Выведение токсинов A + В у стуле пациентов и медицинских работников детского противотуберкулезного отделения

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Оригинальные исследования

Detection of *Clostridium difficile* toxins A and B in the stool specimens from patients and medical staff of the children’s antituberculosis department

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**Key words:** children, *Clostridium difficile* infection (CDI), rifampicin, medical staff.

The objective of our research was to determine the detection frequency of *C. difficile* toxins in the stool specimens from children receiving long-term treatment with rifampicin and in health care workers treating these children in a separate anti-tuberculosis hospital.

**Materials and methods.** 139 children with the average age of 13.6 years were examined; all of them had an infiltrative pulmonary tuberculosis and received long-term treatment with rifampicin at the Zaporizhzhia Regional Tuberculosis Dispensary. Also, 32 medical workers were examined and divided into high and low risk groups of *C. difficile* infection depending on the closeness of their contacts with children at the department. To detect *C. difficile* toxins A/B in the stool an ELI method was applied using the ELISA test system (Diagnostic Automation, Inc., Calabasas, USA). The amount of toxins ranged from 1 ng and more in 1 ml of feces sample was considered as diagnostic.

**Results.** 74 (53 %) children out of the 139 had a diagnostic titer of *C. difficile* toxins in their stool specimens. Among them, 49 (66 %) children had recurrent diarrhea, syndrome of abdominal pain without diarrhea was observed in 20 (27 %) and asymptomatic carrier state of CDI detected by laboratory tests was defined in 5 (7 %) children. Among 32 medical workers in the same department 6 (18.8 %) of them were positive for *C. difficile* toxins. It is noteworthy that three of them had received antibiotics during the last month prior to the study.

**Conclusions.** In the context of professional contacts with symptomatic or asymptomatic CDI children there is the risk of intestinal contamination among the health workers who intake antibiotics regardless of contacts closeness and total years of service at the hospital. At the same time, patients without diarrhea and, possibly, health workers of the department can be considered as an additional reservoir of *C. difficile*.
Introduction
Over the past decade, a significant increase in mortality from an infection caused by Clostridium difficile (C. difficile infection or CDI) has been observed in the North American continent and Europe [1,2]. The increase in the incidence and severity of CDI, as well as the mortality rate among hospitalized patients in recent years, have made this disease a global health care system problem, which makes it necessary to study the evolution of C. difficile and CDI epidemiology [3,4]. The pathomorphosis of CDI could be associated with the spread of the hypervirulent C. difficile strain, BI/NAP1/027, resistant to fluoroquinolone [2]. Genetic analysis points to the unstable C. difficile genome, which facilitates the adaptation of C. difficile to environmental changes and, therefore, leads to the emergence of more virulent strains [5]. A nosocomial model of CDI development as a hospital-acquired infection with diarrhea development, as well as its asymptomatic form, i.e. carriage of C. difficile [6,7], have been proposed. One of the reasons for the high degree of C. difficile seeding could be the formation of highly resistant and easily transferable spores, which requires new approaches to fighting infection and prevention methods [8]. Patients with manifest forms of CDI and asymptomatic carriers could equally spread the spores that lead to both direct (a person-to-person contact) and indirect C. difficile transmission [9]. In 60 % of cases the healthcare personnel clothing was colonized by pathogenic bacteria, including drug-resistant microorganisms [10]. Asymptomatic carriage of C. difficile toxicogenic strains, according to Stoesser N., 2017, could begin as early as after birth. Early C. difficile colonization forms protective properties of the intestine and reduces the risk of CDI development in the future [7]. The role of C. difficile asymptomatic carriage as an infectious reservoir for the CDI development in patients within the hospital is increasingly recognized. This fact involves the transmission of strains from asymptomatic carriers who have begun antibacterial therapy, as well as from patients who have been in hospital for a long time or who have received pathogenic strains from medical personnel [11,12]. The importance of C. difficile asymptomatic carriage in intestinal clostridiosis occurrence requires the revision of measures in order to protect and prevent the development of CDI among patients and hospital staff [13,14].

Materials and methods
The objective of our research was to determine the detection frequency of C. difficile toxins A/B in the stool specimens from children receiving long-term antibiotic treatment (necessarily including rifampicin) and simultaneously in medical personnel treating these children in a separate anti-tuberculosis hospital.

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Original research
Results and discussion

The data of our study showed that C. difficile toxins had been isolated in 74 (53%) of the 139 stool specimens of children treated in the separate specialized department, which is diagnostic for CDI. The clinical course of intestinal infectious disease was different. Among all the children with toxigenic C. difficile the most had recurrent diarrhea (49 or 66%); abdominal pain syndrome without diarrhea was observed in 20 (27%) and asymptomatic carriage of CDI, detected by laboratory tests, was found in 5 (7%) children. Symptoms of C. difficile infection such as abdominal pain, bloating, nausea, glossitis and stomach rumbling and fullness could have occurred even after 2 months of antibiotics treatment. Children suffered particularly from taking several anti-tuberculosis medications. Undulating course of CDI was also observed during a prolonged (up to 12 months) therapy.

The development of CDI in the examined children, in our opinion, was based on two events: the intestinal microbiota alteration (due to the prolonged intake of aggressive antibiotics) and C. difficile spores ingress through the fecal-oral route, which is traditional for the onset of intestinal infections. The risk factors for CDI development in children were long-term antibiotic therapy, the age of some patients younger than 5 years and long-term inpatient treatment in a separate hospital.

Since the potential risks of medical personnel contamination in a separate specialized children’s department following contact with a large number of C. difficile toxins-positive children are insufficiently covered in the literature, we decided to find out the transmission chains in the occurrence of CDI.

We examined 32 health care workers of the same department. All of them were divided into three groups based on the degree of their contact with the children. The 1st group included those who communicated with children most closely, i.e. nannies and nurses. The staff included in the 2nd group, the procedural nurses, had less close communication with children, while tutors, kitchen staff and doctors included in the 3rd group had even less frequent contacts with children. Among health care workers, 6 (18.8%) were C. difficile toxins-positive. It should be noted that three of them received antibiotics during the last month before the study. It has been found that the intensity of contacts with sick children in the department does not affect the incidence of C. difficile infection, since in all groups, both those who had frequent contacts with patients and those who did not have frequent contacts, the number of infected persons did not differ statistically ($\chi^2 = 1.2$, df = 1, P > 0.1). The seniority of medical personnel in the specialized tuberculosis department ranged from 3 to 14 years and also did not affect the frequency of CDI detection in health care workers.

It has been suggested that the source of infection could be hands, furniture and medical equipment as well as healthcare workers’ clothing. Their surfaces were contaminated with C. difficile spores and virulent microorganisms transmitted by both patients and medical personnel. Environmental shedding of C. difficile is possible by both infected individuals with diarrhea and asymptomatic carriers. The latter’s role is particularly important in the definition of reservoirs and carriers. The question of whether these bacteria could cause infection in patients requires further research. Obviously, the transmission routes of C. difficile are different. The figure below shows the expected transmission routes of C. difficile among patients and medical personnel in a pediatric hospital.

However, infection control measures should focus on two goals: reducing patients’ susceptibility to CDI through rationalization of antibiotic therapy and preventing the transmission of microorganisms among patients and medical personnel. In the hospital, detergents containing ammonium salts were used for disinfection of surfaces, which did not prevent the sporulation in Clostridium. The medical personnel used an ethanol-based hand gel for sanitization, which was not effective for the elimination of C. difficile. 10 % sodium hypochlorite, suitable for C. difficile environmental stress, was not used in the hospital. The use of gloves during contacts with patients without diarrhea was rare and did not take into account the risk of contact with carriers of virulent C. difficile strains in patients with asymptomatic forms of CDI. It has been noted that frequent and thorough hand washing with chlorhexidine or water with soap was effective for the mechanical removal of C. difficile spores from the skin of the hands. It is the hygiene and medical skills set of health care workers which are more important than the isolation of infected patients in single rooms.

Conclusions

1. The rate of children receiving treatment for pulmonary tuberculosis at the Zaporizhzhia Regional Tuberculosis Dispensary who had C. difficile toxins in their stool is 53 %.
2. The rate of medical workers in the department with positive tests for A/B C. difficile toxins in their stool is 18.8 %. The fecal excretion of enteropathogenic and necrotic toxins was not accompanied by clinical symptoms of CDI.
3. In the context of professional contacts with symptomatic or asymptomatic CDI children the risk of intestinal contamination development among the health workers increases with antibiotics intake, regardless of contacts closeness and total years of service at the hospital.
4. Patients with manifest CDI are the most important source of C. difficile infection for patients and medical personnel at a pediatric hospital. At the same time, patients without diarrhea and, possibly, medical workers of the department can be considered as an additional reservoir of C. difficile.
Prospects for further research. The search for effective CDI prevention measures among patients and medical personnel in separate tuberculosis treatment facilities should be performed using effective decontamination methods of utensils, furniture surfaces and medical equipment, as well as isolation of patients with CDI from healthy individuals.

Conflicts of interest: authors have no conflict of interest to declare.

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