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Using fecal microbiota transplantation for animal health (review)

Heorhii Yu. Drobot, Sergei K. Shebeko, Alexey M. Ermakov

Don State Technical University, 1 Gagarina sq., Rostov-on-Don 344000, Russia

ABSTRACT

Fecal microbiota transplantation is a procedure when fecal matter from a healthy donor is administered into the intestinal tract of a recipient in order to restore microbial balance and strengthen immune responses. Mainly, fecal microbiota transplantation increases bacterial diversity and facilitates a growth in beneficial microorganisms. Thus, the procedure makes it possible to stabilize and maintain a healthy gut microbiome that inhibits the pathogen growth. In veterinary medicine, fecal microbiota transplantation is considered as a potential alternative to traditional antibiotics amid rising antibiotic resistance. Despite the lack of commonly accepted procedures, studies show that the fecal microbiota transplantation for the purposes of veterinary medicine can be used for a wide range of tasks: starting from disease prevention to immunomodulation. This review is devoted to the use of fecal microbiota transplantation for different animal species. An analysis of scientific literature suggests that most researches into the topic describe the use of fecal microbiota transplantation as a method to treat diarrhea, which is a common disorder in animals. Interestingly, the technique has been successfully used to treat canine atopic dermatitis and monitor age-related changes in fish, thus, confirming the universal nature of this procedure. There are research projects when fecal microbiota transplantation demonstrated only partial effectiveness or no effectiveness at all. Scientific evidence suggests that the effectiveness of fecal microbiota transplantation depends on the delivery route and the donor, and the first factor may have a different impact on the therapy effectiveness depending on the animal species under study. The impact of the second factor on the success of transplantation has been most widely studied for calves. Further research is needed into effects of fecal microbiota transplantation on different animals and standards need to be developed to support large-scale and safe use of the technique for animals.

Keywords: review, fecal microbiota transplantation, microbiota, donor, recipient

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For correspondence: Heorhii Yu. Drobot, Postgraduate Student, Lecturer, Laboratory Assistant, Department of Bioengineering, Don State Technical University, 1 Gagarina sq., Rostov-on-Don 344000, Russia, *georgijdrobot@yandex.ru*

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Использование процедуры трансплантации фекальной микробиоты в ветеринарии (обзор)

Г. Ю. Дробот, С. К. Шебеко, А. М. Ермаков

ФГБОУ ВО «Донской государственный технический университет» (ДГТУ), пл. Гагарина, д. 1, г. Ростов-на-Дону, 344000, Россия

РЕЗЮМЕ

Трансплантация фекальной микробиоты представляет собой процедуру, при которой фекалии здорового донора вводятся в кишечник реципиента для восстановления микробного баланса и укрепления иммунной защиты. Главным образом трансплантация фекальной микробиоты обеспечивает увеличение бактериального разнообразия и повышение численности полезных микроорганизмов, что позволяет стабилизировать и поддерживать здоровый микробиом, ингибирующий рост патогенов. В ветеринарии трансплантация фекальной микробиоты рассматривается как потенциальная альтернатива традиционным антибиотикам в условиях нарастающей антибиотикорезистентности. Несмотря на отсутствие единых протоколов, исследования показывают, что процедура трансплантации фекальной микробиоты в ветеринарии может применяться для широкого спектра задач: от профилактики заболеваний до иммуномодуляции. Данная обзорная статья посвящена аспектам применения трансплантации фекальной микробиоты на разных видах животных. Согласно анализу научной литературы, большинство работ по данной теме описывают использование трансплантации фекальной микробиоты в качестве терапевтического средства против такого распространенного патологического состояния в ветеринарии, как диарея. Также интересно, что методика успешно применялась для лечения атопического дерматита у собак и мониторинга возрастных изменений у рыб, что подтверждает универсальность данной процедуры. Есть исследования, в которых трансплантация фекальной микробиоты проявляет эффективность частично или не проявляет вовсе. Научные данные свидетельствуют о том, что результативность трансплантации фекальной микробиоты зависит от таких факторов, как способ введения фекального материала и выбор донора, причем первый аспект может по-разному влиять на эффективность терапии в зависимости от вида исследуемого животного. Влияние второго фактора на успешность проведения трансплантации наиболее полно изучено для телят. Необходимы дальнейшие исследования механизмов воздействия трансплантации фекальной микробиоты на разных животных и разработка стандартов, которые могли бы обеспечить широкое и безопасное применение методики в ветеринарии.

Ключевые слова: обзор, трансплантация фекальной микробиоты, микробиота, донор, реципиент

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Для корреспонденции: Дробот Георгий Юрьевич, аспирант, преподаватель, лаборант кафедры биоинженерии ДГТУ, пл. Гагарина, 1, г. Ростов-на-Дону, 344000, Россия, *georgijdrobot@yandex.ru*

INTRODUCTION

In 1954, M. Bohnhoff et al. first described the well-known fact that the gut microbiota plays a fundamental role in immune defense as revealed by the study conducted on mice. Streptomycin-fed mice were much more susceptible to experimentally induced *Salmonella* infections than animals that were not administered antibiotics. This observation is explained by the fact that the antibiotic makes the mouse "vulnerable to the introduction of contaminating microorganisms by suppressing or eliminating some of its normal inhabitants" [1]. Today, scientists, particularly veterinarians, are facing a new challenge of antibiotic resistance, so the search is underway for alternative therapies that could replace antimicrobials. Fecal microbiota transplantation (FMT) may be among such new solutions.

There is no universally accepted definition of FMT [2]. The FMT technique involves introduction of fecal matter from a healthy donor into the intestine of a sick recipient to modulate or replace the intestinal microbiota [3]. FMT's history dates back to the 4th century, and since 2013, it has gained recognition, starting from the moment when the United States Food and Drug Administration approved it for treatment of recurrent and refractory *Clostridium difficile* infection in humans [4, 5].

In veterinary medicine, the transfer of gastrointestinal contents for therapeutic purposes has been used for centuries, for example in cattle (rumen transfaunation) [6]. There are reports on regurgitated cuds used for microbial transplantation and this technique was long used in Sweden to treat ruminal indigestion, and the cud beneficial effect even made it possible to refer to it as a "living thing" [7]. An important difference between FMT and transfaunation is the site where microbiota is collected from the gastrointestinal tract (i. e., rectum and rumen); however, conceptually and functionally both techniques are similar [8]. In small animal gastroenterology, intensive use of FMT procedure has only recently begun [8, 9].

The mechanisms underlying FMT therapy are not fully studied [8], however, it is assumed that FMT may increase bacterial diversity, supply bacteriocins and bacteriophages, and stimulate nutrient metabolism, including conversion of primary bile acids. Restoring eubiosis can enhance intestinal barrier mechanisms and bolster immunity [10]. In humane medicine, FMT is still being studied as an option to deal with various conditions such as chronic enteropathies (inflammatory bowel disease, irritable bowel syndrome), liver disease, obesity, metabolic syndrome, and neuropsychiatric disorders. However, most widely FMT is used to treat recurrent infection caused by *Clostridium difficile* resistant to standard therapy [10, 11].

Nevertheless, despite the extensive research into FMT, there are many issues to be clarified and for which there is no generally accepted opinion. For example, the specific FMT mechanism is not unique, but may have different efficacy depending on the disease and animal species [2].

There is still no universal consensus about another key point, i. e. how FMT-based therapies should be considered and legally regulated. Depending on the country, FMT can be considered, for example, as a biological agent (USA), a medicinal product (UK) or as a cell/tissue transplant (Italy) [2]. Finally, although this procedure is considered generally safe, the potential short-term and especially medium- and long-term risks that may be associated with FMT still need to be carefully studied [2, 12, 13].

GENERAL FMT PROCEDURE

The FMT procedure is used in veterinary medicine to achieve the following goals: to reduce pathogens, restore healthy microbiome and ultimately improve overall animal health condition. According to M. C. Niederwerder, the key effect of FMT is associated with an increase in bacterial diversity and an increase in the number of beneficial microorganisms, thus, stabilizing and maintaining a healthy gastrointestinal microbiocenosis and inhibiting the growth of pathogens [8].

It is generally accepted that commensal bacteria in stool are the key component that ensures FMT efficacy. However, other fecal components such as viruses, fungi, immunoglobulins and bacterial metabolites also play an important role in FMT. Preserving these components is crucial during feces preparation [14].

Fecal microbiota transplantation includes several mandatory steps.

1. Donor selection. The donor must be healthy, free of gastroenterological or infectious conditions and shall not have be exposed to antibiotics within the previous 6 months. Hui Y. et al. emphasized the key role of the donor for successful FMT outcome, when recipients from one particular donor were cured of necrotizing enterocolitis and had higher relative lactobacilli counts [15]. Some researchers also refer to the key importance of the thorough pre-FMT examination with the purpose to detect pathogens in feces [2, 3, 12, 16]. Typically, the animal donor is selected based on its medical history and following tests for a wide range of infectious pathogens. In humane medicine, the universal stool bank model is often applied, since it allows using pre-selected and frozen preparations for FMT [2]. This approach reduces costs due its large scales and improves safety due to standardized procedures and monitoring.

2. Preparing fecal matter solution. Donor material is usually mixed with saline or water (sometimes glycerol is added) and then filtered to remove large particles. This material can be stored frozen, but freshly prepared suspensions are more preferable for tests in animals because they preserve microbial diversity and microbiota much better. In addition, some preparations are commercially available: either for self-filling capsules and ingestion (mainly for humans) or as microbiome tablets for small animals, which may contain fresh or freeze-dried preparations derived from intestinal microbiota [9].

3. Transplantation procedure. Administering the on-site prepared suspension via enema [17, 18, 19], endoscopy [20, 21], nasogastric tube [3, 22, 23], or orally [24, 25, 26, 27].

There is still no strictly established and approved FMT procedure; therefore, it needs to be adapted to specific cases and conditions.

FMT FOR ANIMALS

Nowadays FMT studies in humans are more specific and detailed than in animals, particularly in dogs. Nevertheless, the gut microbiota of dogs closely resembles the human gut microbiota [28]. Accordingly, bacteria, viruses, bacterial fragments, fungi, mucin, immunoglobulin A (IgA) and bacterial metabolites may be important components of FMT both in dogs [14] and in humans [29].

Currently, there are three main directions of FMT use in animals. FMT in animals is currently applied in three main directions: therapeutic, prophylactic and stimulation of pathogen-specific immunity [8].

The FMT therapeutic use is necessary when the goal is to treat clinical signs or eliminate chronic diseases. FMT-based prophylaxis may be a useful part of preventive medicine since it boosts beneficial bacteria before the body is exposed to pathogens. Finally, FMT can be used as an immunostimulant just like vaccination, where transplant material stimulates pathogen-specific immunity to enhance immunoglobulin transfer.

Most scientific sources on FMT are devoted to its therapeutic effect on the evident clinical signs after the diagnosis is made, although its preventive effect and immunogenetic use were primarily tested in pigs and poultry.

As publicly available sources suggest, FMT has been tested in different animal species: fish, mice, chickens, cats, dogs, monkeys, pigs, calves, horses. It can be used as an independent procedure, as well as in combination with other therapeutic tools. The number of FMT iterations also varies across different experiments, ranging from single injections to dozens, which confirms the lack of a unified procedure or of a standardized technique for animals.

Systematized and generalized information and literature sources within the review scope [13, 15–19, 21–27, 30–44] are presented in Table in the Additional Files section at: https://doi.org/10.29326/2304-196X-2024-13-4-314-321

FMT in pets. FMT effects have been best studied in dogs (see Table) to mainly treat gastroenterological disorders together with other diseases, such as atopic dermatitis [25]. It is noteworthy that FMT has proven to be an effective method that makes it possible to achieve complete cure or significantly improve the recipients condition in all mentioned cases. The FMT procedure was mainly performed independently, however, there were a number of exceptions [17, 21, 24, 44], when the tool was applied together with other methods. The successful use of this independent procedure in most cases indicates the possibility of simple FMT standardization which will require no extra costs. Notably, most pet experiments involved a single FMT procedure with successful outcomes, however, during the experiment held by C. A. Rojas et al. the observed cats received totally 50 capsules [31]. As for the route of FMT administration to pets, faecal material is inserted rectally and orally, via a tube.

The key gastrointestinal metabolites that regulate host immunity and maintain immune homeostasis are short-chain fatty acids (SCFAs), which affect lipid metabolism [37]. It is worth noting that when FMT is done orally, SCFAs are rapidly absorbed and oxidized, therefore, enemas or colonoscopy are more preferable. At the same time, oral administration of fecal matter may allow bacteria to colonize the small intestine and ileum, and may allow metabolites that are produced by enteric bacteria (secondary bile acids), to penetrate into the small intestine and ileum. Therefore, combining both FMT administration routes (oral and enema/colonoscopy) is the most reasonable approach [14].

FMT in pig farming. Tests in pigs provide extensive data on FMT effectiveness from different perspectives which include prevention of intestinal diseases, improved feed conversion ratio and boosted immunity [15, 32, 33, 34, 35]. In most experiments, fecal suspension was administered to pigs via nasogastric or rectal tubes. At the same time, A. Brunse et al. (2019) studied the combined administration of the matter to preterm piglets, which showed that this administration route was associated with a higher risk of gut colonization with pathogenic bacteria ultimately resulting in a mortality increase [32]. Whereas purely rectal FMT proved to be effective in reducing the frequency of necrotizing enterocolitis without any negative consequences. This observation contrasts with the conclusion made by K. Li et al. regarding dogs. Perhaps combined administration is not the most effective transplantation route for all animal species [14].

In 2021, A. Brunse et al. conducted a research, where piglets received antibacterial drugs together with FTM. It partially restored microbial diversity and reduced the number of antibiotic-resistant bacteria such as *Enterobacter cloacae* and *Pseudomonas aeruginosa*. The FMT procedure alone (without any prior antibiotic therapy) proved to be more effective to restore healthy microbiota in piglets' large intestines. Concentrations of such cytokines as IL-6 and CXCL-8 were higher in the group that received just FMT treatment ($p < 0.05$), unlike the other group that was treated using a combined approach. Thus, the combined use of antimicrobials and FMT turned out to be less effective, which suggests there are antagonistic interactions between them [33].

As mentioned above, the correct choice of a donor is one of the key factors behind the FMT success. Thus, piglet experiments show that only the matter from a particular donor reduces the risks of necrotic enterocolitis. PERMANOVA tests (Multivariate Analysis of Variance) conducted between groups at the level of microbiota genera and species ($R^2 = 0.45$ for 16S rRNA; $p = 0.001$), revealed that the microbiome exposed to the fecal matter from this donor differed significantly from other groups. There was a decrease in the concentration of *Enterobacter cloacae*, *Staphylococcus aureus* and other pathogens, and a relative increase in *Limosilactobacillus reuteri* and *Lactobacillus crispatus* counts [15]. Evidence suggests that FMT is effective in treating porcine viral diseases. Thus, M. C. Niederwerder et al. describe how the procedure was successfully used to control circovirus disease and porcine reproductive respiratory syndrome. It contributed to changes in the intestinal microbiocenosis, reducing the count of opportunistic bacteria such as *Vibrionaceae* and *Spirochaetaceae*, as well as increasing the level of antibodies in infected piglets [35].

Feed conversion ratio is a critically important economical parameter in pig farming. As demonstrated by the related research, FMT in sows increases the efficiency of their piglets in converting food into body mass [34]. These animals showed better feed conversion ratios, i.e. reduced residual feed intake and increased microbial diversity. It is due to an increase in bacteria involved in fiber fermentation which account for improved feed digestibility. The inulin addition also contributed to an increase in beneficial bacteria counts and decreased levels of certain pathogens (for example, *Chlamydia*), although this did not lead to significant weight gain. Thus, FMT combined with prebiotics can be an effective strategy to increase productivity in pig farming.

FMT in poultry farming. There are a number of studies on successful FMT use in chickens. Such disorders as intestinal infections [39], changes in circadian rhythms [36] were studied, as well as FMT effect on growth, immune balance [38] and lipid metabolism in birds [37]. Pang J. et al. studied FMT effectiveness for chickens infected with *Campylobacter jejuni*. They got infected either by direct introduction of bacterial suspension into the body or as a results of housing healthy chickens together with the infected ones. FMT turned out to be effective in reducing *C. jejuni* colonization during direct infection. *C. jejuni* counts in this group were reduced by 2.5; 1.2 and 1.7 times compared to the control group on day 5, 10 and 15, respectively ($p < 0.0001$). The number of *Butyricimonas*, *Parabacteroides* and *Parasutterella* colonies grew, thus, enhancing resistance to pathogen colonization. On the contrary, FMT did not have a significant effect in chickens infected via a contact with the sick poultry [39]. This result suggests that the procedure lacks flexibility, and deeper research is required, since the second variant of infection (through contact with the infected poultry) is the most real in poultry farming.

As in pig farming, FMT can help improve economic development of poultry farming. As shown in research conducted by Z. Ma et al., the weight of chickens in the group that received FMT was 10.6% higher than in the control group (627.4 g vs 567.3 g; $p < 0.0001$). The FMT importance for the recipient's immune system was also demonstrated: lactobacilli found in the intestine enhanced tryptophan metabolism, which stimulates Treg cells and suppresses Th17, thus, boosting immune response, reducing inflammation, and, therefore, promoting chicken growth [38]. Excessive fat accumulation in broilers adversely affects poultry farming economics. Impact of fecal microbiota transplantation on lipid metabolism has also been studied [37]. The FMT stimulated growth of *Oscillospira* and *Streptococcus* bacteria, which are known for their ability to produce SCFAs associated with a decrease in fat mass. Thus, FMT contributed to reduction of abdominal fat deposits, confirming the importance of gastrointestinal microbiocenosis in lipid metabolism. Another research was focused on using FMT to correct negative effects coming from the disrupted circadian rhythms in chickens [36]. At the same time, FMT significantly improved the level of mitochondrial DNA and decreased oxidative stress, normalizing the expression of genes associated with the cell cycle. Changes were observed in hormone- and inflammation-associated genes when circadian rhythms were disrupted, but they returned to normal after transplantation.

FMT in cattle. Researches on calves showed that FMT is more effective than antibiotics to restore beneficial intestinal microbiota (*Bacteroides* and *Firmicutes*) which increases the SCFAs levels and reduces diarrhea symptoms [40]. FMT led to an active growth in calves, thus, confirming FMT potential to increase livestock productivity. Islam J. et al. conducted a large-scale analysis (metagenomic, metabolomic and biochemical) to identify factors contributing to FMT effects and to improve the donor and recipient selection procedure. The procedure was successful in 70% of cases and the success was proved to be dependant a lot on amino acids and SCFAs [16]. Representatives of the *Veillonellaceae* family and the *Selenomonas* genus in donors and recipients were considered as key microorganisms behind the FMT effectiveness, whereas sporobacteria (*Sporobacter*) have been proposed as a marker of an optimal donor. The research conducted by Y. Li et al. was not focused on the FMT procedure itself, but it was devoted to studying the effect of two strains of *Lactobacillus reuteri* L81 and *Lactobacillus johnsonii* L29 isolated from cow feces after FMT on growth, immunity and intestinal barrier function of weaned calves. As a result, *L. reuteri* L81 and *L. johnsonii* L29 increased calve growth rates, reduced the frequency of diarrhea, boosted immunity and reduced markers of intestinal permeability [45].

FMT in horses. Research conducted by D. P. M. Dias et al. showed that FMT is a highly effective tool to treat acute colitis in horses, since just within one day after a single procedure clinical symptoms completely disappeared in all the recipients. This method turned out to be faster and cheaper than traditional antibiotic therapy, moreover, no side effects such as dysbiosis or antibiotic resistance were observed [22]. In another research conducted by Y. Kinoshita et al., the FMT application did not lead to a successful outcome in horses with metronidazole-induced intestinal dysbiosis [23].

FMT in other animal species. The overall effect of FMT on the recipient's gut microbiota has been studied in a number of experiments. One of them, conducted by C. N. Ross and K. R. Reveles, showed that FMT is safe for common marmoset (*Callithrix jacchus*), which is confirmed by the absence of side effects, although microflora changes directly depended on the basic intestinal condition of the recipients than on the microbiota of donors. Variations in relative abundances of bacterial taxa demonstrate FMT potential to ensure stable changes in the intestinal microbiome of common marmosets [43]. For experiments in mice, domestic and wild pigs were selected as donors. The best effect on intestinal microbiocenosis was demonstrated in the mice who had FMT from wild pigs and sticked to a diet rich in dietary fiber. There was also an increase in concentration of beneficial fatty acids (nicotinic) [44].

Research on fish was also conducted. Thus, Z. Han et al. focused on FMT ability to accelerate restoration of intestinal microbiota in koi carp with florfenicol-induced dysbiosis [41]. The researchers demonstrated effectiveness of this procedure, accompanied by restored levels of beneficial bacteria such as *Lactobacillus*, *Bifidobacterium*, *Bacteroides* and *Faecalibacterium*. It was also determined that such metabolites as aromatic amino acids and glutathione compounds play a key role in normalizing intestinal metabolism after dysbiosis. Other experiments were devoted to the FMT effect on the life cycle and health status of the middle-aged African fish *Nothobranchius furzeri* who received FMT from the young donors [42]. As a result, the life span of the FMT fish recipients increased by 37% as compared to the control group (Logrank test, $p < 0.001$). Such bacterial genera as *Exiguobacterium*, *Planococcus*, *Propionigenium* and *Psychrobacter*, that are typical for young fish, remained in the aging fish who received FMT. The average distance covered by the FMT-treated aging fish within 20 minutes was 15% longer compared to the control group, thus, suggesting that they were physically as active as the young stock.

USING FMT: CHALLENGES AND PROSPECTS

Despite promising results, many aspects of FMT effectiveness and safety remain understudied, especially in the veterinary field, where there are still no standardized FMT procedures [9]. The lack of variety among strains included into the fecal matter used for FMT does not allow to classify FMT as a probiotic [2, 46]. Therefore, further FMT development is primarily associated with the possibility to develop targeted microbial communities that will allow to produce "clean" products without potentially hazardous microorganisms, which result in standardization and will increase safety of the method [8].

Fecal microbiota transplantation has a number of undeniable advantages (support of the mucosal immune system, mucosal barrier and homeostasis, colonization resistance) [3], but now there are not so many peer-reviewed scientific papers that reveal the true value of FMT in treatment of gastrointestinal diseases. Although the valuable data on FMT design, disease, choice of donor and recipient, FMT procedure, and following observations are publicly available, they are limited, thus, more research is needed [24]. In addition, the choice of donor and recipient in the veterinary field is likely to vary greatly depending on geographical differences in infectious and non-communicable gastrointestinal diseases, as well as other factors [8, 9].

Fecal microbiota transplantation has great prospects in livestock sector, but there are still some challenges in place. First, it is critically important to chose the administration route and the donor since these factor directly impact the procedure outcome [15, 32]. Although the FMT use for treatment of viral infections demonstrates positive results [35], it also requires additional testing on large samples and under different conditions. FMT may not always be considered as a highly effective method in real conditions. For example, as the study conducted by J. Pang et al. shows FMT is effective only in case of direct administration to recipients, and when recipients get infected via a contact with sick individuals, clinical indicators do not improve after FMT from the donor [39]. In another case, the FMT in horses did not lead to a successful outcome either [23]. This requires a detailed search for the underlying reasons.

The good potential of further FMT use in livestock sector is confirmed by the research that demonstrates how effectively the procedure increases livestock productivity [34, 37, 38]. Experiments in fish are also interesting, where FMT has proven to be a promising tool to treat intestinal diseases [41] and as an approach that promotes the rejuvenation of aging individuals [42].

Thus, although FMT, as an independent tool, has many times proven its high effectiveness in treating a number of gastrointestinal diseases and other indirectly related disorders, further research is needed to understand the exact mechanisms of transplantation and to develop standard operational procedures that should both increase FMT effects and reduce risks for recipients.

CONCLUSION

Research on FMT use for animals demonstrated its potential as an effective preventive, therapeutic and immunomodulatory intervention. The results show that FMT is capable of restoring healthy intestinal microbiota of the recipient, which is especially important under conditions of antibiotic resistance and the increasing need for alternative approaches to treat animal diseases. Although the procedure has already demonstrated positive results for some animal species, it is still required to standardize protocols and to study more precisely its effect on the body, so that in future it will be possible to classify FMT as a probiotic approach in the veterinary medicine.

The FMT success primarily depends on the folowing key factors: a pathogen-free donor shall be carefully selected; and the fecal material shall be properly prepared and an adequate administration route shall be chosen depending on the animal species. In most successful cases of FMT use, it was a procedure applied alone, however, its combination with, for example, prebiotics, also proved to be highly effective.

Positive FMT results are observed in treating both bacterial and viral animal infections. The FMT in farm animals confirms its potential for improving feed conversion rate and weight gain, which is of economic significance in livestock sector. The tests in fish have demonstrated the FTM "anti-ageing" potential.

The published data provide confirming evidence that FMT can be considered as a potential alternative to antibiotic therapy for animals, however, more extensive research is required taking into account unique features of different animal species.

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INFORMATION ABOUT THE AUTHORS / ИНФОРМАЦИЯ ОБ АВТОРАХ

Heorhii Yu. Drobot, Postgraduate Student, Lecturer, Laboratory Assistant, Department of Bioengineering, Don State Technical University, Rostov-on-Don, Russia;
https://orcid.org/0009-0007-7884-0041, georgijdrobot@yandex.ru

Дробот Георгий Юрьевич, аспирант, преподаватель, лаборант кафедры биоинженерии ДГТУ, г. Ростов-на-Дону, Россия; *https://orcid.org/0009-0007-7884-0041, georgijdrobot@yandex.ru*

Sergei K. Shebeko, Dr. Sci. (Pharmacology), Professor, Head of Department of Biotechnical and Medical Systems and Technologies, Don State Technical University, Rostov-on-Don, Russia; *https://orcid.org/0000-0001-9350-7588, shebeko_sk@mail.ru*

Alexey M. Ermakov, Dr. Sci. (Biology), Professor, Dean of the Faculty of Bioengineering and Veterinary Medicine, Don State Technical University, Rostov-on-Don, Russia; *https://orcid.org/0000-0002-9834-3989, amermakov@ya.ru*

Шебеко Сергей Константинович, д-р фарм. наук, профессор, заведующий кафедрой биотехнических и медицинских систем и технологий ДГТУ, г. Ростов-на-Дону, Россия; *https://orcid.org/0000-0001-9350-7588, shebeko_sk@mail.ru*

Ермаков Алексей Михайлович, д-р биол. наук, профессор, декан факультета биоинженерии и ветеринарной медицины ДГТУ, г. Ростов-на-Дону, Россия; *https://orcid.org/0000-0002-9834-3989, amermakov@ya.ru*

Contribution: Drobot H. Yu. – working with literature; text preparation, analysis and generalization; Shebeko S. K. – scientific consulting, concept of presenting materials; Ermakov A. M. – administration, text editing.

Вклад авторов: Дробот Г. Ю. – работа с литературой, подготовка текста, анализ и обобщение; Шебеко С. К. – научное консультирование, концепция представления материалов; Ермаков А. М. – администрирование, редактирование текста.