SHORT COMMUNICATION

The risk of developing a *Clostridium difficile* infection from the administration of different classes of antibiotics and their combinations to children in an oncological hospital

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ABSTRACT

Patients in pediatric oncological hospitals are at risk of developing a *Clostridium difficile* infection. The purpose of this study was to determine the risk of developing a *Clostridium difficile* infection in patients who are treated with antibiotics of different classes and their combinations by way of a retrospective analysis of 122 patient records. It was shown that the administration of antibacterial chemotherapeutic drugs that belong to the classes of nitrofurans (enterofuryl), sulfonamides (biseptol), cephalosporins, and macrolides/azalides significantly increased the risk of developing a *Clostridium difficile* infection in pediatric patients. On the contrary, treatment with antibiotics of different classes, such as linezolid, colistin, and metronidazole, significantly reduced the risk of developing a *Clostridium difficile* infection. The use of penicillins, aminoglycosides, fluoroquinolones, glycopeptides, and carbapenems was not associated with the risk of developing a *Clostridium difficile* infection in pediatric patients. The administration of one or two antimicrobial drugs of different classes increased the risk of developing a *Clostridium difficile* infection while a combination of three different types of antimicrobial drugs lowered the rate of this infection in pediatric patients.

INTRODUCTION

One side effect of antibiotics is the development of a multiple drug resistance of opportunistic microflora and the inhibition of the growth of indigenous human microflora. In these circumstances, conditionally pathogenic human microflora can cause serious diseases. Therefore, the predominance of *Clostridium difficile* (*C. difficile*) in the intestinal microbiota can cause both mild disease and serious illnesses, such as pseudomembranous colitis, toxic megacolon, intestinal perforation, and intestinal bleeding [1]. *C. difficile* diarrhea has been the cause of increased morbidity and mortality among hospitalized patients worldwide since 2000 [2, 3]. According to the Centers for Disease Control and Prevention (CDC, USA), in the United States alone, there are more than 400,000 cases of *C. difficile* infection with 29,000 fatalities every year [4]. Infections acquired in hospitals account for about two thirds of this amount. *C. difficile* is an anaerobic spore-forming Gram-positive bacterium of the *Peptostreptococcaceae* family of the *Clostridia* class, which belongs to opportunistic microorganisms present in the colon that develop during dysbiosis [5]. The development of a *C. difficile* infection is associated with the production of cellular toxins A (enterotoxin) and B (cytotoxin). These toxins bind to the surface of intestinal epithelial cells causing their death and lead to local inflammation [6].

A weakened immune status, disruption of the mucous membranes, and reduced conversion of primary bile salts into secondary ones observed in patients with impaired intestinal microflora are the main factors contributing to the disease [7]. Cancer patients who undergo anticancer chemotherapy and treatment with antimicrobial drugs over the course of long-term hospitalization have a high risk of developing a *C. difficile* infection [8-10]. According to Garzotto *et al.*, one of the main factors in the development of a *C. difficile* infection is treatment with antibiotics rather than the type of tumor or anticancer therapy [11]. However, Anand *et al.* showed that cytotoxic chemotherapeutic agents themselves are capable of causing a *C. difficile* infection in the absence of antibiotics [12].

When treating children with an anticipated long stay in the hospital, it is common practice to supplement the main therapy with several groups of antibiotics [13]. Simultaneous administration of several antibiotics significantly increases the risk of *C. difficile* infection in immunosuppressed patients [14]. The objective of this study was to find the correlation between the administration

of different classes of antibiotics and their combinations with the incidence of a *C. difficile* infection in children in an oncological hospital.

MATERIALS AND METHODS

Patients and study design

A retrospective observational study was carried out in an oncological hospital – Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology, and Immunology in Moscow (NSPC PHOI, Russia). A retrospective analysis of 122 patient records of children aged 0 to 18 years was carried out including 48 cases with diagnosed and confirmed *C. difficile* antibiotic-associated enterocolitis. The control group consisted of 74 patients treated in the same hospital at the same time, but without symptoms of intestinal damage and with a negative test for toxins A and B in the feces. At the time of detection of a *C. difficile* infection, the patients were undergoing treatment for the main disease with the addition of the following antimicrobial chemotherapeutic drugs: nitrofurans (enterofuryl), sulfonamides (biseptol), cephalosporins, macrolides/azalides, aminoglycosides, carbapenems, penicillins, fluoroquinolones, lipopeptides (colistin), and oxazolidines (linezolid). The control group received the same drugs.

Confirmation of a *C. difficile* infection in patients was carried out by the detection of toxins A and B in feces using a competitive ELISA RIDASCREEN test system (R-Biopharm, Germany).

The name and quantity of drugs used over the course of treatment of the main disease were recorded according to the patient's medical history. All of the data were collected and entered into a laboratory information system (SGM Analytix Explorer, Sweden). The statistical significance of the results was assessed by the Pearson χ^2 test at a significance level of $p < 0.05$.

RESULTS AND DISCUSSION

Analyzing the results of the therapy of children – patients of the oncological hospital NSPC PHOI, we calculated the frequency of *C. difficile* infections (by toxins A and B detection in the feces) in patients treated with different classes of antibacterial drugs. The results that are shown in Table 1 demonstrate a clear correlation between the use of antibacterial drugs that belong to the classes of nitrofurans, sulfonamides, cephalosporins, and macrolides/azalides and the development of a *C. difficile* infection in patients.

Treatment with enterofuryl (class of nitrofurans, the first group of antibacterials (Table 1)) led to the highest rate (66%) of *C. difficile* infections in patients. Kumar *et al.* showed the highest frequency of formation of resistant *C. difficile* mutants under the action of nitrofurans [15]. This effect explains the high probability of changing the microbiota composition in patients treated with drugs of the nitrofuran class due to the formation of resistant forms of *C. difficile* that in turn can cause the development of a pathological process.

Treatment with sulfonamides including biseptol – the second group of antibacterial drugs – led to less frequent development (55.1%) of *C. difficile* infections. However, according to Zakharova *et al.*, sulfonamides belong to the group of antimicrobials with a low risk of *C. difficile* infection development. This discrepancy may be due to the wider use of biseptol in children undergoing treatment in an oncological hospital compared with other groups of patients [16].

Table 1. The incidence of *C. difficile* infection development depending on the class of ACDs co-administered in the course of treatment of the main disease compared with the control group.

Antibiotic classes	Group size		Frequency of *C. difficile* infection occurrence, %	Statistical significance, p
	C. difficile infection	Control group		
Nitrofurans (enterofuryl)	4	2	66.7***	0.000035
Sulfonamides (biseptol)	27	22	55.1**	0.0017
Cephalosporins	12	10	54.5**	0.0020
Macrolides/azalides	6	7	46.2*	0.022
Aminoglycosides	7	10	41.2	0.07
Carbapenems	11	17	39.3	0.12
Penicillins	7	17	29.2	0.7
Fluoroquinolones	4	11	26.7	1
Glycopeptides	9	26	25.7	0.8
Metronidazole	2	32	5.9###	0.00027
Polypeptide cyclic (colistin)	0	6	0###	0.00000024
Oxazolidines (linezolid)	0	5	0###	0.00000024

* – p<0.05, ** – p<0.01, *** – p<0.001 indicates the statistically significant increase in the incidence of a *C. difficile* infection in cases with the administration of ACDs.

– p<0.001 indicates the statistically significant decrease in the incidence of *C. difficile* infection in cases with the administration of ACDs.

The administration of the drugs that belong to the third group – cephalosporin antibiotics – caused the development of *C. difficile* infections in children at a lower rate of 54.5%. This finding is consistent with literature data based on the results of meta-analysis of studies that showed the strongest relationship between the third-generation cephalosporins and *C. difficile* infections acquired in hospitals (hospital-acquired infections, HAIs) [17, 18].

The fourth group of antimicrobials, which includes macrolide/azalide antibiotics, showed a statistically significant correlation with the development of *C. difficile* infections in patients with the lowest rate of 46.2%, which agrees well with the literature data [18]. According to our data, the frequency of the *C. difficile* infection cases after the treatment of patients with carbapenems did not have statistical significance that contradicts the data of Vardakas *et al.* [19]. This could probably be explained by choosing meropenem for our study – the antibacterial agent that has anti-anaerobic activity.

Therefore, we have shown (Table 1) that the use of such antimicrobial chemotherapeutic drugs (ACDs) as nitrofurans, sulfonamides, cephalosporins, and macrolides/azalides in children – patients of an oncological hospital – was associated with the development of *C. difficile* infection. The differences in their effect on patients are possibly related to the patient's age and the course of treatment of the main disease.

Our data showed that the use of linezolid (group of oxazolidines) and colistin (a cyclic polypeptide antibiotic) significantly reduced the risk of *C. difficile* infection. This observation is consistent with the literature data on the activity of linezolid *in vitro* against *C. difficile* strains [20] and a low risk of developing a *C. difficile* infection over the course of treatment of patients with colistin [21]. In addition, it should be noted that, in our study, colistin was administered together with anti-anaerobic drugs, which reduces the risk of *C. difficile* infections.

Currently, two antimicrobial drugs registered for the treatment and prevention of *C. difficile* infections are used in Russian pediatric oncological hospitals: vancomycin and metronidazole [22]. It should be noted that, in our study, 2 patients developed a *C. difficile* infection while taking metronidazole and 9 patients – while treating the main disease with vancomycin. That could be explained by the emergence of *C. difficile* strains resistant to these drugs, and it could also be related to the route of administration of the drugs [23]. This issue requires a separate study. Since the problem of the treatment and prevention of *C. difficile* infection in a pediatric oncological clinic remains relevant, it is necessary to search for a new approach to combat this illness.

To assess the risk of the *C. difficile* infection development due to the simultaneous administration of 2 or 3 antibiotics, we compared the results from groups of patients treated with 2 or 3 drugs, group treated with 1 antibiotic as well as a control group that was not treated with antimicrobials. Our results showed (Table 2) that the use of 1 drug or combination of 2 drugs in the treatment significantly increased the risk of *C. difficile* infection development, while the simultaneous administration of 3 antibiotics reduced it. According to Lopes Cançado *et al.*, the amount of antibiotics used during hospitalization played a significant role in the development of *C. difficile* infections [24]. In our study, the reduced risk of *C. difficile* infections in cases where a combination of 3 or more antibiotics were used for the treatment of the patients could be explained by the inclusion of an anti-anaerobic component in this combination.

Therefore, the use of ACDs that belong to the following classes – nitrofurans (enterofuryl), sulfonamides (biseptol), cephalosporins, and macrolides/azalides – significantly increased the risk of the *C. difficile* infection development in children – patients of an oncological hospital. On the contrary, the treatment of pediatric patients with colistin, linezolid, and metronidazole significantly reduced the risk of development of the *C. difficile* infection, whereas the use of penicillins, aminoglycosides, fluoroquinolones, glycopeptides, and carbapenems was not associated with *C. difficile* infection development. The administration of one or two different classes of antimicrobials significantly increased the risk of the *C. difficile* infection development. On the contrary, the simultaneous administration of 3 different classes of antimicrobial drugs reduced the risk of *C. difficile* infection development.

Table 2. Frequency of *C. difficile* infection depending on the number of ACDs co-administered in the course of treatment of the main disease

	Frequency of *C. difficile* infection depending on the number of ACDs, %			
	0 ACD	**1 ACD**	**2 ACDs**	**3 ACDs and more**
Development risk of *C. difficile* infection, %	26.6 n=15	53.3 n=30 p=0.0029[a]	50.0 n=32 p=0.0077[a] p=0.74[b]	27.2 n=44 p=0.93[a] p=0.0037[b] p=0.0036[c]

n – group size

[a] – p value corresponding to an increase in the incidence of a *C. difficile* infection with the use of antimicrobial drugs compared with the group in which ACDs were not used.

[b] – p value corresponding to a decrease in the incidence of a *C. difficile* infection with the use of ACDs compared to the group in which 1 ACD was used.

[c] – p value corresponding to a decrease in the incidence of a *C. difficile* infection with the use of ACDs compared with the group in which 2 ACDs were used.

CONFLICT OF INTEREST

The authors have no commercial or financial interests.

CITATION

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