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FECAL MICROBIOTA TRANSPLANTATION IN THE TREATMENT OF ASTROVIRUS INFECTION IN A RECIPIENT OF AN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT: A CLINICAL CASE

J.A. Bespyatykh[1, 2, 3], A.V. Gospodarik[1], E.A. Zhuravel[4], G.Z. Seregin[4], A.V. Komarova[1, 3], S.S. Esiev[1], G.O. Bronin[4], Ya.D. Shansky[1]

[1] Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine, Moscow, Russian Federation

[2] N.A. Semashko National Research Institute of Public Health, Moscow, Russian Federation

[3] Mendeleev University of Chemical Technology of Russia, Moscow, Russian Federation

[4] Morozov Children's Municipal Clinical Hospital, Moscow, Russian Federation

Background: *Secondary immunodeficiency in recipients after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the pediatric practice is often accompanied by bacterial and viral infections of the gastrointestinal tract (GIT), resistant to conventional therapy. Fecal microbiota transplantation (FMT) promotes intestinal recolonization and eradication of gastrointestinal symptoms.* ***Clinical case description:*** *A 2.5-year-old patient underwent allo-HSCT from a haploidentical related donor (father) as a part of the treatment of acute myeloid leukemia. A month after the last procedure, diarrhea (up to 10 times a day) and abdominal pain appeared. The astrovirus RNA and Clostridium difficile toxin A were detected in the feces. The FMT was prescribed. After two FMT procedures, the intestinal syndrome leveled out, and the tests for the astrovirus RNA and clostridial toxins were negative. The content of cholic and, in particular, deoxycholic acids, as well as their conjugates with glycine and taurine, in the feces increased; the acetic acid content increased with a simultaneous decrease in the level of propionic acid, which indicates the restoration of the intestinal microbiota's functional potential.* ***Conclusion:*** *FMT contributes to the restoration of the normal intestinal microflora, the elimination of clostridial toxins, enteroinvasive E. coli and astrovirus infection in allo-HSCT recipients, as evidenced by the indicators of the intestinal microbiota activity, and can be used in allo-HSCT recipients with infections refractory to conventional therapy.*

Keywords: *allogeneic hematopoietic stem cells transplantation; bile acids; short chain fatty acids.*

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BACKGROUND

Infectious gastrointestinal tract lesions are prevalent in children. For instance, acute gastroenteritis causes diarrhea in 1.7 billion children aged <5 years [1]. Bacterial infections account for ~30% of cases. A well-studied example is hospital-acquired clostridial infection associated with antibiotic use, caused by *Clostridioides* (formerly *Clostridium*) *difficile* A and B toxins [2]. Gastroenteritis is often caused by viruses, including *Norovirus, Rotavirus, Adenovirus, Sapovirus*, and *Astrovirus* [3]. This is true in 70% of cases, even in immunosuppressive conditions such as allogeneic hematopoietic stem cell transplantation (allo-HSCT). Viral etiology accounts for 20% of all episodes of HSCT-associated diarrhea [4]. However, only 4.2% of cases of acute gastroenteritis in children are associated with *Astrovirus* infection [5], making it difficult to determine an optimal therapy regimen for viral gastrointestinal tract diseases.

Fecal microbiota transplantation (FMT) is an effective method of intestinal recolonization that can reduce the antibiotic resistance of pathogenic microbiota. This makes it a suitable method for preventing and treating life-threatening complications in immunocompromised patients [4, 6]. Previous studies have demonstrated the efficacy of FMT in treating intestinal infections caused by *C. difficile* [7]. However, its effectiveness in treating viral diseases has not been sufficiently studied.

CLINICAL CASE

Patient

Patient E, a 2.5-year-old, was diagnosed with acute myeloid leukemia, M1 morphological variant, t(8;21) (RUNX1-RUNX1T1), based on morphocytochemical,

ТРАНСПЛАНТАЦИЯ ФЕКАЛЬНОЙ МИКРОБИОТЫ ПРИ АСТРОВИРУСНОЙ ИНФЕКЦИИ У РЕЦИПИЕНТА АЛЛОГЕННОЙ ТРАНСПЛАНТАЦИИ ГЕМОПОЭТИЧЕСКИХ СТВОЛОВЫХ КЛЕТОК: КЛИНИЧЕСКИЙ СЛУЧАЙ

Ю.А. Беспятых[1, 2, 3], А.В. Господарик[1], Е.А. Журавель[4], Г.З. Серёгин[4], А.В. Комарова[1, 3], С.С. Есиев[1], Г.О. Бронин[4], Я.Д. Шанский[1]

[1] Федеральный научно-клинический центр физико-химической медицины имени академика Ю.М. Лопухина, Москва, Российская Федерация

[2] Национальный научно-исследовательский институт общественного здоровья имени Н.А. Семашко, Москва, Российская Федерация

[3] Российский химико-технологический университет имени Д.И. Менделеева, Москва, Российская Федерация

[4] Морозовская детская городская клиническая больница, Москва, Российская Федерация

Обоснование. *Вторичный иммунодефицит у реципиентов аллогенной трансплантации гемопоэтических стволовых клеток (алло-ТГСК) в педиатрической практике часто сопровождается бактериальными и вирусными инфекциями желудочно-кишечного тракта, резистентными к конвенциональным методам терапии. Трансплантация фекальной микробиоты способствует реколонизации кишечника и купированию симптомов поражения желудочно-кишечного тракта.* ***Описание клинического случая.*** *Пациентке 2,5 лет в рамках терапии острого миелоидного лейкоза проведена алло-ТГСК от гаплоидентичного родственного донора (отца). Через месяц от последней процедуры появились боли в животе, жидкий стул до 10 раз в сутки. В кале обнаружена РНК астровируса, определялся положительный клостридиальный токсин А. Принято решение о трансплантации фекальной микробиоты. После двух процедур нивелирован кишечный синдром, анализы на РНК астровируса и клостридиальные токсины отрицательные. Увеличилось содержание холевой и особенно дезоксихолевой кислот в кале, а также их конъюгатов с глицином и таурином; увеличилось содержание уксусной кислоты с одновременным снижением уровня пропионовой кислоты, что указывает на восстановление функционального потенциала кишечной микробиоты.* ***Заключение.*** *Трансплантация фекальной микробиоты способствует восстановлению нормальной микрофлоры кишечника, устранению клостридиальных токсинов, энтероинвазивной кишечной палочки и астровирусной инфекции у реципиентов алло-ТГСК, что подтверждается показателями активности микробиоты кишечника, и может быть использована у реципиентов алло-ТГСК с течением инфекций, рефрактерных к конвенциональному лечению.*

Ключевые слова: *астровирус; аллогенная трансплантация гемопоэтических стволовых клеток; желчные кислоты; короткоцепочечные жирные кислоты.*

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immunological, and molecular-genetic methods of bone marrow cell research.

Laboratory and instrumental diagnosis

The patient's feces were evaluated for the presence of pathogenic intestinal flora, including *Shigella* spp., *Salmonella* spp., and *Campylobacter* spp., and viruses such as *Adenovirus F, Norovirus* 2nd genotype, *Rotavirus A*, and *Astrovirus*. Additionally, *C. difficile* A and B toxins were assessed before and after FMT using polymerase chain reaction (PCR). Moreover, bacteriological analysis of feces, including determination of antibiotic sensitivity, was conducted (Table 1). Furthermore, the patient's feces were assessed for qualitative and quantitative composition of short-chain fatty acids

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Table 1

Results of the fecal analysis for the presence of infectious agents (bacterial and viral)

Index	Before fecal microbiota transplantation	After fecal microbiota transplantation
Clostridioide difficile toxin A	**Found**	Not found
Clostridioide difficile toxin B	Not found	Not found
Viral infections		
Rotavirus	Not found	Not found
Norovirus	Not found	Not found
Adenovirus	Not found	Not found
Astrovirus	**Found**	Not found
Bacterial infections		
Shigella spp.	Not found	Not found
Salmonella spp.	Not found	Not found
Campylobacter spp.	Not found	Not found
Enteroinvasive *Escherichia coli*	**Found**	Not found
Escherichia coli	Found (IV degree of contamination)	Found (IV degree of contamination)
Klebsiella pneumoniae	Found (II degree of contamination)	Found (IV degree of contamination)
Candida albicans	**Found (III degree of contamination)**	Not found
Staphylococcus epidermidis	Found (III degree of contamination)	Found (IV degree of contamination)
Streptococcus mitis	Not found	Found (IV degree of contamination)
Streptococcus oralis	Not found	Found (IV degree of contamination)

(SCFAs) and bile acids as indicators of the intestinal microbiota. Bile acids were analyzed using high-performance liquid chromatography with tandem mass spectrometric detection, whereas SCFAs were examined using gas–liquid chromatography with flame ionization detection [8].

The concentrations of free and conjugated bile acids and the total and individual concentrations of SCFAs in feces were evaluated. Table 2 shows the concentrations of 13 bile acids. The following bile acids were identified: taurocholic acid (TCA), glycoursodeoxycholic acid (GUDCA), taurochenodeoxycholic acid, glycocholic acid, tauroursodeoxycholic acid, glycochenodeoxycholic acid, cholic acid, chenodeoxycholic acid, taurodesoxycholic acid, deoxycholic acid (DCA), ursodeoxycholic acid, taurolithocholic acid, and lithocholic acid.

Table 3 presents the concentrations of SCFAs, including acetic, propionic, butyric, isobutyric, valeric, isovaleric, and caproic acids and their total content, anaerobic index, and the ratio of isomers and homologs of SCFAs ($isoC_n/C_n$).

Treatment and condition dynamics

Polychemotherapy was performed according to the ALL-BFM-2004 protocol after obtaining informed parental consent. Clinical and hematologic remission was achieved after the first course of polychemotherapy. However, a study of minimal residual disease (MRD) showed that the chimeric transcript RUNX1-RUNX1T1 persisted in the bone marrow after three courses of polychemotherapy, indicating a refractory course of the disease. Therefore, allo-HSCT was performed. A haploidentical donor, the child's father, was selected. Comprehensive pretransplantation examination of both donors and recipients revealed no absolute contraindications to allo-HSCT.

Conditioning (per course) included treosulfan (42 g/m^2), fludarabine (150 mg/m^2), etoposide (60 mg/kg), and rituximab (375 mg/m^2). Unmanipulated peripheral stem cells were used as the graft source. The volume of material was 70 ml, with a leukocyte count of 232×10^9/l, $CD34^+$ count of 6×10^6/kg, and $CD3^+$ count of 26.5%. The transplantation was well tolerated by the child.

Table 2

Concentration of bile acids in the recipient's feces

Bile acids	Content. μg/g	
	Before fecal microbiota transplantation	After fecal microbiota transplantation
Taurocholic acid	-	0.11
Glycoursodeoxycholic acid	0	0.27
Taurochenodeoxycholic acid	-	-
Glycocholic acid	-	-
Tauroursodeoxycholic acid	-	0.15
Glycochenodeoxycholic acid	0	-
Cholic acid	-	0.27
Chenodeoxycholic acid	-	-
Taurodeoxycholic acid	-	-
Deoxycholic acid	0	1.56
Ursodeoxycholic acid	-	-
Lithocholic acid	-	-
Taurolithocholic acid	-	-

Table 3

Concentrations of short-chain fatty acids in the recipient's feces and related parameters

Analyzed parameter	Content, μg/g	
	Before fecal microbiota transplantation	After fecal microbiota transplantation
Acetic acid	1.599	4.508
Propionic acid	0.421	0.258
Isobutyric acid	0.032	0.036
Butyric acid	0.158	0.183
Isovaleric acid	0.056	0.041
Valeric acid	0.063	0.031
Caproic acid	0.044	0.054
Total	2.373	5.110
Ratio of the total content of branched-chain acids to unbranched-chain acids, $isoC_n/C_n$	0.039	0.015
Anaerobic index	0.362	0.098

Prophylaxis for the graft versus host reaction after allo-HSCT includes tacrolimus and mycophenolate mofetil starting on day 1 and cyclophosphane at a dose of 100 mg/kg per course on days 3 and 4.

During the early post-transplantation period, the patient experienced several complications, including grade III febrile neutropenia, grade II dermatological toxicity, grade II gastrointestinal toxicity, and grade IV hematologic toxicity. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events 5.0 scale. Stool rotavirus was detected once by PCR during febrile neutropenia. All complications were treated with complex accompanying therapy.

Engraftment of the graft was achieved on day 16. The patient was discharged from the hospital on day 19 without any signs of diarrhea or infection. On day 30, clinical and hematologic remission was achieved, along with complete donor chimerism and MRD-negative status (as evidenced by the absence of RUNX1-RUNX1T1 expression in the bone marrow).

Since day 30, the child has been experiencing abdominal pain and diarrhea. Stool examination revealed the presence of *Astrovirus* and confirmed the presence of clostridial toxin A. Infusion therapy was administered to correct electrolyte disorders, as well as substitution transfusions of 20% albumin

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solution. Combined antimicrobial therapy was used, including a combination of broad-spectrum antibiotics such as meropenem, metronidazole, vancomycin, sodium colistimethate, rifaximin, antimycotics such as caspofungin and amphotericin B, and antiviral drugs such as acyclovir. Additionally, transfusions of 10% intravenous immunoglobulin were performed. The child's overall condition improved; however, she continued to have liquid stools up to 10 times a day with a total volume of up to 1.5 liters per day. Thus, FMT was conducted.

FMT, in suspension form, was performed using liquid fecal material obtained from a healthy female donor, aged 38, following the method previously described [9]. The donor underwent preliminary laboratory examinations, including basic hematologic and biochemical blood tests and tests for hepatitis B and C, human immunodeficiency virus, and syphilis. Additionally, general urinalysis, coprogram, fecal analysis for hidden blood, protozoa, and helminth eggs, bacterial stool culture, as well as fecal PCR for pathogenic intestinal flora, presence of *C. difficile* A and B toxins, and presence of genetic markers of drug resistance were conducted. The material was collected while the investigated parameters were within normal values.

The patient underwent FMT without any complications. The microbial community was administered via a nasogastric tube. On day 3 after the procedure, a decrease was noted in the frequency and volume of defecation; however, the consistency of the stool remained liquid. At 1-week follow-up after FMT, the analysis for *Astrovirus* in the feces was positive. A second FMT procedure was performed, after which the intestinal syndrome subsided.

Outcomes and prognosis

Repeated examinations of the patient's fecal samples did not detect *Astrovirus* and clostridial toxins. The child was discharged from the hospital and observed on an outpatient basis for 8 months. No episodes of diarrhea were noted during this period.

Currently, the graft is functioning, and donor chimerism is preserved, indicating remission. Long-term active follow-up in the transplantation clinic for at least 1 year followed by vaccination once full immune reconstitution is achieved is planned.

DISCUSSION

Microbial and viral antigens from the intestinal microbiota play a crucial role in the proper development and function of the immune system, particularly during childhood [10]. The success of allo-HSCT relies on the effective treatment of HSCT-associated diarrhea, which can be fatal. This diarrhea is caused by the interaction between the patient's immune system, which is disrupted during this period, and the intestinal ecosystem, which is severely altered by the use of multicomponent antimicrobial therapy [10].

In this case, FMT demonstrated a positive effect in treating infectious intestinal damage following allo-HSCT caused by *Astrovirus* infection. The patient's general condition improved, intestinal syndrome was eliminated, and normalization of intestinal microflora was observed based on bile acids and SCFA indices. The PCR study results indicate that the first FMT was effective in treating clostridial infection [11], including in children [12], as *C. difficile* toxin A was not detected in the patient's feces. Moreover, enteroinvasive *Escherichia coli* were not detected after FMT, and a significant decrease was found in the bacterial contamination of *Klebsiella pneumoniae*.

The significance of FMT in *Astrovirus* infection is because this pathogen is responsible for necrotizing enterocolitis, which has a high mortality rate in newborns [5]. *Astrovirus* infection is a cause of intestinal syndrome in patients with immunodeficiency, including after allo-HSCT [5, 13]. In the present case, *Astrovirus* RNA was undetectable after repeated FMT. A previous study has shown the efficacy of FMT in restoring gut microbiota in patients with HIV [14]. In preclinical studies, FMT led to a more rapid favorable outcome in parvovirus diarrhea [15]. This clinical case presents the first successful application of FMT for *Astrovirus* infection after allo-HSCT, which has a rare incidence [13, 16].

Gut microbiota dysfunction reduces primary conjugated bile acids transforming into secondary bile acids. This could explain the low levels of individual bile acids found in the recipient (Table 2) [17]. After therapy, an increase was observed in the primary (CA) and secondary (DCA) bile acid levels as well as in taurine-conjugated bile acid (TCA, TUDCA) and glycine-conjugated bile acid (GUDCA) concentrations (Table 2).

DCA is a powerful antimicrobial agent that can reduce inflammation in cases of microbiota dysfunction [18]. Increased DCA levels in the recipient after FMT indicate improved gut microbiota function [17]. The presence of conjugated bile acids in feces may indicate reduced activity or low numbers of *Firmicutes* and *Bacteroidetes* that regulate bile acid deconjugation [19].

The recipient's SCFAs assay showed a significant increase in acetic acid levels, slight decrease in propionic acid, less significant increase in butyric acid, isobutyric acid, and caproic acid levels, as well as a decrease in valerian and isovaleric acids (Table 3). These changes may indicate an improvement in gastrointestinal function. Butyrate plays a critical role in regulating immune response and exhibiting anti-inflammatory activity among SCFAs [20, 21]. However, the insignificant change in butyrate levels after FMT and the lack of experimental data do not allow us to draw conclusions about its contribution to changes in the functioning of the recipient microbiota.

CONCLUSIONS

This study presents the first clinical evaluation of FMT efficacy in the treatment of *Astrovirus* infection of the gastrointestinal tract after allo-HSCT, including SCFAs and bile acid indices. This study demonstrated a decrease in the bacterial load of *Klebsiella pneumoniae* and complete elimination of *Candida albicans* and enteroinvasive *Escherichia coli*. Furthermore, the presence of *Streptococcus mitis* and *Streptococcus oralis* following FMT may indicate a gradual restoration of the normal microflora of the gastrointestinal tract.

Based on the available literature and our own studies, it can be assumed that FMT has a positive effect on the treatment of allo-HSCT recipients, including those with *Astrovirus* infection of the gastrointestinal tract. The improvement in SCFA and bile acid levels indicates the efficacy of FMT in improving the state and functioning of the gut microbiota. However, to confirm the results and make reliable judgments about therapy effectiveness, a larger number of experimental points after FMT is required.

INFORMED CONSENT

Written voluntary informed consent was received from the patient for the publication medical data for scientific purposes in the journal Clinical Practice. Ethic committee vote was granted by Morozov Children's Hospital № 176 on 24.05.2022 and Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine № 2022/05/31 on 31.05 2022. The legal representative has signed written voluntary informed consent on publication the clinical case description, medical data (results of diagnosis, treatment and observation in medical journal, electronic version included (signed on 17.06.2022).

ADDITIONAL INFORMATION

Authors' contribution. *J.A. Bespyatykh* — study concept, clinical data analysis, final manuscript editing; *A.V. Gospodarik* — collection and pre-treatment of biological samples; *E.A. Juravehl* — treatment of patients; *G.Z. Seregin* — FTM coordination and control; *A.V. Komarova*, *S.S. Esiev* — laboratory studies; *G.O. Bronin* — FTM coordination, writing the text of the article; *Ya.D. Shansky* — laboratory studies, data acquisition and analysis, manuscript writing, data statistical analysis. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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AUTHORS’ INFO

The author responsible for the correspondence:
Julia A. Bespyatykh, PhD, Associate Professor;
address: 1a Malaya Pirogovskaya street,
119435 Moscow, Russia;
e-mail: JuliaBes@rcpcm.org; eLibrary SPIN: 6003-9246;
ORCID: https://orcid.org/0000-0002-4408-503X

Co-authors:

Alina V. Gospodarik, PhD, Research Associate;
e-mail: alina.gospodaryk@rcpcm.org

Evgeny A. Zhuravel;
e-mail: zhuravel_evgeniy93@yandex.ru

George Z. Seregin;
e-mail: jorggg@mail.ru

Anastacia V. Komarova, Junior Research Associate;
e-mail: komaanasta@yandex.ru

ОБ АВТОРАХ

Автор, ответственный за переписку:
Беспятых Юлия Андреевна, к.б.н., доцент;
адрес: Россия, 119435, Москва,
ул. Малая Пироговская, д. 1А;
e-mail: JuliaBes@rcpcm.org; eLibrary SPIN: 6003-9246;
ORCID: https://orcid.org/0000-0002-4408-503X

Соавторы:

Господарик Алина Владимировна, к.б.н., н.с.;
e-mail: alina.gospodaryk@rcpcm.org

Журавель Евгений Андреевич;
e-mail: zhuravel_evgeniy93@yandex.ru

Серёгин Георгий Зурабович;
e-mail: jorggg@mail.ru

Комарова Анастасия Валерьевна, м.н.с.;
e-mail: komaanasta@yandex.ru

Sulejman S. Esiev;
e-mail: kap20081@gmail.com; eLibrary SPIN: 9593-2893

Gleb O. Bronin, MD, PhD;
e-mail: gbronin@morozdgkb.ru; eLibrary SPIN: 6485-2648;
ORCID: https://orcid.org/0000-0002-0694-3996

Yaroslav D. Shansky, PhD, Research Associate;
e-mail: yar.shansky@rcpcm.org; eLibrary SPIN: 7640-5940;
ORCID: https://orcid.org/0000-0003-4672-2474

Есиев Сулейман Сергеевич;
e-mail: kap20081@gmail.com; eLibrary SPIN: 9593-2893

Бронин Глеб Олегович, к.м.н.;
e-mail: gbronin@morozdgkb.ru; eLibrary SPIN: 6485-2648;
ORCID: https://orcid.org/0000-0002-0694-3996

Шанский Ярослав Дмитриевич, к.б.н., н.с.;
e-mail: yar.shansky@rcpcm.org; eLibrary SPIN: 7640-5940;
ORCID: https://orcid.org/0000-0003-4672-2474

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