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DYNAMICS OF MICROBIOME DEVELOPMENT IN A CHILD HOSPITALIZED IN THE INTENSIVE CARE UNIT FOR A LONG PERIOD OF TIME. CLINICAL CASE

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Abstract. The article presents the dynamics of microbiome development in a child hospitalized for a long time in the intensive care unit of a tertiary perinatal center. The species composition of the patient's microbiome did not meet the age norms. The risk factors that led to the disruption of microbiome formation were prolonged hospitalization in the NICU, short duration of breastfeeding, artificial nutrition with formulas based on deeply hydrolyzed cow's milk protein, and massive antibiotic therapy. Decrease in biodiversity of non-pathogenic microorganisms led to an increase in the proportion of pathogens, development of nosocomial diseases.

Key words: *microbiome formation; children; intensive care unit patient; 16s rRNA.*

ДИНАМИКА РАЗВИТИЯ МИКРОБИОМА РЕБЕНКА, ДЛИТЕЛЬНО ГОСПИТАЛИЗИРОВАННОГО В ОТДЕЛЕНИИ ИНТЕНСИВНОЙ ТЕРАПИИ. КЛИНИЧЕСКИЙ СЛУЧАЙ

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Резюме. В статье приводится динамика развития микробиома у ребенка, длительное время госпитализированного в отделение реанимации и интенсивной терапии перинатального центра третьего уровня. Видовой состав микробиома пациента не соответствовал возрастным нормам. К факторам риска, приведшим к нарушению формирования микробиома, относят длительную госпитализацию в отделение интенсивной терапии, короткую продолжительность грудного вскармливания, искусственное питание формулами на основе глубоко гидролизованного белка коровьего молока, массивную антибактериальную терапию. Снижение биоразнообразия непатогенных микроорганизмов привело к увеличению доли патогенов, развитию нозокомиальных заболеваний.

Ключевые слова: *формирование микробиома; дети; пациент отделения реанимации; 16s рРНК.*

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INTRODUCTION

Despite the presence of evidence of intrauterine development of the fetal microbiome, active colonization of microflora in children begins during the process of vaginal delivery (in utero) and continues after the birth of the child [1–4]. The microflora of parents, the environment and medical workers is of leading importance [5–12]. The method of delivery has an important role in the development of the microbiome: during natural delivery, representatives of the mother's vaginal microbiome (*Lactobacillus*, *Bifidobacterium* and *Bacteroides*) predominate, while during tomotocia, representatives of the skin microbiota (*Staphylococcus*, *Klebsiella* spp., *Enterococcus* spp. and *Clostridium* spp.) predominate [13–19].

The breast milk is of great importance in the development of gut microbiota, promoting the growth of *Lactobacillus* spp. and *Bifidobacterium* spp. [20–22]. In the first days after birth, the child's body begins to be colonized by representatives of *Enterobacteriaceae*, and then strict anaerobes: *Bifidobacterium*, *Clostridium* and *Bacteroides* [23–27]. *Bifidobacterium* are an essential component of a child's normal microflora; their development especially promoted by breastfeeding [28, 29]. The number of *Bacteroides* increases rapidly during the first 2–4 weeks of life [29]. During the weaning period, with the introduction of solid food, the abundance of *Bifidobacteriaceae* decreases, and *Bacteroides*, *Ruminococcus* and *Clostridium* predominate [30–32]. The microbiome of a child in the first few months of life characterized by a poor diversity of microorganisms [33]. It undergoes the greatest development with the introduction of complementary foods containing polysaccharides, which leads to the appearance of *Lachnospiracea*, *Clostridiaceae* and *Ruminococcaceae* and a sharp decrease in *Bifidobacterium* [3, 18, 34].

A disruption of the stages of development of the child's microflora in general and the intestines in particular can lead to the development of complications in various organs and systems [28, 35–39], and can also affect the prognosis [15, 40–42]. Children hospitalized in intensive care units from birth are susceptible to microbiome developmental disorders, which must be taken into account when providing medical care [43–51].

In order to demonstrate the detailed dynamics of changes in the microbiome of a child who was in the intensive care unit for a long time, we present our own observation.

CLINICAL CASE

A clinical case of a 10-month-old child, who was hospitalized from birth and was in the intensive care unit of a third-level perinatal center, was presented. The diagnosis is:

- Main disease: Non-epileptic paroxysms. Perinatal mixed damage to the central nervous system (CNS), early recovery period.
- Complications of the underlying disease: Movement disorder syndrome. Hyperkinetic syndrome. Bulbar syndrome. Delayed psychomotor development. Compensated biventricular occlusive hydrocephalus, a condition after ventriculoperitoneal shunting on the right.
- Concomitant diseases: Congenital malformation of the central nervous system — spina bifida, spinal hernia of the sacral spine, condition after plastic surgery. Microsurgical plastic surgery of myelomeningoradiculocele (rachischisis) of the sacral spine using local tissues. Arnold–Chiari syndrome type II. External ventricular drainage on the right under stereotactic ultrasound navigation. Distal paraparesis without dysfunction of the pelvic organs.
- Complications: Carrier of tracheostomy, gastrostomy. Stomach bleeding (3 episodes). Atopic dermatitis.

Anamnesis vitae. A child from the fourth pregnancy, which occurred against the of gestosis of the first half. The mother, 29 years old, was observed in the antenatal clinic from 21/22 weeks. During an examination of the mother at 27/28 weeks, positive IgG to rubella was detected (she had not previously had rubella, she was vaccinated). According to an ultrasound examination of the fetus at 36/37 weeks of gestation, a congenital malformation of the central nervous system of the fetus was diagnosed — spina bifida, occlusive hydrocephalus, Arnold-Chiari syndrome type II. In the area of the sacral region, a spinal defect with a hernial protrusion was visualized; the dimensions of the hernial sac were 27 × 10 mm, the diameter of the defect was 41 mm. During an ultrasound examination of the fetal head, the lateral ventricles are dilated to 23 mm, the anterior horns — to 24 mm. The cerebellum is displaced caudally.

Previous pregnancies ended in the birth of healthy children (2014, 2016, 2017). This birth was urgent at the 38th week by caesarean section in the lower segment of the uterus in a specialized perinatal center. The amniotic fluid was light.

Objective status at birth. At birth, the child's body weight was 3280 g, body length was 53 cm, head circumference was 36 cm, chest circumference was 34 cm. The Apgar score in the first minute was 7 points, in the fifth minute — 8 points. The child's condition at birth was assessed as severe due to the underlying disease—identified combined malformations of the central nervous system. At birth, a cry of medium strength, short-lived, against the background of tactile stimulation and sanitation of the upper respiratory tract. The head is round in shape. The large fontanel 1.0×1.0 cm, normotonic; the small fontanelle 0.3×0.3 cm, sutures at the junction. A spontaneous motor activity is symmetrically reduced. A muscle tone is symmetrical and semiflexor. The skin is bright pink, clean, acrocyanosis. The telangiectasia on the forehead. Visible mucous membranes are pink, moist, clean. Heart sounds are clear, rhythmic, no noise is heard, heart rate is 152 beats per minute. The breathing is symmetrical, weakened, vesicular, without wheezing, respiratory rate — 54 per minute, transcutaneous blood oxygen saturation — 97%. The abdomen is soft, not swollen, accessible to palpation. The liver protrudes from under the lower edge of the costal arch by 1.5 cm, the edge is smooth, elastic, the spleen is not palpable. The genitals are formed according to the male type, the testicles are lowered into the scrotum. No abdominal or femoral hernias were detected. Didn't urinate, anus closed. The meconium did not pass. In the lumbosacral region, there was a violation of the integrity of the skin and a hernial protrusion of myelomeningoradiculocele (rachischisis) measuring 5.5×7.0 cm with the flow of cerebrospinal fluid.

On the first day of life, an emergency surgical intervention was performed involving microsurgical plastic surgery of the myelomeningoradiculocele of the sacral spine using local tissues. The early postoperative period was uneventful. Due to increasing ventriculomegaly, on the 6th day of life, a diagnostic and unloading ventricular puncture was performed (cerebrospinal fluid without pathology). On the 8th day of life, due to increasing ventriculomegaly, emergency surgery was performed using external ventricular drainage on the right under stereotactic ultrasound navigation. The early postoperative period was without any features, respiratory support for two days using invasive artificial ventilation, analgosedation was continued, after that there was a planned transfer to spontaneous breathing, without any features, then without the need for respiratory support. During postoperative observation of the patient, no seizures or focal neurological symptoms were noted. The child was hemodynamically stable, did not require inotropic support. Enteral nutrition with expressed breast milk and physiological formula for children from birth with expansion up to 70 ml, absorbed. Due to an improvement in his condition, at the age of 11 days, the child was transferred to a specialized department, where the observation, treatment, nutrition were carried out with a gradual increase in the volume of enteral feeding.

From the 22nd day of life, a deterioration in the child's condition was noted in the form of the appearance and increase in the dynamics of bulbar disorders, hypersalivation, and an increase in respiratory failure; the child was transferred to the intensive care unit (ICU). Against the background of the child's anxiety, hyperdrainage was noted, against which background the development of general cerebral neurological symptoms was observed, migration of the drainage into the brain parenchyma was detected, and therefore the drainage was tightened under ultrasound navigation. According to control blood tests, an increase in laboratory inflammatory activity was noted (an increase in C-reactive protein to 33 mg/L), and therefore a control study of the cerebrospinal fluid was carried out — cytosis was detected up to 627 thirds. According to a bacteriological examination of blood and feces, carried out routinely as part of bacteriological control, E. coli was detected, and therefore antibacterial therapy was started based on sensitivity with control of bacterial cultures.

On the 23rd day of life, there was a decrease in saturation to 48%, bradycardia with a heart rate of up to 58 beats per minute, severe pallor of the skin, with diffuse cyanosis, focal neurological symptoms and dysphagia persisted. In this regard, an enteral nutrition was canceled, and the child was transferred to total parenteral nutrition.

At the age of 1 month, surgical intervention was performed to remove the external ventricular drainage on the right and implantation of the external ventricular drainage on the right.

On the 45th day of life, a repeated decrease in saturation to 45–60% was revealed during sleep, which was repeated several times; restoration of consciousness occurred after tactile stimulation. Due to persistent dysphagia, enteral nutrition was administered through a nasogastric tube and was completely absorbed. Similar episodes of desaturation due to apnea were observed on the 56th day. In this regard, the patient was transferred to invasive artificial lung

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ventilation (ALV) through an endotracheal tube, and anticonvulsant therapy was prescribed.

From the age of three months, given the developed atopic dermatitis, the patient was switched to formulas based on deeply hydrolyzed cow's milk protein.

Taking into account dysphagia and prolonged insertion of the tube, the boy was installed with a percutaneous endoscopic gastrostomy at 4,5 months age.

During the therapy, the child's condition remained severe due to respiratory failure of the I–II degree against the background of aspiration pneumonia, neurological symptoms: bulbar syndrome, paroxysmal nonepileptic seizures with desaturation and autonomic disorders, a syndrome of motor disorders, flaccid distal paraparesis without dysfunction of the pelvic organs, hyperkinetic syndrome.

Attempts at extubation and transfer to spontaneous breathing were unsuccessful, and therefore at 5,5 months age a tracheostomy was performed and mechanical breathing was continued. During observation, cough and swallowing reflexes were absent.

At 5,5, 6,5 and 7,5 months of age, episodes of gastrointestinal bleeding were recorded against the background of erosive esophagitis, superficial widespread gastritis and duodenal bulb ulcer.

The planned change of the tracheostomy cannula was carried out at 6,5 months age, and the gastrostomy tube — at 8 months age.

Results of changes in the patient's microbiome

The patient in the ICU during hospitalization periodically collected biological material (urine, feces, venous blood, tracheostomy discharge, gastric contents, swabs from the oropharynx and nasal cavity). At the age of 8,5 months, 16S rRNA sequencing of saliva, gastrostomy fluid and feces was performed. All isolated bacteria were identified by genus and species. 20 species of microorganisms have been identified, which are grouped into 3 bacterial phyla, 2 classes, 4 orders, 13 families and 15 genera.

When sequencing biological media, 3 bacterial phyla were identified: Firmicutes (represented by *Clostridium* spp., *Blautia* spp., *Lactobacillus* spp., *Enterococcus* spp., *Veillonella* spp., etc.), Proteobacteria (represented by the family *Enterobacteriaceae*), *Bacteroidota* (represented by *Elizabethkingia meningoseptica*). The dominant number of microorganisms contains the order *Proteobacteria* (65%), *Firmicutes* (32%) and *Bacteroidota* (3%). Sequencing analysis of numerous phyla *Proteobacteria* showed the presence of *Enterobacter* (41,068607), *Enterococcus* (31,280665) in large numbers.

Table 1. Summary of oral microflora data by culture and culturing method

Таблица 1. Суммарные данные микрофлоры ротовой полости культуральным методом и методом культивирования

Microorganisms	Oropharyngeal culture data	
	7 months	8,5 months
Streptococcus viridans	2	3
Serratia marcescens	0	2
Pseudomonas aeruginosa	0	2
Enterococcus faecalis	1	0

The cultivation of the contents of the oral cavity showed the presence of *Streptococcus viridans*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*. At the same time, an increase in the species diversity of pathogenic microflora in the oral cavity was noted (Table 1).

When sequencing a saliva sample, 300 OTUs were identified, which, in accordance with modern prokaryotic nomenclature, are divided into 8 bacterial phylum, 10 classes, 18 families, 22 genera and 27 species bacteria. The most pathogenic microorganisms isolated by sequencing from the oral cavity are Haemophilus influenzae, which may contribute to the development of aspiration pneumonia.

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Features of development gastrostomy microbiome

When sequencing a gastrostomy sample, 300 OTUs were identified, which, according to the modern nomenclature of prokaryotes, are divided into 7 bacterial phyla, 9 classes, 25 families, 38 genera and 34 species of bacteria. The equencing of gastrostomy fluid revealed 6 different phyla of bacteria and 1 unidentified phylum (Table 2, Fig. 1).

Table 2. Type diversity of the gastrostomy microbiome according to sequencing data

Таблица 2. Типовое разнообразие микробиома гастростомы по данным секвенирования

Microorganisms	Phylum	Ratio,%
Proteobacteria	76,88726	77
Cyanobacteria	21,001	21
Firmicutes	1,474338	1
Bacteroidota	0,515464	1
Fusobacteriota	0,077597	0
Actinobacteriota	0,033256	0
Unclassified	0,011085	0

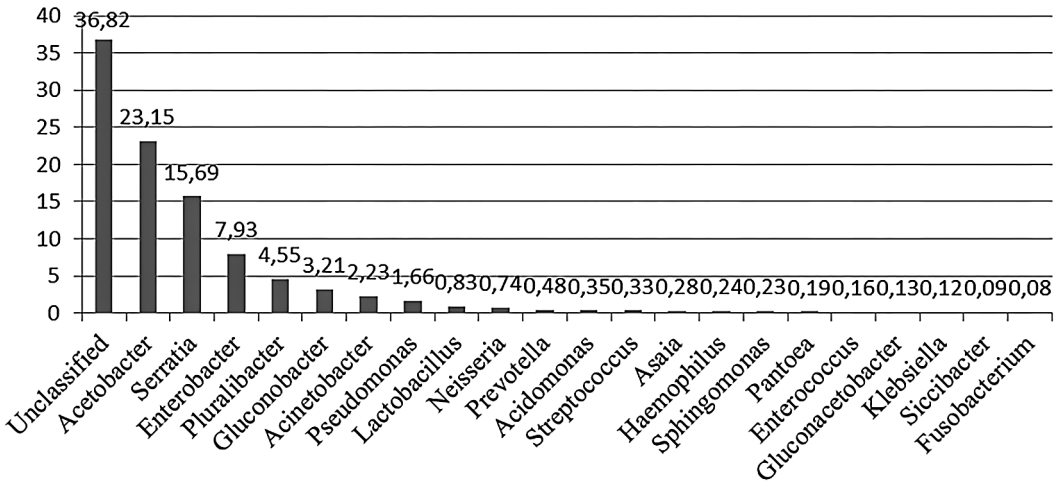

Fig. 1. Diversity of genera of the gastrostomy microbiome (%)

Рис. 1. Разнообразие родов микробиома гастростомы (%)

Table 3. Comparative composition of Genus 16S rRNA from stools

Таблица 3. Сравнительный состав Genus 16S rRNA из стула

Microorganisms	Class	Ratio,%	Microorganisms	Class	Ratio,%
Acinetobacter	0,04158		*Kluyvera*	0,00832	0
Anaerococcus	3,60915	4	*Morganella*	4,92308	5
Atlantibacter	0,01247	0	*Pseudocitrobacter*	0,02495	0
Cedecea	0,00832	0	*Raoultella*	0,56549	1
Citrobacter	2,75676	3	*Serratia*	0,59044	1
Enterobacter	41,0686	41	*Shimwellia*	0,19543	0
Enterococcus	31,2807	31	*Siccibacter*	0,00832	0
Escherichia/Shigella	5,40125	5	*Streptococcus*	0,01663	0
Klebsiella	2,17048	2	*Unclassified*	7,31809	7

Features of the development of the gut microbiome

The stool study was carried out using the culture method and the 16S rRNA method. The use of the cultural method for stool analysis showed the presence of 6 types of microorganisms: *Candida* sp., *Escherichia coli*, *Citrobacter* sp., *Enterobacter* sp., *Morganella morganii*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Enterococcus* sp. Microorganisms did not have a clear pattern of appearance in the stool throughout the patient's entire stay in the ICU.

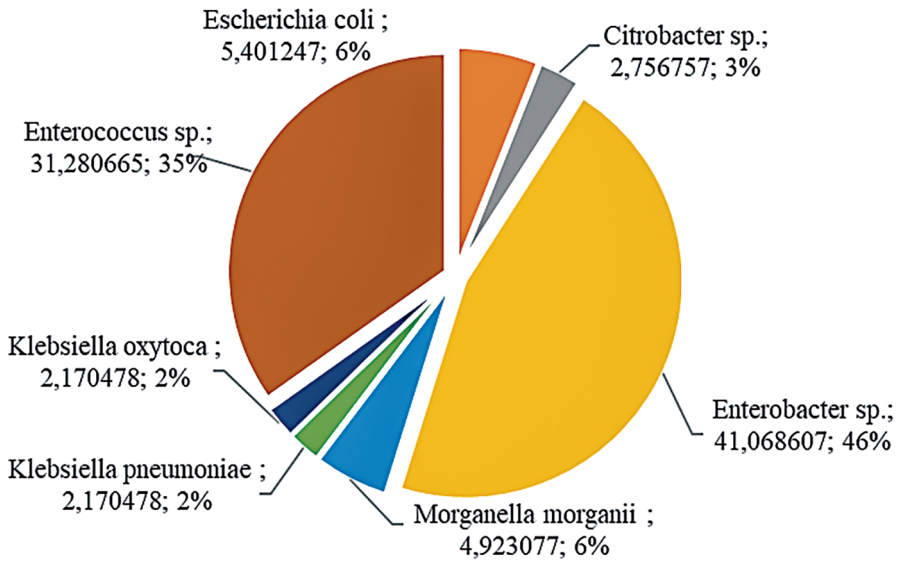

Fig. 2. Ratio of bacterial genera represented in fecal matter by 16S rRNA data

Рис. 2. Соотношение родов бактерий, представленных в каловых массах по данным 16S rRNA

Table 4. Comparative composition of Phylum 16S rRNA from oral cavity, gastrostomy and stools

Таблица 4. Сравнительный состав Phylum 16S rRNA из ротовой полости, гастростомы и стула

Phylum	Oral cavity	Contents of the gastrostomy	Stool microbiome
Firmicutes	48,69559	1,474338	37,75468
Proteobacteria	40,86186	76,887263	62,24532
Bacteroidota	7,979071	0,515464	0
Fusobacteriota	2,201875	0,077597	0
Patescibacteria	0,181673	0	0
Actinobacteriota	0,029068	0,033256	0
Unclassified	0,029068	0,011085	0
Campilobacterota	0,021801	0	0
Cyanobacteria	0	21,000998	0

When sequencing a stool sample, 274 OTUs were identified, which, according to the modern nomenclature of prokaryotes, are divided into 2 bacterial phyla, 4 classes, 19 genera and 17 species of bacteria (Table 3). The Biodiversity Index is 1,3118. Butyrate- and propionate-producing bacteria are practically absent in the feces of a child.

A comparison of two methods of stool analysis showed the presence of 7 identical genera of bacteria that had pathological activity (Fig. 2).

A generic comparison of microorganisms identified by stool sequencing revealed a significant predominance of Enterobacter (46%) and Enterococcus (35%). A large number of pathogenic strains associated with the provision of medical care were identified: 6% — Morganella morganii, 3% — Citrobacter sp., 2% — Klebsiella pneumoniae and 2% — Klebsiella oxytoca. Based on the data obtained, it can be assumed that these microorganisms contributed to the development of nosocomial infection (Table 4).

A comparative analysis of biological media obtained by sequencing showed that Firmicutes are present in three media, but the largest number of them is observed in the contents of gastrostomy tubes (48.69559) and stool samples (37.75468). The Proteobacteria occurs across the three environments, being the most abundant phylum. The largest number of phyla of microorganisms was isolated from the oral cavity.

In addition to 16S rRNA and cultivation, data from laboratory studies over time was analyzed.

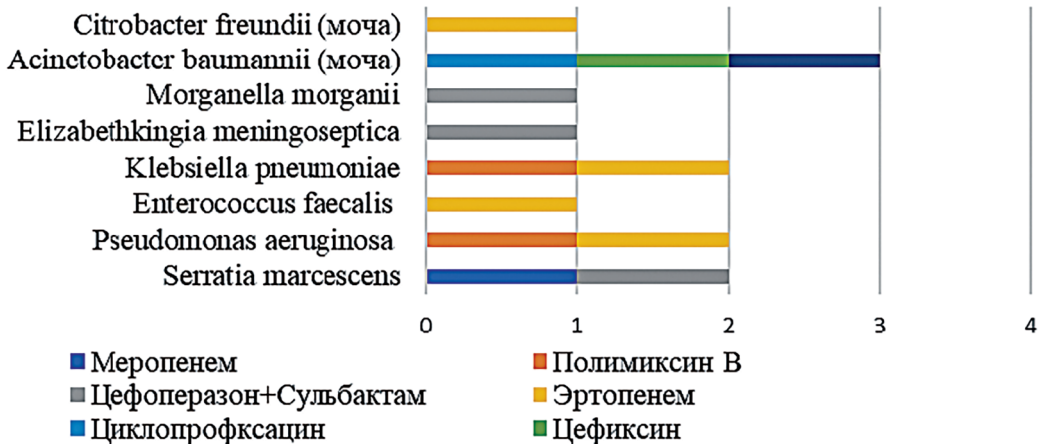

Fig. 3. Sensitivity of microorganisms to antibiotics

Рис. 3. Чувствительность микроорганизмов к антибактериальным препаратам

Throughout the entire period of treatment in the ICU, the patient observed a decrease in the concentration of total bilirubin, increased C-reactive protein in a biochemical blood test, eosinophilia and leukocytosis in a clinical analysis, which indicated the course of an inflammatory reaction.

Based on the dynamics of the increase in C-reactive protein, a positive procalcitonin test and the results of bacteriological studies, the patient was given antimicrobial therapy. The therapy with 10 antibacterial drugs selected according to sensitivity to specific pathogenic microorganisms was carried out during 8 months (Fig. 3).

DISCUSSION

Studies of different authors give an idea that the amount of Proteobacteria depends on the type of nutrition of the child: higher levels of phyla content are observed in children who are breastfed. It is also emphasized that, depending on nutrition, there is a different ratio of bacterial genera. Thus, with artificial feeding there is a predominance of *Clostridium difficile*, *Bacteroides* spp., *Prevotella* spp. and *Lactobacillus* spp. [1, 3, 29].

The smallest phylum isolated from the patient is *Bacteroidota* (3%), represented by *Elizabethkingia meningoseptica*. This species was isolated by cultivating bacteria from the contents of a gastrostomy tube. Considering the pathogenic properties of the microorganism, when it was isolated, treatment was carried out with antibacterial drugs of the reserve group (cefoperazone and sulbactam), against which positive dynamics were noted.

A detailed assessment of the bacterial phylum of the oral microbiome revealed 49% of unclassified microorganisms; among the classified ones, 49% belonged to *Firmicutes*, 41% to *Proteobacteria*, 8% to *Bacteroidota* (Fig. 1). Among the genera, the dominant ones were *Streptococcus* (29,55454), *Neisseria* (19,758738) and *Haemophilus* (18,828574). When examining the contents of the gastrostomy tube, microorganisms of 38 genera of bacteria were identified, the predominant of which were bacteria of the genus *Acetobacter* (23,14599) and *Serratia* (15,69117), which indicates the development of nosocomial infection. This fact is confirmed by other microorganisms present in the sequencing results: the genera *Acinetobacter* (2,228134), *Neisseria* (0,737169), *Pseudomonas* (1,657244).

In the species composition, *Lactobacillus* (0,825851) was identified in small quantities. They have immunomodulatory and anti-inflammatory effects and are involved in glucose metabolism [3]. Breastfed babies have a large number of bacteria. The patient was, firstly, artificially fed with formulas based on deep hydrolysis of cow's milk protein, and, secondly, received massive antibacterial therapy.

It was found that normal microflora predominated in the feces, represented by *Enterobacter* (41,0686), *Enterococcus* (31, 2807). However, pathogenic *Escherichia/Shigella species* (5,40125) have been observed, which should not normally be present in infants. Based on this, we can assume the development of pathogenetic processes in the child's gastrointestinal tract [33].

It was noted that the microbiota of the studied child does not differ in a large variety of microorganisms, as evidenced by the results of 16S rRNA sequencing.

CONCLUSION

The composition of the microbiome of a child hospitalized for a long time in the ICU does not correspond to age standards. Long stays in the ICU, short duration of breastfeeding and the transition to artificial nutrition with formulas based on deeply hydrolyzed protein led to poor microbiological diversity of the intestinal tube. The long-term massive antibacterial therapy with broad-spectrum drugs led to a decrease in the biodiversity index of microorganisms and a decrease in the number of bacterial colonies producing short-chain fatty acids.

Thus, the method of birth, type of nutrition, and use of antimicrobial drugs have a significant impact on the formation of the child's normal microflora.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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