain strains of Escherichia and any non-bacterial organisms such as Saccharomyces boulardii\textsuperscript{28}. This is primarily due to the understanding that they are members of the intestinal microflora. Furthermore, these bacteria have traditionally been used in the production of fermented dairy products and have the status of "GRAS: generally recommended as safe"\textsuperscript{33}. Most of these organisms are derived from feces of healthy people, safe for human use and are available in large numbers. Due to the continuing skepticism of such products, the European Union has established research groups, including medical, scientific and industrial interests that have harmonized the criteria for the selection and application of probiotics. In order to meet the criteria, probiotic micro-organisms should be of human origin, to show non-pathogenic behavior, even in immunocompromised hosts, to demonstrate resistance to technological processes, have proven resistance to acids of the stomach and bile, adhere to epithelial tissue, be able to shortly survive in the gastrointestinal tract, produce antimicrobial substances, modulate immune responses, and can have the ability to influence metabolic activities (such as, for example, cholesterol assimilation, lactase activity, and vitamin
Nevertheless, a product can be classified as a probiotic if it contains another bacterium that is accepted as not harmful or commensal, and where no serious adverse effects are expected. As a consequence of its classification as a food supplement, the main challenge of probiotics arises – lack of regulation and rigorosity in the process of manufacturing.

The effects of probiotics are known to be dependent on the strain and dose as well as for their transitory effect. In addition, the commercial formulation of probiotic product can be significant factor in bacteria delivering process. Considering the commercial success of probiotics in previous years, many clinical trials were conducted and published, mostly praising their therapeutic effect. Francavilla et al. reported that the 6-week probiotic supplementation with 5 combined strains of lactic acid bacteria and Bifidobacteria (Lactobacillus casei 101/37 (LMG P-17504), Lactobacillus plantarum (CECT 4528), Bifidobacterium animalis subsp. lactis Bi1 (LMG P-17502), Bifidobacterium breve Bbr8 (LMG P-17501) and B. breve B110 (LMG P-17500)) reduced severity of irritable bowel syndrome related symptoms in patients suffering from celiac disease with IBS on strict gluten free diet.

Oh and al. conducted randomized controlled trial where they examined effect of probiotics supplementation on gut microflora during standard triple therapy for Helicobacter pylori eradication (clarithromycin, amoxicillin, and lansoprazole). As probiotics supplementation Medilac-S® was used, that consists of Streptococcus faecium and Bacillus subtilis. After two weeks of treatment, proportions of the gut microbiota in the group that received triple therapy for Helicobacter pylori eradication were higher than those in the group that received same therapy combined with probiotics. They also noticed an increase in the levels of antibiotic-resistant bacteria, where higher levels were present in the conventional treatment group than in the probiotics one. In addition, Haghoost et al. conducted a trial where they examined the effect of triple therapy for the eradication of H. pylori combined with probiotic supplement in the form of capsules that contain strains Lactobacillus and Bifidobacterium. Although, in this case, supplementation continued up to 4 weeks after triple therapy, while during this time control group received placebo. The authors found that the eradication rate of H. pylori infection was higher in probiotic group and the adverse events were less prevalent in patients that received probiotic supplementation. Thus, they
found no significant difference in terms of infection recurrence during a 6-month follow-up.

Ljungquist et al. examined the effect of eight different living bacterial strains mixture administration in adult patients intestinally colonized for at least three months with extended spectrum β-lactamase producing Enterobacteriaceae. Probiotic supplement contained eight living bacterial strains: Bifidobacterium longum, B. infantis, B. breve and Streptococcus thermophiles, Lactobacillus plantarum, L. paracasai, L. acidophilus, L. delbrueckii ssp. bulgaricus. Administration lasted for two months in placebo-controlled, single-blind clinical trial. Finally, 12.5% of the patients in the probiotic group achieved successful eradication of extended spectrum β-lactamase producing Enterobacteriaceae, where in the placebo group 5% of the patients achieved successful eradication. The authors of the study concluded that probiotic supplementation was not superior compared to placebo for intestinal decolonization in patients with chronic colonization of extended spectrum β-lactamase producing Enterobacteriaceae.

Despite various reports, there is a difficulty for consumers, as well as for physicians when one should choose specific probiotic product. The state of seemingly “organized chaos” within the probiotic industry market is a result of their non-standardized manufacturing, as well as intense and often false advertising for potential beneficial effect of their products. Moreover, in cases where a therapeutic effect of probiotics lacks, the highest price is paid by the patient themselves, depending on their socio-economic position as well as their health status.

Regarding future probiotic applications, there is no doubt that treatment should be approached in an individualized manner that considers the patient’s diet, hygiene habits, comorbidities, and current health status. No space should be left for biased decisions to be made. And indeed, studies that included personalized probiotic treatment showed an advantage over commercial products.

**Fecal bacteriotherapy**

Fecal bacteriotherapy/fecal microbiota transplantation/microbiota transfer therapy represents transplantation of the fecal bacterial flora from a healthy donor into the gastrointestinal tract of the recipient.
Repulsive for some, FBT has been reported as highly effective in the treatment of recurrent Clostridium difficile infection (CDI), slow-transit constipation, inflammatory bowel disease and IBS, where quality of life improvement lasted up to 28 weeks. The donor can be a healthy person that is a near or distant relative of the patient or a community member. A major advantage of this approach is the high probability of genetic compatibility between donor and recipient, as well as the related living habits and diets that have influence on gut microbiota composition. With the growing interest in fecal bacteriotherapy, novel indications are emerging that are not directly related to gastrointestinal diseases. Promising effects were shown in patients with metabolic syndrome, hepatic encephalopathy, hepatitis B infection, and neurobiological disorders.

European consensus conference strongly recommends fecal bacteriotherapy for treatment of CDI, although Food and Drug Agency (FDA) recommends it as alternative therapy for recurrent CDI after pulsed application of vancomycin. The most reported adverse effects related to FBT recipients, are “abdominal discomfort” and predominantly after treatment that involved upper gastrointestinal routes of application (nasogastic tube, nasojejunal tube, gastroscopy). Kelly et al. reported death of one patient directly related to FBT treatment, where aspiration of inoculum during sedation phase occurred. Thus, that incident can be attributed to complications related to application rather than a hazard of FBT itself.

Addressing the unpleasant method of application of fecal microbiota by colonoscopy or by upper gastrointestinal route infusion, several research groups reported that the effect of fecal microbiota delivered via oral capsules did not differ from classical delivery in adult patients with CDI. Therefore, with the introduction of more conventional ways of microbiota administration we could expect the elimination of most adverse effects related to FBT.

Arbel et al. addressed cost effectiveness of FBT through the treatment of nosocomial CDIs, compared to other regiments, including probiotics. Since appearance of recurring hospital CDIs has turned into common and severe incidents, costs related to CDIs with current treatment regimens in the United States are exceeding $3.2 billion/year. As mentioned previously, FDA approves offering of FBT to patient only when a relapse of recurrent CDI occurs after treatment with vancomycin, with or without probiotics. Regarding that, FBT showed admirable effects with resolution rates up to 94% in treatment.
of recurrent CDIs. It is believed that FBT induces repopulation of Firmicutes and Bacteroides spp., which are deficient in patients with recurrent CDIs. Moreover, other study groups reported that FBT showed better cost-effectiveness and outcomes when compared to vancomycin treatment.

During 2019 FDA released Safety Alert due to two serious adverse reactions in immunocompromised patients that resulted from a transplantation of fecal microbiota. The Safety Alert highlighted that donor material contained extended-spectrum beta-lactamase-producing Escherichia coli, which was causative agent of lethal outcome in one of the two patients. FDA finally recommended thorough screening of donors for risk factors that can lead to possible infection with Multi-Drug Resistant Organisms and screening of donor samples for presence of Multi-Drug Resistant Organisms.

Addressing the effects of FBT on extra-intestinal diseases, there are several possible indications that deserve to be mentioned here. To our knowledge Vrieze et al. conducted the only human study related to FBT effect in patients with metabolic syndrome. Authors reported that six weeks after the infusion of microbiota via duodenal tube from donors, insulin sensitivity of recipients significantly increased, as well as levels of butyrate-producing intestinal microbiota.

Hepatic encephalopathy represents a common complication of liver cirrhosis. Kao et al. presented a case where a patient suffering from liver cirrhosis and hepatitis C infection was treated with FBT. The patient received FBT treatments during seven weeks, after which authors reported a "dramatic clinical improvement", and thus the beneficial effect of FBT faded after discontinuation of treatments.

Another possible link of gut microbiota with progression of liver diseases was addressed by Ren et al. where 18 persistently HBeAg positive patients resistant to standard entecavir or tenofovir disoproxil fumarate based therapy were enrolled in research. Thus, from total number, only five patients received FBT, while others served as a control. Authors reported that HBeAg titer declined gradually after each treatment of FBT applicated side by side with standard therapy.

Several authors reported possible link of autism specter disorder severity with alteration of microbiota composition in children.

Xu et al. found lower percentages of several bacterial strains, including Bacteroides, Bifidobacterium, and Parabacteroides and a higher percentage of Faecalibacterium and
higher abundance of Lactobacillus in the total detected microflora, compared to control specimens.

Kang et al. conducted an open-label clinical trial, where children with autism specter disorder were treated with FBT for seven or eight weeks after two-week antibiotic treatment. Authors reported that behavioral symptoms in children improved significantly and remained improved eight weeks after treatment ended. Moreover, increased bacterial diversity was registered and the abundance of Bifidobacterium, Prevotella, and Desulfovibrio, among the others.

Unlike probiotics, the current situation with FBT is not a case of introducing another poorly regulated food supplement. Thus, it is reasonable to assume that there is still a long way for FBT to become routinely used for wide specter of indications. Furthermore, when compared to probiotic products, its classification as an emerging therapeutic treatment is one of the biggest advantages of fecal bacteriotherapy. One could expect that if fecal bacteriotherapy fulfills given requirements and becomes classified as therapeutic treatment, the much needed line between deception and actual treatment related to microbial therapy will be drawn.

**Conclusion**

Although probiotics are accepted as beneficial products, there is a great burden of production inconsistencies between manufacturers leading to the deception of patients as well as physicians in cases of non-adequate selection of dose, strain or formulation. The future of probiotic should be oriented to a personalized probiotic treatment that considers patients diets, hygiene habits, comorbidities and current health status. On the other hand, fecal bacteriotherapy is conducted by strict regulations and currently is under process of evaluation as genuine treatment option for many indications. Considering current data, fecal bacteriotherapy represents an emerging and promising low-cost solution to diseases with which antibiotic and probiotic products have been struggling for years.
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