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Probiotics and fecal bacteriotherapy: the line between deception and treatment

Probiotici i fekalna bakterioterapija: linija između obmane i lečenja

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Introduction

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 [1]. Initially, they were applied as an alternative therapy or simply healthy food. However, their reputation in medicine had problems due to the extravagant claims of the producers of the probiotics. 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 [2, 3].

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 a disease that is related to gut microbiota alteration. Reports of FBT effect in Western literature started to appear in the previous 60 years, first as a treatment for antibiotic-associated diarrhea [4], although the first use of this treatment was recorded 1,700 years ago [5]. Today, the admirable effect of this approach is reported in various conditions. However, it is still classified as an investigational treatment, so it requires further standardization and developing.

Gastrointestinal flora

Coevolution 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 the integration of gut microflora with various signaling pathways in the central nervous system [6–8]. 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 colon [13–17]. 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 individual [6, 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 liver [17, 20].

Gram positive species, above all *Lactobacillus*, are the most common isolates since they have tolerance to stomach acids. Below the ileocecal valve, the number of bacteria grows. Out 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

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bacteria within an individual appears to be relatively constant [16]. The importance of intestinal microflora is reflected in the creation of a barrier against any potentially transient pathogens. The examples of the proliferation of pathogens 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, the initiation and maintenance of intestinal disturbances, such as ulcerative colitis and Crohn's disease can occur in persons with genetic predisposition [21–23].

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 [24]. After giving birth (either natural or by 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* [25, 26].

For breastfed babies, *Bifidobacteria* are bacterial species that is dominated by 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 [25]. Recently, this has influenced the development of artificial baby foods based on formulas with bifidogenic properties similar to mother's milk in an attempt to reduce the development of enterocolitis. Twelve to 24 months after birth, independently of diet or probiotic intake, children's flora becomes much more complex and more similar to that of adults' [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* [28]. This is primarily due to the understanding that they are the 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" [29]. 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 microorganisms should be of human origin, show nonpathogenic behavior, even in immunocompromised hosts, 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 production) [1]. 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 – the lack of regulation and rigorousness 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 a significant factor in bacteria delivering process [29, 30]. Considering the commercial success of probiotics in the previous years, many clinical trials were conducted and published, mostly praising their therapeutic effect. Francavilla et al. [31] 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 *Bifidobacterium breve* Bl10 (LMG P-17500)] reduced the severity of irritable bowel syndrome-related symptoms in patients suffering from celiac disease with IBS on strict gluten-free diet.

Oh et al. [32] conducted a randomly controlled trial where they examined the effect of probiotic supplementation on gut microflora during standard triple therapy for *Helicobacter pylori* eradication (clarithromycin, amoxicillin, and lansoprazole). As probiotic supplementation Medilac-S® was used. It consists of *Streptococcus faecium* and *Bacillus subtilis*. After two weeks of the 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 the 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 probiotic one. In addition, Haghdoost et al. [33] conducted a trial where they examined the effect of a triple therapy for the eradication of *Helicobacter pylori* combined with probiotic supplement in the form of capsules that contain strains *Lactobacillus* and *Bifidobacterium*. In this case, the supplementation continued up to 4 weeks after the triple therapy, while during this time control group received placebo. The authors found that the eradication rate of *Helicobacter 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 the infection recurrence during a 6-month follow-up.

Ljungquist et al. [34] 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*, *Bibidobacterium infantis*, *Bifidobacterium breve* and *Streptococcus thermophiles*, *Lactobacillus plantarum*, *Lactobacillus paracasai*, *Lactobacillus acidophilus*, *Lactobacillus 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*, while 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 a specific probiotic product [35]. 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 effects of their products. Moreover, in cases where a therapeutic effect of probiotics lacks, the highest price is paid by the patients themselves, depending on their socioeconomic position, as well as their health status [36–39].

Regarding future probiotic applications, there is no doubt that a 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, the studies that included a personalized probiotic treatment showed an advantage over commercial products [40, 41].

Fecal bacteriotherapy

Fecal bacteriotherapy (FBT) or 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 for up to 28 weeks [42–46]. The donor can be a healthy person that is a near or distant relative of the patient or a community member. The major advantage of this approach is the high probability of genetic compatibility between a donor and a recipient, as well as the related living habits and diets that have influence on gut microbiota composition. With the growing interest in FBT, novel indications that are not directly related to gastrointestinal diseases are emerging. Promising effects were shown in patients with metabolic syndrome [47], hepatic encephalopathy [48], hepatitis B infection [49], and neurobiological disorders [50, 51].

European consensus conference strongly recommends FBT for the treatment of CDI [43], although Food and Drug Administration (FDA) recommends it as an alternative therapy for the recurrent CDI after the pulsed application of vancomycin [52]. The most reported adverse effect related to FBT recipients is "abdominal discomfort", predominantly after the treatment that involved upper gastrointestinal routes of application (nasogastric tube, nasojejunal tube, gastroscopy) [53]. Kelly et al. [54] reported the death of one patient directly related to FBT treatment, where the aspiration of inoculum during a sedation phase occurred. Thus, that incident can be attributed to the complications related to the application rather than a hazard of FBT itself.

Addressing the unpleasant method of the 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 [44, 55, 56]. 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. [57] addressed the cost-effectiveness of FBT through the treatment of nosocomial CDIs, compared to other regiments, including probiotics. Since the appearance of the 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 per year.

As mentioned previously, FDA approves of offering FBT to a patient only when a relapse of the recurrent CDI occurs after the treatment with vancomycin, with or without probiotics [52]. Regarding that, FBT showed admirable effects with the resolution rates up to 94% in the treatment of the recurrent CDIs. It is believed that FBT induces the repopulation of *Firmicutes* and *Bacteroides* spp., which are deficient in patients with the recurrent CDIs [57]. Moreover, other study groups reported that FBT showed better cost-effectiveness and outcomes when compared to vancomycin treatment [58].

During 2019, FDA released Safety Alert due to two serious adverse reactions in immunocompromised patients that resulted from the transplantation of fecal microbiota. The Safety Alert highlighted that donor material contained extended-spectrum beta-lactamase-producing *Escherichia coli*, which was the 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 [59].

Addressing the effects of FBT on extraintestinal diseases, there are several possible indications that deserve to be mentioned here. To our knowledge, Vrieze et al. [47] conducted the only human study related to FBT effect in patients with metabolic syndrome. The authors reported that six weeks after the infusion of microbiota via duodenal tube from donors, insulin sensitivity of recipients significantly increased, as well as the levels of butyrate-producing intestinal microbiota.

Hepatic encephalopathy represents a common complication of liver cirrhosis. Kao et al. [48] 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 the authors reported a "dramatic clinical improvement", and thus the beneficial effect of FBT faded after the discontinuation of treatments.

Another possible link between gut microbiota and the progression of liver diseases was addressed by Ren et al. [49] where 18 persistently HBeAg positive patients resistant to standard entecavir or tenofovir disoproxil fumarate-based therapy were enrolled in the research. Thus, from the total number, only five patients received FBT, while others served as a control. The authors reported that HBeAg titer declined gradually after each treatment of FBT given parallel with the standard therapy.

Several authors reported a possible link between autism spectrum disorder severity and the alteration of microbiota composition in children [50, 60].

Xu et al. [60] 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. [50] conducted an open-label clinical trial, where children with autism spectrum disorder were treated with FBT for seven or eight weeks after two-week antibiotic treatment. The authors reported that behavioral symptoms in children improved significantly and remained improved eight weeks after the treatment ended. Moreover, increased bacterial diversity was registered and the abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio*, among 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 FBT. One could expect that if FBT fulfills the given requirements and becomes classified as a 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 inadequate selection of a dose, strain or formulation. The future of probiotics 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 is currently under the process of evaluation as a 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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Conflict of interest

The authors declare no conflict of interest.

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