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Research Article

Infection and Non-infection Cause of Diarrhea in Child Patients an Oncological Clinic

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Abstract

Diarrhea is one of the common symptoms in the treatment of cancer patients. Improving the preventive and therapeutic treatment of diarrhea can be made through a better understanding of risk factors for this disease in the pediatric oncology hospital. 503 stool samples of patients were examined by the bacteriological and ELISA methods (to determine the *Clostridioides difficile* toxin A/B) in feces followed by analysis of 187 case histories of these patients retrospectively. *Clostridioides difficile, Clostridium perfringens, Klebsiella* sp., *Citrobacter* sp., *Enterobacter* sp., *Enterococcus* sp., *Pseudomonas aeruginosa* can cause diarrhea in children, particularly in patients of pediatric oncological hospital. There is a significant change in the composition of intestinal flora in patients with diarrhea; especially important is a decrease in *Escherichia coli*. The effect of nitroimidazoles (metronidazole) on the development of diarrhea in a pediatric oncological hospital was noted. Stool samples from all patients at the pediatric oncological center who have diarrhea, and especially those receiving chemotherapy and nitroimidazoles (metronidazole), should be regularly sent for testing to determine the exact cause of the diarrhea.

Keywords: Diarrhea; Children; Chemotherapy; Microbiome; Clostridioides difficile Infection

Introduction

Therapy in an oncological hospital is a complex process using aggressive methods of treatment. It should be considered that diarrhea is a common manifestation of intestinal mucosa damage induced by chemotherapy, radiotherapy, hematopoietic stem cell transplantation, or antibiotic therapy. Any of these treatments could lead to development of bacterial superinfection and eventually to sepsis [1]. Often, diarrhea in an oncological hospital is associated with neutropenic enterocolitis, the pathogenesis of which is not fully understood. Immunosuppression and frequent use of antimicrobial drugs in the presence of neutropenic enterocolitis can alter the normal intestinal flora and facilitate infection with less common agents [2].

For more than four decades, *Clostridioides difficile* (*C. difficile*) has been a common intestinal pathogen in humans. This is due to the use of antimicrobial drugs, which usually disrupt the microbiota of the gastrointestinal tract [3].

With the use of antibiotics, there is a sharp change in the intestine microbial population, characterized by a decrease in microbial diversity, which is followed by colonization of the intestine with *C. difficile* that can lead to excessive growth of other aerobic and anaerobic opportunistic bacterial flora [4]. To date there is no univocal opinion whether coinfection with other microorganisms can affect the outcome of CDI [5]. In this study we investigated the microbiome of pediatric oncology patients with CDI in combination with other pathogens and describe part of the microbiome that could be isolated by cultivation.

Children who are undergoing treatment in oncological hospital often receive massive antibiotic therapy which results in dysbiosis and inflammation of the intestinal mucosa. But the problem is that in Russia there is no monitoring and tracking of anaerobic opportunistic intestinal flora, which means that antibiotic treatment is prescribed exclusively empirically.

At the same time, the carriage of toxigenic strains of *C. difficile* is widespread among children [6], which is an additional risk factor for the development of *C. difficile*-associated enterocolitis in patients of pediatric oncological hospital. The significance of toxigenic *C. difficile* strains in children with no clinical manifestations of enterocolitis is unclear; opinions differ as to whether treatment should be prescribed [7].

Prolonged hospitalization of children in the oncological hospital as well as long and repeated courses of antibiotic treatment lead to formation of a resistant flora. Fecal carriage of resistant bacteria poses a potential risk of sepsis and increases mortality in immunosuppressed patients [1,8]. These data highlight the need for strict infection control to contain this potential reservoir of drug-resistant infection [9].

In the United States, *Salmonella, Campylobacter*, and *Shigella* are the three most common bacteria that cause diarrhea among children - patients of oncological hospital; all these bacteria are identified by routine stool culture [10]. Determination of the type of pathogen common in each group of patients and typical for a given hospital will help to improve the methods of prevention and control of diseases. In Russia, this question remains open. Thus, it is necessary to study the etiology of intestinal complications in the form of enterocolitis in children at an oncological hospital for improving the quality of timely medical care.

Objective

To determine the infectious and non-infectious etiology of diarrhea in children undergoing treatment in a pediatric oncological hospital.

Materials and Methods

The study included 503 stool samples (1 patient - 1 sample) from patients aged 0 to 18 years who were treated for their underlying disease at the Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology, and Immunology in the period from 2012 to 2015. Fifty-four patients with confirmed *C. difficile* infection (CDI); 403 - with diarrhea, but with a negative test for the presence of *C. difficile* A/B toxin (non-CDI); 46 patients - control group. For the purpose of study, the risk factors for the development of CDI, 187 case histories of patients from this group were analyzed retrospectively, among them: with CDI - 54, non-CDI - 87, control group - 46. All stool samples were examined by enzyme immunoassay (RIDASCREEN R-Biopharm, Germany) for the presence of *C. difficile* toxin A\B. In parallel, all studied samples were inoculated on solid nutrient media to cultivate aerobic intestinal flora: blood agar (Oxoid, UK), McConkie's medium (Oxoid, UK), Brilliance ESBL agar (Oxoid, UK), Brilliance agar for Salmonella (Oxoid, UK), VRE agar (Oxoid, UK), SS agar (Oxoid, UK), Salt mannitol agar (Chapman's medium) (Oxoid, UK), Sabouraud agar (Oxoid, UK). The inoculated Petri dishes were incubated at 37 ºC for 24-48 hours. For inoculation of anaerobic flora, liver broth and anaerobic agar with the addition of nitrocefin were used according to the manufacturer's protocol (Oxoid, UK). The material was incubated anaerobically using AnaeroGen 2.5L sachets with 2.5L jar (Thermo Scientific, Oxoid, UK) for 48 hours. Subsequent identification of the species of the colonies was carried out using MALDI-TOF spectrometry according to the manufacturer's protocol (Bruker Daltonic, Germany). The following discs were used to confirm ESBL: cefpodoxime and cefpodoxime/clavulanic acid (Oxoid, UK). The names of the antibiotics used in the treatment of the underlying disease were obtained from the patient's medical history. Data collection and calculations were performed using a laboratory information system (SGM Analytix, Sweden) and QlikView Personal Edition software (SGM Analytix Explorer, Sweden). The Pearson's goodness-of-fit test (χ^2) and the odds ratio with a confidence interval level of 95% were used to assess the statistical significance of the results for the study groups.

Results and Discussion

Diarrhea is a common complication in children with cancer and can be caused by several factors [11].

The causes of diarrhea in patients of oncological hospital may be infectious pathogens such as *C. difficile*, *Clostridium perfringens*, *Clostridium* spp., *Bacteroids* spp., *Klebsiella* sp, *Candida* sp., *Es. coli*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*; non-infectious components, such as the type of treatment of the underlying disease, antibiotic therapy, diagnosis, length of hospitalization [12-15].

The fraction of toxigenic *C. difficile* strains in the structure of diarrhea in the children's oncological hospital constituted 11.8% for the period of our study (Table 1). According to the results of study in a Russian multidisciplinary hospital conducted by Boronina L.G. [16], the detection rate of *C. difficile* toxins in children with diarrheal syndrome reached 37.4%. The difference may be due to the fact pediatric oncology patients are at risk of developing CDI and receive empiric vancomycin and metronidazole therapy.

	CDI (n = 54)	non-CDI (n = 403	KG (n = 46)	χ^2 CDI/ non-CDI	χ^2 CDI/KG	χ^2 non-CDI/ KG	CDI OR (95%CI)	non-CDI OR (95% CI)
C. difficile tox	54	0	4					
C. difficile non-tox	0	134	10					
C. perfringens	7	109	6	4.99[a]	0	4.25[a]	0.993 (0.308-3.196)	0.118[a] (0.038-0.368)
Other *Clostridia*	53	213	34	40.16[a]	12.9[a]	7.4[b]	18.706[a] (2.325-150.48)	0.396[b] (0.199-0.786)
Bacteroides fragilis	1	22	0	1.3	0.86	2.64	B	B
Other *Bacteroides*	11	61	18	0.98	4.25[b]	16.39[b]	0.398[b] (0.164-0.967)	0.277[b] (0.145-0.532)
Lactobacillus sp.	5	56	8	0.89	1.45	0.41	0.485 (0.147-1.601)	0.767 (0.340-1.728)
Pediococcus sp.	1	10	2	0.08	0.53	0.55	0.415 (0.036-4.732)	0.560 (0.119-2.637)
Propionobacterium acnes	0	2	0	0.27	0	0.23	HP	B
Granulicatella sp.	0	2	0	0.27	0	0.23	HP	B
Flavonifactor sp.	7	12	0	11.92[a]	6.41[a]	1.4	B	B
Veilonella sp.	10	93	10	0.57	0.16	0.04	0.818 (0.307-2.182)	1.080 (0.516-2.259)
Fusobacterium nucleatum	2	9	0	0.44	1.74	1.04	B	B
Megamonas sp.	0	0	2	0	2.4	17.6[b]	HP	0
Megaspherae sp.	1	2	2	1.34	0.53	6.94[b]	0.415 (0.036-4.732)	0.110[b] (0.015-0.798)
Alishtipes sp.	2	4	2	2.7	0.03	3.53	0.846 (0.114-6.257)	0.221 (0.039-1.239)
Streptomyces sp.	0	2	2	0.27	2.4	6.94[b]	0	0.110[b] (0.015-0.798)
Microbacter sp.	0	1	0	0.13	0.03	0.11	HP	B

Blautia sp.	0	3	0	0.4	2.4	0.34	HP	B
Cuprivadus sp.	0	1	0	0.13	2.4	0.11	HP	B
Eubacterium sp.	1	7	0	0	0.86	0.81	B	B
Prevotella sp.	0	12	0	1.65	2.4	1.41	HP	B
Bifidobacter sp.	0	3	1	0.4	1.19	0.96	0	0.337 (0.034-3.313)
Peptostreptococcus sp.	0	5	2	0.68	2.4	2.6	0	0.276 (0.052-1.467)
Es. coli	18	166	26	1.222	5.421[b]	3.965[b]	0.385[b] (0.171-0.867)	0.539[b] (0.291-0.997)
Es coli ESBL	7	79	8	1.37	0.38	0.13		
Klebsiella sp.	24	106	4	7.70[a]	15.74[a]	6.92[a]	7.875[a] (2.483-24.97)	3.747[a] (1.312-10.70)
Klebsiella sp. ESBL	11	54	2	1.89	5.64[a]	3.1	5.628* (1.178-26.895)	3.365 (0.793-14.286)
Enterobacter sp.	14	49	5	7.594[a]	3.659	0.065	2.870 (0.946-8.710)	1.135 (0.428-3.010)
Enterobacter sp. ESBL	5	19	3	1.98	0.25	0.29	1.463 (0.330-6.482)	0.709 (0.202-2.495)
Citrobacter sp.	10	22	2	12.47[a]	4.724[a]	0.101	4.773 (0.987-23.079)	1.213 (0.275-5.339)
Citrobacter sp. ESBL	4	5	0	9.38[a]	3.55	0.58	B	B
Morganella sp.*Proteus* sp.	4	15	2	1.623	0.412	0.044	1.680 (0.293-9.632)	0.812 (0.179-3.673)
Morganella spp.\ *Proteus* sp. ESBL	1	2	2	1.34	0,53	6.94[b]	0.415 (0.036-4.732)	0.110* (0.015-0.798)
Salmonella sp.	0	2	0	0.27	0	0.23	HP	B
Pseudomonas aeruginosa	0	39	2	5.713[b]	2.396	1.413	0	2.250 (0.524-9.654)
Pseudomonas aeruginosa MDR	0	16	2	2.22	2.4	0.02	0	0.910 (0.202-4.087)
Stenotrophomonas maltophilia	2	6	2	1.35	0.03	1.93	0.846 (0.114-6.257)	0.332 (0.065-1.698)
Acinetobacter sp.	0	2	2	0.27	2.4	6.94[b]	0	0.110[b] (0.015-0.798)
Enterococcus sp.	39	200	20	9.745[a]	7.251[a]	0.276	3.12[a] (1.346-7.232)	1.182 (0.633-2.208)
Enterococcus sp. VRE	3	30	0	0.25	2.63	3.67	B	B
Staphylococcus aureus	0	3	0	0.4	0	0.34	HP	B
Staphylococcus sp.	4	16	0	1.344	3.549	1.894	B	B
Stpeptococcus sp.	0	6	2	0.81	2.4	1.93	0	B
Candida sp.	6	26	2	1.59	1.54	0.31	2.750 (0.527-14.34)	1.517 (0.348-6.610)
Mold fungi	0	1	0	0.13	2.4	0.11	HP	B
Bacillus sp.	1	5	2	0.14	0.53	2.6	0.415 (0.036-4.732)	0.276 (0.052-1.467)

Haemophilus sp.	1	1	0	2.81	0.86	0.11	B	B
Corynebacterium sp.	0	3	0	0.4	0	0.34	HP	B

Table 1: Comparative characteristics of aerobic and anaerobic flora in diarrhea of various etiology in patients of pediatric oncological hospital.

[a] - value corresponding to an increase in the frequency of occurrence of the microorganism, $p < 0.05$;

[b] - value corresponding to a decrease in the frequency of occurrence of the microorganism; $p < 0.05$;

n - Group Size; *C difficile* tox - toxigenic strains of *C difficile; C difficile* non-tox - nontoxigenic strains of *C difficile;* CDI - *C. difficile* infection; non-CDI - diarrhea caused by other etiological factors; CG - Control Group; *HP - undefined result; B - chance tends to infinity without a confidence interval; 0 - chance tends to zero without a confidence interval;* χ^2 - Pearson Criterion; OR (95% CI) - Odds Ratio.

Our study showed that 8.7% of children undergoing treatment in an oncological hospital, were asymptomatic carriers of toxigenic strains (Table 1). At the same time European data [6] show quite different numbers – 15 - > 54%, which correspond to much higher levels of toxigenic strains than those presented by us. Perhaps this difference is due to the detection method. In Russian microbiological laboratories one method is mostly used for CDI diagnostics, while the European Society of Microbiologists (ESCMID) recommends the use of a two-stage diagnostic algorithm [17].

Among patients with diarrhea, the carriage of nontoxigenic *C. difficile* strains was detected in 29.3% of patients (Table 1). According to Nagaro [18] nontoxigenic strains of *C. difficile* can have a protective effect and reduce the likelihood of infection with toxigenic strains. However, according to Polish researchers [19] nontoxigenic strains can cause nosocomial diarrhea, as well as horizontal gene transfer from the bacterial pathogenicity locus converting nontoxigenic *C. difficile* into toxicogenic strains [20]. Thus, now there is no consensus regarding the role of nontoxigenic *C. difficile* strains in the human microbiome. Our study shows that the carriage of nontoxigenic strains among children in the oncological hospital is quite widespread and requires monitoring, and this problem needs further research.

Gut microbiota may be a potential contributor to severe CDI [21]. After treatment with antibiotics, susceptibility to colonization by *C. difficile* strains is associated with a decrease in bacterial diversity, an increase in proteobacteria, and a decrease in the number of Bacteroides [22]. On the other hand, it was shown by means of statistical modeling that the loss of Bacteroides, *Lachnospiraceae*, and *Ruminococcaceae* was associated with CDI in humans [23], which is consistent with our data. In the accompanying flora in CDI (Table 1) we noted an increase in opportunistic flora: other *Clostridia*, *Flavonifactor* sp., *Klebsiella* sp., *Citrobacter* sp., *Enterococcus* sp., with a simultaneous decrease in the normal intestinal flora - *Es. coli* and other Bacteroides in comparison with the control group. At the same time, we found the following changes in the structure of flora in absence of CDI: an increase in *Clostridium perfringens, Klebsiella sp*. and a decrease in other clostridia, other bacteroids, *Megamonas* spp., *Megaspherae* sp., *Streptomyces* sp., *Escherichia coli, Acinetobacter* sp.(Table 1).

Lawley T.D., *et al.* [24] identified *Klebsiella* sp., *Proteus* sp. and *Enterococcus* sp. in the microbiota of patients with CDI. Our results are concurrent with these data, except for the identification of *Proteus* sp. This is due to the peculiarities of the growth of this microorganism on anaerobic agar - the phenomenon of swarming. The results of analysis that did not lead to the isolation of the pure cultures of anaerobic bacteria were excluded from the study.

C. difficile promotes colonization of the intestine in young children by *Klebsiella* [25], which, as a concomitant pathogen, possibly leads to the development of severe forms of CDI [6]. Fisher., *et al.* report *Klebsiella* sp. is excreted with a high frequency in the presence of hemorrhagic antibiotic-associated enterocolitis not associated with *C. difficile* [26]. In our study, a statistically significant increase in *Klebsiella* sp. was noted in both groups (CDI and non-CDI) in comparison with the control group. Also, we detected an increase in *Klebsiella* sp. in patients with CDI versus non-CDI patients (Table 1). Our data show that the role of *Klebsiella* sp. is underestimated in the structure of diarrhea in the pediatric oncological hospital, and, therefore, additional monitoring of this nosology is required.

According to Sherief., *et al*. the most common pathogen along with *Klebsiella* sp. is *Candida* sp. [11]. In our study, *Candida* sp. was isolated from a small percentage of patients from all the studied groups (Table 1). This is due to the fact 44.9% of children received antifungal therapy (Table 3). *Stenotrophomonas maltophilia* was also rarely isolated from the intestines of cancer patients in our hospital. This is explained by the widespread administration of trimethoprim/sulfamethoxazole (biseptol) to cancer patients for the prevention of Pneumocystis pneumonia. 47.1% of all patients were treated with this drug, which is the antibiotic of choice for the treatment of *Stenotrophomonas maltophilia* (Table 3).

Salmonella spp., *Staphylococcus aureus, Clostridium perfringens* are pathogens associated with cases of diarrhea [27]. We did not obtain the statistically significant confirmation that *Salmonella* spp. and *Staphylococcus aureus* are associated with diarrhea (Table1). Perhaps this is due to the strict infection control of all children admitted to the oncological hospital for treatment. On the contrary, we found *Clostridium perfringens* in most cases of patients with diarrhea (Table 1). At the moment, identification of this pathogen is not included in the routine practice of the microbiological laboratory in the children's oncological hospital.

A statistically significant decrease in the frequency of occurrence of such microorganisms as *Pseudomonas aeruginosa* and *Clostridium perfringens* and an increase in *Clostridium* sp., *Flavonifactor* sp., *Klebsiella* sp., *Citrobacter* sp., *Enterobacter* sp., *and Enterococcus* sp. were found in patients with CDI versus non-CDI patients. Comparison of CDI patients with the control group gave similar results apart from 2 microorganisms - *Pseudomonas aeruginosa and Enterobacter* sp. (Table1).

Ueda., *et al*. [28] showed that biochemical derivatives produced by Pseudomonas aeruginosa exhibit high activity against *C. difficile.* In our study no *Pseudomonas aeruginosa* strains were detected in patients with CDI ($p < 0.05$), which may be considered as a clinical confirmation of results obtained by Ueda., *et al.* that is of great importance for the cancer patients (Table 1). Thus, it is possible that studying the roles and interaction of *Pseudomonas aeruginosa* and *C. difficile* will help to improve the methods of prevention and treatment of these infections.

In a study by Vervoort., *et al.* gram-negative ESBL strains were detected in 37% of stool samples from patients with diarrhea. Patients infected with *C. difficile* showed a significantly higher incidence of intestinal colonization with ESBL strains compared with patients not infected with *C. difficile* (62% versus 31%) [9]. In our study, ESBL strains were identified in 40.9% of cases (Table 1). We found no statistically significant difference in the rate of intestinal colonization with resistant strains among patients with CDI, non-CDI diarrhea and the control group with the exception of an increased proportion of *Klebsiella* sp. *ESBL* and *Citrobacter* sp. *ESBL* in patients with CDI (Table 1). Perhaps this is due to the mandatory screening of resistant flora for all patients newly admitted to the pediatric oncological hospital. At the same time, the fraction of all resistant strains reached almost 50%, which presents certain difficulties in treating the underlying disease and shows the need to tighten the infection control.

According to Krishnamurthi., *et al*. chemotherapy-induced diarrhea is a common problem in cancer patients in the United States [10]. Our data (Table 2) are consistent with this study - diarrhea was observed in patients with CDI and in non-CDI patients who underwent the chemotherapy treatment. The impact of the other risk factors on diarrhea development (diagnosis, age, other methods of treatment of the underlying disease) did not show statistically reliable data, which does not agree with the study of L.N. Mazankova. and S.G. Perlovskaya [15]. Perhaps this is due to the difference in protocols for the cancer treatment as well as to distinct approaches to antibiotic therapy.

		CDI (n = 54)	non-CDI (n = 87)	KG (n = 46)	OR (95% CI) CDI/KG	OR (95% CI) non-CDI /KG
Diagnosis	Lymphomas	5	7	2	2.245 (0.414-12.162)	1.770 (0.353-8.880)
	Leukemia	28	44	16	2.019 (0.900-4.531)	1.919 (0.917-4.014)
	MN	12	18	8	1.357 (0.501-3.676)	2.375 (0.919-6.138)

	AA	2	5	9	0.158 (0.032-0.775) *	0.251 (0.079-0.800) *
	IDS	7	10	11	0.474 (0.167-1.346)	0.413 (0.161-1.063)
	Examination	0	3	0	HP	B
Age	0-1 years	5	5	0	B	B
	1-5 years	21	51	24	0.583 (0.263-1.293)	1.299 (0.633-2.665)
	5 years+	28	31	22	1.175 (0.535-2.581)	0.604 (0.292-1.248)
Treatment	CT	30	22	13	3.173 (1.374-7.326)*	0.859 (0.385-1.919)
	RT	3	0	2	1.294 (0.207-8.101)	0
	HSCT (up to 1 month)	7	27	14	0.340 (0.124-0.937)	1.029 (0.474-2.233)
	HSCT (1-6 month)	11	28	8	1.215 (0.443-3.336)	2.254 (0.930-5.463)
	Examination	3	10	9	0.242 (0.061-0.955) *	0.534 (0.200-1.426)
Sex	Male	28	59	32	0.471 (0.207-1.074)	0.922 (0.426-1.996)
	Female	26	28	14	2.122 (0.931-4.840)	1.085 (0.501-2.349)

Table 2: Assessment of risk factors for diarrhea development at pediatric oncological hospital.

n - Group Size; CDI - C Difficile Infection; non-CDI - Diarrhea Caused by Other Etiological Factors; CG - Control Group; MN - Malignant Neoplasm; AA - Aplastic Anemia; IDS - Immunodeficiency State; CT - Chemotherapy; RT - Radiation Therapy; HSCT - Hematopoietic Stem Cell Transplantation; HP - Undefined Result; B - Chance Tends to Infinity Without a Confidence Interval; 0 - Chance Tends to zero without a confidence interval; OR> 1 - high probability of detecting a risk factor for diarrhea; OR <1 - high probability of detecting a risk factor with normal stool; * - Statistical Reliability $p < 0.05$; χ^2 - Pearson criterion; OR (95% CI) - odds ratio.

According to our results, CDI was detected in the group of children 0-1 years old (Table 2). This finding differs significantly from international data stating that children under one year old are mainly carriers of CDI and do not get the disease [29]. Thus, our study demonstrated that this issue in pediatric oncology has not been fully studied because there is no unequivocal opinion on this subject in the scientific community.

It is known that treatment with antibiotics increases the risk of developing CDI in any of the control groups. Thus, administration of fluoroquinolones - the most used class of antibiotics, followed by penicillins and cephalosporins [30,31] - presents the risk of diarrhea development in hospitalized patients, which is consistent with our data. Statistical analysis showed that the chance of CDI development is higher in the case of treatment with the following classes of antibiotics: carbapenems, cephalosporins, sulfonamides, nitroimidazoles (metronidazole), glycopeptides, penicillins, and the chance of developing of non-CDI is higher in the case of the use of antibiotics of the nitroimidazole class (metronidazole) and penicillins (Table 3). Nitroimidazoles (metronidazole) and glycopeptides (vancomycin) are the main drugs for the treatment of CDI [32]. Our data demonstrate that nitroimidazoles (metronidazole) act as a risk factor for diarrhea development in CDI and non-CDI patients. This is probably because

this drug has been used in clinical practice for a long time and antibiotic resistance to it has formed already. According to Tereshchenko., *et al*. more than 80% of strains of anaerobic microorganisms are resistant to metronidazole [33]. It is interesting to note, that patients treated with glycopeptides (vancomycin) are also at risk of developing CDI, which is associated with the route of drug administration [34]. The patients of the pediatric oncological hospital received this drug intravenously for treatment of the underlying disease. Another trend that was observed is that CDI development decreases with the use of antimycotics, which contradicts the data presented above. Perhaps this is due to the peculiarities of the treatment of the underlying disease as well as the administration of antimycotics in combination with anti-anaerobic drugs.

	CDI (n = 54)	non-CDI (n = 87)	KG (n = 46)	χ^2	OR (95% CI) CDI/KG	OR (95% CI) non-CDI /KG
Carbapenems	27	17	8	18.696*	4.750 (1.873-12.045)	1.154 (0.456-2.919)
Cephalosporins	20	11	7	13.226*	3.277 (1.235-8.696)	0.806 (0.290-2.244)
Aminoglycosides	16	10	6	8.438*	2.807 (0.994-7.926)	0.866 (0.293-2.554)
Sulfonamides (Biseptol)	49	23	16	58.992*	18.375 (6.103-55.324)	0.674 (0.312-1.457)
Nitroimidazole (Metronidazole)	34	38	9	19.062*	6.989 (2.801-17.436)	3.188 (1.373-7.405)
Oxazolidinones (Linezolid)	5	5	2	1.119	2.245 (0.414-12.162)	1.341 (0.250-7.200)
Fluroquinolones	15	11	7	5.499	2.143 (0.788-5.830)	0.806 (0.290-2.244)
Without antibiotics	4	10	8	2.397	0.380 (0.106-1.356)	0.617 (0.225-1.690)
Glycopeptides (Vancomycin)	35	26	10	24.083*	6.632 (2.707-16.246)	1.534 (0.664-3.546)
Macrolides/azalide	12	7	8	5.851	1.357 (0.501-3.676)	0.416 (0.140-1.231)
Penicillins	24	22	4	16.38*	8.400 (2.640-26.731)	3.554 (1.144-11.044)
Nitrofuran (Enterofuryl)	6	2	0	9.045*	-	-
Polypeptide (Colistin)	6	6	4	0.758	1.313 (0.347-4.969)	0.778 (0.208-2.908)
Antifungals	10	44	30	30.923*	0.121 (0.048- 0.303)	0.546 (0.261- 1.142)

Table 3: Influence of different groups of antibiotics on the development of diarrhea at pediatric oncological hospital.

n - Group Size; CDI - C. Difficile Infection; non-CDI - Diarrhea caused by other etiological factors; KG - Control Group; * - Statistical Reliability $p < 0.05$; χ^2 - Pearson Criterion; OR (95% CI) - Odds Ratio.

Conclusion

From the foregoing, the causes of diarrhea in the children's oncological hospital remain poorly understood. The role of bacteria as a factor in the development of loose stools needs to be investigated more thoroughly. Antibiotic using against anaerobic flora can cause antibiotic-associated diarrhea.

The improvement of methods for the prevention and treatment of diarrhea in the children's oncological hospital must necessarily include the corresponding analyses in a bacteriological laboratory, particularly study of bacterial cultures. This project raises many issues that remain unresolved and require monitoring, control and additional study.

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Conflict of Interest

Authors declare there is not any financial interest or any conflict of interest.

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