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Fecal Microbiota Transplantation: Past, Present and Future

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ABSTRACT In this review, we have summarized the latest evidence, indications, and methods of fecal microbiota transplantation (FMT), and analyzed the prospects and therapeutic potentials of this procedure. In recent years, FMT has attracted great interest, especially due to the global Clostridium difficile infection (CDI). FMT is now recommended as alternative therapy for recurrent CDI when standard treatment with antibiotics fails. It involves putting suspended biomaterial with intestinal microorganisms of a healthy donor into the intestine of a patient. Although the exact mechanism of action is not entirely clear, it is believed to restore the composition and function of the intestinal microbiota in diseased patients. The efficacy varies depending on the route of administration, quality and volume of donor biomaterial, and treatment before the procedure.

Keywords: fecal microbiota transplantation, alternative therapy, recurrent Clostridium difficile infection

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CDI – Clostridium difficile infection
FMT – fecal microbiota transplantation
GIT – gastrointestinal tract

The important role of the microbiota of the gastrointestinal tract (GIT) in maintaining normal physiological processes in the human body has long been widely recognized. However, mechanisms regulating the relation between the human body and the microbiota are still not known. It is clear that the interaction is carried out at once on many levels, so attempts to somehow unidirectionally influence the microbiota are not successful. Currently, there are already numerous data indicating the role of certain gastrointestinal dysbiotic disorders while maintaining such pathological conditions as obesity, Crohn's disease, ulcerative colitis, irritable bowel syndrome, fatty liver hepatosis, diabetes mellitus, autism and disseminated sclerosis [1, 2]. Weak efficiency, and sometimes improper use of modern antibacterial drugs in the treatment of dysbiotic disorders, prompted doctors to search for new, non-traditional methods of treatment. Therefore, the interest in fecal microbiota transplantation (FMT) observed in recent years is far from accidental. This method of treating diarrhea and infectious diseases of the gastrointestinal tract has more than 1,500 years, but it was recalled only in the second half of the 20th century.

Today, the results of studies confirming the high efficacy of FMT in the treatment of chronic recurrent pseudomembranous colitis caused by *Clostridium difficile* [3–8] have been convincingly recognized. The increase in the number of cases of pseudomembranous colitis in recent years has already become an epidemic and covers all countries, including economically developed ones. The appearance of antibiotic resistant strains is of particular concern [9–14].

FECAL MICROBIOTA TRANSPLANTATION

The essence of FMT is to transfer the stool microflora of a healthy donor to the gastrointestinal tract of a recipient in order to restore the disturbed microflora, that is, sharing the microflora of healthy donors and supplanting the pathogenic microflora causing inflammatory diseases. In fact, FMT is the introduction of the donor's stool solution into the patient's gastrointestinal tract.

If we turn to history, this method has long been used in veterinary medicine (treatment of colitis, accompanied by diarrhea in horses). There are first references in medical treatises of the 4th century AD, found in China, where a case of successful treatment of food poisoning was described [6].

The official medicine, initially not having a sufficiently convincing experimental, evidence-based scientific and legal basis necessary for use in the general practice of any treatment method, reacted to the FMT more than skeptically. In addition, there were initially no proven approaches to the selection of donors, methods of preserving the biomaterial, and methods of its introduction. The safety problem was not resolved either, it was unknown how high the risk of side effects is, including nausea, spasms, pain, inflammatory reactions and infections [12–16].

The main result of FMT is colonization of the patient's colon with microorganisms living in the donor's large intestine, which ultimately leads to the recovery of the high species diversity of a healthy human microbiome [7, 8]. In fact, the material transplanted with FMT is a kind of "complex probiotic". Among the "restored" species, Gram-positive microorganisms are most often found — representatives of *Lachnospiraceae*, *Ruminococcaceae*, as well as clostridia and fusobacteria [7]. It is quite interesting that the result of transplantation (restoration of a multicomponent microbiome)

varied greatly among different patients, although the donor material was the same. It is possible that it is not only the individual characteristics of the human organism that is to blame, but also the limited capabilities of the 16*S* DNA sequencing methods, which help identify certain phylogenetic groups of microorganisms.

FMT FOR THE TREATMENT OF *CLOSTRIDIUM DIFFICILE*-ASSOCIATED INFECTION *(CDI)*

The first publication on the use of *FMT* for the treatment of pseudomembranous colitis appeared in 1958, when it hasn't been known yet that *C. difficile* was the etiological factor causing this disease (the etiological role of *C. difficile* was proved in the late 70s) [17]. Pseudomembranous colitis is an extreme manifestation of *CDI*, in which *C. difficile* toxins cause acute inflammation of the colon, accompanied by the appearance of diffuse hyperemia, swelling of the mucous membrane with thickening of its wall and the formation of foci of fibrinous plaques ("pseudomembrane") of yellowish-white color. The result of FMT was quite encouraging, as after the first procedure there was an improvement in the patient's condition.

By 2014, the number of completed and documented FMTs exceeded 500 [17]. At the same time, the first small randomized controlled studies were conducted only in 2013.

In 2013, the US Food and Drug Administration (FDA, USA) recognized the donor fecal material as a new investigational drug, which can be used in a situation where pseudomembranous colitis does not respond antibiotic treatment [18, 19]. This status requires a lot of legal approvals and does not facilitate the introduction of *FMT* into wide practice. By this time, guidelines for the selection of donors had been developed, the procedure for cryopreservation of biomaterial and its storage had been standardized. The first depository banks of donor material appeared in the USA and Europe, financially supported by non-governmental organizations, for example, *OpenBiome* (USA).

Currently, the medical community has established that FMT is an effective method to manage recurrent CDI. For making a diagnosis of chronic (recurrent) CDI, the presence of such symptoms as a relapse of the disease after initial therapy, the presence of toxins and frequent stools (at least 3 times a day) are sufficient. The efficacy of antibiotic therapy in the case of chronic CDI varies from 30 to 88% and depends on the chosen treatment plan, as well as the number of relapses [9-14]. The higher is the frequency of relapses, the lower is the efficacy of therapy. The use of drugs such as Metronidazole, Bacitrocin and Vancomycin does not give the expected results. Fidaxomycin (15% *vs.* 25%; p=0.005) proved to be slightly more active than Vancomycin [9]. It should be noted, however, that the first recurrence was treated in this study. These results cannot be extrapolated to a situation with multiple CDI episodes.

In 2016, the European Conciliation Conference on the legality of the use of FMT was held [20]. Leading experts from 10 European countries tried to develop common approaches to assessing the possibility of FMT in treating not only CDI, but also other diseases, such as inflammatory bowel disease (ulcerative colitis), functional and autoimmune bowel disease. There was a lack of randomized controlled trials with a high degree of evidence. The studies with a moderate degree of evidence were sligthly more numerous — multicenter *well-designed* studies based on extensive clinical material, but not randomized. The results were also considered with a low degree of evidence, when at least 80% of experts accepted them as credible.

The analysis of the accumulated data has shown that FMT may definitely be recommended for the treatment of chronic (recurrent) CDI, both moderate and severe. This is evidenced by the results of two open, randomized controlled trials [4, 21], which showed a higher efficacy of FMT compared to treatment with Vancomycin (the percentage of patients with positive dynamics — 90% and 94% *vs.* 31% and 26%). It should be noted, however, that the sample (the number of patients) and the observation period were small. The reasonability of treating primary CDI infection hasn't hadconvincing clinical evidence yet [20]. There is also no reliable evidence of the efficacy of using FMT to treat the first episode of CDI infection caused by antibiotic-resistant strains of *C. difficile* (the so-called *"refractory* CDI*"*), where *C. difficile*-associated diarrhea cannot be managed with antibacterial drugs.

The special care should be devoted to problems associated with preservation of transplanted material. Large-scale studies were conducted to compare the effectiveness of using standard frozen samples and fresh material [22–26]. The use of frozen and freshly selected biomaterial revealed no significant differences. At the same time, an insignificant number of undesirable side effects was noted, provided that the donor was carefully selected and the optimal way of introducing the material was selected.

At present, the procedure for cryopreservation of samples of biomaterials is greatly elaborated. It includes the steps of dilution in saline, the addition of glycerin, freezing at –80°C. All this must be completed no later than 6 hours after sampling. If fast freezing is impossible, the storage under anaerobic conditions is allowed at 20–30°C for at least a few more hours [20, 22]. Samples processing before freezing is also performed under aerobic conditions, since at least one third of the intestinal microbiome of healthy donors is anaerobic gram-positive spore-forming bacteria that can survive long periods of contact with oxygen in the form of spores [27].

Requirements for donors are almost universal. In case of FMT, they include a study of blood and feces for a wide range of bacterial, viral and parasitic pathogens. The list of requirements has been adittionally expanded and considers such parameters as living in countries with a tropical and subtropical climate, in which their very specific bacterial, viral and parasitic infections circulate. Also, the donor is prohibited from taking antibiotics and immunomodulators for 3 months prior to sampling. Not only hereditary diseases are taken into account, but also such indicators as mental and neurological status, work in the medical or veterinary field [20].

The European Consensus Conference reviewed the amount of transplanted material needed and how it was administered to the patient. The introduction of 30–50 g of material and 150 ml of saline is considered to be minimal. Within 3 days before transplantation, antibiotic therapy (Vancomycin or Fidaxomycin) should be administered in order to suppress the activity of *C. difficile*. The antibiotic therapy should be discintinued 12–48 hours before transplantation [20].

Regarding the method of administration (during colonoscopy, using an enema, via a nasogastric tube or a gastrostomy tube), there should be no preference [28]. In practice, colonoscopy and enema are used more often than the others, as it has the advantage of administering a large amount up to 500 ml. In addition, it is possible to apply a more liquid suspension, and the procedure is performed faster. Administration with an enema is the easiest and most affordable way. Most often it is used in pediatric practice and for patients of intensive care units, mostly elderly ones [21]. According to some studies, the introduction of material through the upper digestive tract using a gastroscope, a

nasogastric probe, or through a gastrostoma, gives a slightly higher percentage of complications (vomiting, gastric spasm, aspiration pneumonia, acute inflammatory reaction) [29, 30]. In addition, the introduction through the upper digestive tract has a number of limitations: a small volume of material (25–50 ml) and a low introduction rate [20]. Currently, there are great expectations concerning the development of capsules containing a transplantable biomaterial [20].

Speaking about the adverse effects of FMT, it is worthwhile to say that cases of severe fatal complications are extremely rare, and usually occur in patients in intensive care units (due to the particular severity of the patients' condition) [27-30]. The reasonability of FMT in such cases hasn't not had the convincing evidence yet.

The treatment of pseudomembranous colitis is possible only with repeated FMT [19, 30]. The success of treatment depends largely on the severity of the patient's condition associated with the presence of concomitant pathologies, previous antibiotic therapy, frequency and duration of stay in hospitals, etc. Even the volume of the material is important, since the effect greatly increases.

The weakest point in studies of the therapeutic effect of FMT is the lack of consideration of medium- and long-term effects when the patient is on the outpatient treatment. Meanwhile, the observation period rarely exceeds 8 weeks [18, 20].

THE USE OF FMT FOR THE TREATMENT OF OTHER PATHOLOGIES

Researches on the possibilities of FMT for the treatment of other inflammatory diseases of the gastrointestinal tract, not related to CDI, which are most often accompanied by various dysbiotic disorders, continue. Encouraging results were obtained when using FMT for the treatment of ulcerative colitis [31, 32] and irritable bowel syndrome [33]. Regarding Crohn's disease and other autoimmune diseases, there is still no consensus, but the need for correction of the gastrointestinal microflora is beyond doubt. The possibility of managing the state of the gastrointestinal tract with the help of FMT in transplantology is being investigated in the treatment of the reaction of an acute immune response after the introduction of stem cells [34]. In addition, they try to use FMT in the complex treatment of metabolic syndrome, as well as for the correction of autism in children during complex therapy [20]. The evidence base for the treatment of these pathologies is still insufficient, but there are encouraging results.

THE PRACTICE OF USING FMT TO TREAT CDI IN RUSSIA

In Russia, the number of CDI hasn't not been recorded yet. But this problem undoubtedly exists and requires its own solution. The National Association for the Control of Infections Related to Medical Care issues the Federal Clinical Guidelines "*Clostridium difficile*-associated diarrhea" every 3 years. The last guidelines were published in 2017. The first transplantations of normal intestinal microflora in Russia have been successfully completed at the Center of New Medical Technologies of Novosibirsk. In Moscow, FSCC of FMBA anf FSCC of Physical and Chemical Medicine developed for the treatment of inflammatory bowel disease and antibiotic-associated diarrhea using intestinal microbiota transplantation.

CONCLUSION

The validity of using the fecal microbiota transplantation method for treating *Clostridium difficile*-associated infections is no longer in doubt. Today, the effectiveness of fecal microbiom transplantation in the treatment of chronic forms of *Clostridium difficile*-associated infections in adult patients has been proven. However, technical, economic, and organizational and legal issues related to the widespread introduction of fecal microbiom transplantation into practice have not been regulated both in the European and Russian medical community yet. The research status of fecal microbiome transplantation in both Europe and Russia does not significantly expand its use in actual practice and slows the creation of specialized centers and a single bank of biomaterials for transplantation.

The problem of the safety of a particular method of treatment always remains one of the most acute ones. Therefore, the study of the long-term effects of fecal microbial transplantation continues.

The idea of the human microbiome as a special "organ" capable of regulating the work of all systems of the human body suggests a broader therapeutic potential of fecal microbiome transplantation. Attempts have already been made and encouraging results have been obtained of using it in transplantology and treatment of autoimmune diseases, metabolic syndrome, and even autism.

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