

ANALYSIS OF REPORTED CASES OF *CLOSTRIDIODES DIFFICILE* INFECTIONS IN HEALTHCARE FACILITIES IN MARTIN DISTRICT DURING 3-YEAR SURVEILLANCE
ANALÝZA HLÁSENÝCH PRÍPADOV INFEKČII *CLOSTRIDIODES DIFFICILE* V ZDRAVOTNÍCKYCH ZARIADENIACH V OKRESE MARTIN V PRIEBEHU TROJROČNEJ SURVEILLANCE

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ABSTRACT

Background: Healthcare-associated infections are the threat for hospitalized patients. *Clostridioides difficile* infections of the bowel have become leading medical interest because of their increasing number in the present.

Aim: To analyse the occurrence of *Clostridioides difficile* infections in Martin District.

Methods: The research group consisted of patients with CDI enterocolitis hospitalized in Martin District and reported to Epidemiological Information System of the Slovak Republic. The group of hospitalized patients was studied and analyzed prospectively. To collect the patient data, we used "Form C: Case Data" from the European Centre for Disease Prevention and Control protocol "European surveillance of *Clostridioides difficile* infections" version 2.2, later updated to version 2.3. The data were gathered in the period from the 1st of October 2016 to the 30th of September 2019.

Results: We identified 407 cases of *Clostridioides difficile* infections, 326 (80.1 %) of them were hospital-acquired infections. The largest age group of patients with CDI were patients over 65 years, with 261 cases. Previous hospitalization in the last three months before the occurrence of CDI is a significant risk factor. The average time from admission to hospital to the emergence of CDI symptoms was 11.1 days.

Conclusion: *Clostridioides difficile* infections are a very serious problem in Martin District. Especially in risk population of older patients. The preventive measures such as correct hand-washing protocol and continuous surveillance are important tools to manage the problem.

Key words: Healthcare-associated infection. *Clostridioides difficile*. Antibiotic resistance. Surveillance. ECDC.

ABSTRAKT

Východiská: Nozokomiálne nákazy predstavujú hrozbu pre pacientov v zdravotníckych zariadeniach. V súčasnosti sa dostávajú do popredia medicínskeho záujmu klostrídiové infekcie čreva kvôli ich narastajúcemu výskytu.

Ciel': Analyzovať výskyt infekcií spôsobených *Clostridioides difficile* (CDI) v okrese Martin.

Metódy: Súbor tvorili pacienti s CDI enterokolitídou hospitalizovaní v okrese Martin a hlásení do Epidemiologického informačného systému Slovenskej republiky. Súbor bol študovaný a analyzovaný prospektívne. Na zber údajov o pacientovi bol použitý „Formulár C: Údaje o prípade“ z protokolu Európskeho centra pre prevenciu a kontrolu chorôb (ECDC) „Európska

surveillance infekcií *Clostridium difficile*“ verzie 2.2, neskôr aktualizované na verziu 2.3. Údaje boli zhromaždené v období od 1. októbra 2016 do 30. septembra 2019.

Výsledky: Identifikovali sme 407 prípadov infekcií spôsobených *Clostridioides difficile*, z toho 326 (80,1 %) boli nozokomiálne nákazy. Najväčšou vekovou skupinou pacientov s CDI boli pacienti starší ako 65 rokov, s 261 prípadmi. Predchádzajúca hospitalizácia za posledné tri mesiace pred výskytom CDI je významným rizikovým faktorom. Priemerný čas od prijatia do nemocnice po objavenie príznakov CDI bol 11,1 dňa.

Záver: Infekcie *Clostridioides difficile* sú v okrese Martin veľmi vážnym problémom. Najmä v rizikovej populácii starších pacientov. Preventívne opatrenia, ako napríklad správny protokol umývania rúk a nepretržitý dohľad, sú dôležitými nástrojmi na riešenie problému.

Kľúčové slová: Infekcia spojená so zdravotnou starostlivosťou. *Clostridioides difficile*. Rezistencia na antibiotiká. Dohľad. ECDC.

INTRODUCTION

Clostridioides difficile (formerly *Clostridium difficile*) is a sporulating anaerobic gram-positive toxigenic bacterium that easily attaches to the colon mucosa. It produces toxins A and B or binary toxin A/B. If it does not have the right conditions for life, it can transform into spores, allowing it to live on a variety of surfaces, clothing, towels, and others. After ingestion of spores and vegetative forms, *Clostridioides difficile* enters the stomach in which the acidic environment destroys vegetative forms [1]. If there is little acid in the stomach, the spores can enter the small intestine. Insufficiently acidic stomach environment is found in patients treated by e.g. proton pump blockers [2]. In the small intestine due to bile acids, the spores germinate, get into the large intestine, where they easily adhere to the mucosa and begin to produce toxins. Toxin A is an enterotoxin, it causes water secretion into the intestine,

and toxin B is a cytotoxin, it breaks the connection between the colonocytes, it destroys the cytoskeleton of the colonocyte. It can also affect intestinal smooth muscle and vegetative nerves of the large intestine. These mechanisms result in secretory diarrhoea, but also intestinal paralysis, hypomotility, which allows bacteria to remain longer in the intestine to multiply there [3, 4].

Diarrhoea serves as a defense mechanism of the body that tries to eliminate toxins from the intestine. Due to the effects of toxins on the vegetative nerves of the intestine, patients do not have much abdominal pain, as in various other acute colitis. Adherence of the microorganism to the intestinal wall results in ulceration. If the disease persists, it can cause a slowdown until the peristalsis of the intestine stops, leading to an ileus condition. The gradual loss of the barrier protective function of the intestinal mucosa can lead to the formation of megacolon. The bacteria from the intestine subsequently enter the bloodstream as well as the intestine. This can cause septic conditions or even lead to the death of the patient [5].

Existence of correct and exact information about the *Clostridioides difficile* infections (CDI) is required for preparation of correct and effective regulations leading to the decrease of incidence of CDI and their impact. Standardized periodical or continual surveillance enables the determination of epidemiological changes. A prospective active approach to surveillance of hospital-acquired infections helps to prevent hospital-onset of infections and is cost-beneficial to diagnosis and treatment of infections [6, 7].

In the Slovak Republic and district of Martin, the incidence of CDI increased during the years 2010 to 2017. Diseases had predominantly healthcare-associated – nosocomial-character, targeting mostly older patients (65+ - 24/10 000 in the Slovak Republic and 62/10,000 in the district of Martin) [8]. *Clostridioides difficile* is currently the most frequent pathogen causing hospital-acquired infections in the Slovak Republic [9]. The aim of our study was to analyse the occurrence of *Clostridioides difficile* infections in the district of Martin.

PATIENTS AND METHODS

The analyzed group consisted of hospitalized patients in medical facilities in the Martin District with reported enterocolitis due to *Clostridioides difficile*. To collect the patient data we used the "Form C:

Case Data" from European Centre for Disease Prevention and Control protocol "European surveillance of *Clostridioides difficile* infections" version 2.2, later updated to version 2.3 [10, 11].

The data were then entered into the Epidemiological Information System of the Slovak Republic. Data collection took place over a period of two years, from 01.10.2016 to 30.09.2019.

We used the ECDC case definition CDI. According to the ECDC protocol, a case of CDI must meet at least one of the following criteria:

- diarrhoea or toxic megacolon and a positive laboratory result for toxin *Clostridioides difficile* A and/or B in stool or toxin-producing *Clostridioides difficile* detected in faeces by culture or as a positive PCR result;
- pseudomembranous colitis as detected by endoscopy of the lower gastrointestinal tract;
- colon histopathology characteristic CDI (with or without diarrhoea) on the sample obtained during endoscopy, colectomy, or autopsy.

Healthcare-associated form of hospitalized case of CDI was considered if the onset of symptoms occurred on the third day after admission to the healthcare facility or within 4 weeks of discharge from the healthcare facility. A community form of infection was considered to have been the first signs of symptoms outside the healthcare facility and not discharged within the previous 12 weeks, or within the first two days of admission to hospital.

In addition to baseline data on patients, gender and age, we investigated previous hospitalization within three months prior to the onset of CDI. We asked about the severity of the underlying disease, the date of the start and end of hospitalization, and the outcome of the patient. We investigated whether the patient had been discharged alive or whether he had died, and if so, whether the death had been related to CDI. We also assessed the complexity of CDI cases according to the protocol and whether the patient had been taking antibiotics before the infection occurred.

All acute care departments were included in the data collection. All hospitalized patients were included, including children aged 2 years or less. The patient was considered hospitalized when he was registered in the hospital system. Excluded cases were one-day cases, e.g. one-day surgery, emergency patients, dialysis patients (outpatient), and others.

RESULTS

From the total number of 407 of CDI, 211 patients (51.8 %) were women and 196 patients were men (48.2 %). There were 326 healthcare-associated cases (80.1 %) and 81 community-associated cases (19.9 %) of CDI. Gender difference between the types of infection was not statistically significant ($p > 0.05$) (Tab. 1).

The largest age group of patients with *Clostridioides difficile* infections were patients over 65 years with 261 cases (64.1 %). Average age of patients was 66.4 years (Median = 70, Mode = 79, Standard Deviation = 19.5). No *Clostridioides difficile* infections cases were reported in the 10–14 years old category (Chart 1).

Most patients – 325 (79.9 %) with *Clostridioides difficile* infections had non-fatal underlying disease. Fifty-two patients (12.8 %) had diagnosis, which was ultimately fatal. 30 patients (7.4 %) had a rapidly fatal underlying disease. One hundred and twenty patients (29.5 %) had *Clostridioides difficile* infections symptoms upon their admission to a hospital. Of the 407 *Clostridioides difficile* infections patients, 88 (21.6 %) had a complicated course of the disease.

Most patients with CDI (230; 56.5 %) were hospitalized in the previous three months prior to the onset of an infection. Most patients with healthcare-associated CDI (379, 93.1 %) were discharged from hospital alive. In twenty-seven cases (6.6 %) the patient died, but unrelated to a *C. difficile* infection and in one case (0.2 %) the relationship to CDI was unknown (Table 2). We found that previous hospitalization in the last three months before occurrence of healthcare-associated CDI is a significant risk factor ($p < 0.05$) (Table 3).

The average time from admission to hospital to emergence of CDI symptoms was 11.1 days (Me-

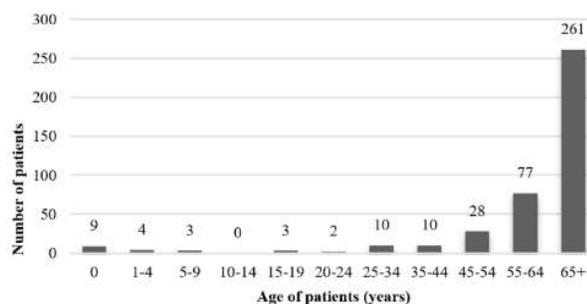


Chart 1 Age distribution of hospitalized patients with *Clostridioides difficile* infection (N = 283)

Table 1 Occurrence of healthcare-associated and community-associated *Clostridioides difficile* infections between genders (N = 407)

Gender	Healthcare-associated CDI		Community-associated CDI		Total	
	N	%	N	%	N	%
Women	167	41.0	44	10.8	211	51.8
Men	159	39.1	37	9.1	196	48.2
Total	326	80.1	81	19.9	407	100

Table 2 Hospitalized patient indicators – *Clostridioides difficile* infection

Parameter	N	%	
McCabe score	Rapidly fatal underlying disease (survival < 1 year)	30	7.4
	Ultimately fatal underlying disease (survival 1–4 years)	52	12.8
	Non-fatal underlying disease (survival at least 5 years)	325	79.9
CDI definitely contributed to death	0	0.0	
Healthcare-associated CDI	326	80.1	
Previous antibiotic treatment	279	68.6	
Symptoms of CDI present at admission	120	29.5	
Previous healthcare admission in the last 3 months	230	56.5	
Complicated course of CDI	88	21.6	

Table 3 Occurrence of healthcare-associated and community-associated *Clostridioides difficile* infections between the patients with and without previous hospitalization (N = 407)

Previous hospitalization	Community-associated CDI		Healthcare-associated CDI		Total	
	N	%	N	%	N	%
With	33	8.1	197	48.4	230	56.5
Without	48	11.8	129	31.7	177	43.5
Total	81	19.9	326	80.1	407	100

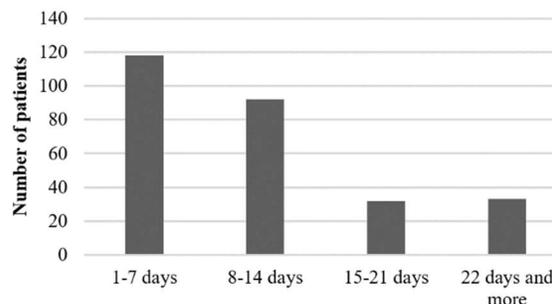


Chart 2 Number of days of hospitalization before healthcare-associated *Clostridioides difficile* infection occurrence (N=326)

dian 8 days, Mode 4 days, Standard Deviation 9.8). Healthcare-associated CDI most commonly occurred during the first week of treatment (118; 36.2 %) (Chart 2). The most reported healthcare-associated cases of CDI were from internal medicine departments (259; 79.5 %). Fifty-one cases were from surgical wards (15.6 %), nine from paediatric wards (2.8 %) and seven from anaesthesia-resuscitation wards (2.2 %) (Chart 3).

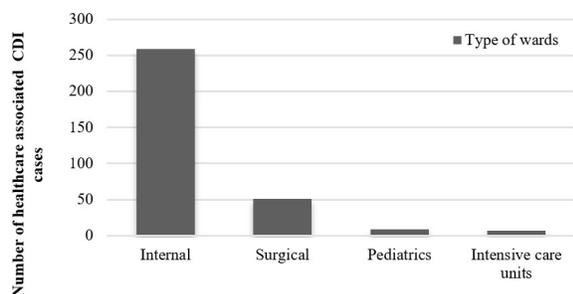


Chart 3 Occurrence of healthcare-associated *Clostridioides difficile* infection by type of hospital ward (N=326)

DISCUSSION

In line with the above results, even during our surveillance, the healthcare-associated CDI represented a larger group than the community-associated cases. With an 80.1 % share, the representation was slightly larger than the national average in 2018 (79.4 %) [9]. Both men and women were represented in approximately equal numbers.

According to a report by the Annual Epidemiological Report for 2016 Healthcare-associated infections: CDI [12], 62.6% of patients diagnosed with CDI were hospitalized in the previous three months prior to the onset of infection. Our results show a similar figure, namely 56.5 %.

An important indicator of healthcare-associated *Clostridioides difficile* infection (HA-CDI) is the time of onset since the start of hospitalization. During the first two days, CDI could not yet be a nosocomial case, so the first cases started only from the third day of hospitalization. Despite that, the HA-CDI were most common in the first week of hospitalization.

ATB treatment also contributes to the development of CDI during hospitalization. The ECDC protocol we used to collect the data did not ask whether the patient had been taking antibiotics, what type and how long [10, 11]. In future data collections, we will certainly focus also on previous antibiotic treatment, as it is, in the scientific litera-

ture, considered to be one of the most common and significant risk factors of developing a case of CDI.

HA-CDI were most commonly found in internal clinics (259 out of 326 available cases) where due to the nature of diagnosis an antibiotic therapy is usually more common than in surgical and other types of the ward. Therefore, consistent, and effective indication of antibiotic therapy is an important form of preventing the occurrence of HA-CDI. Another preventive measure is the presence of probiotic prophylaxis [13-15]. A minor problem that we encountered in the study of scientific literature was obtaining the data on CDI distribution by hospital wards in other countries. We wanted to compare our findings with the world, but we could not find any relevant data. In the "Form C: Case Data" was question about in which department the CDI occurred, however, this information is not a part of the ECDC CDI Surveillance Report [12].

Although HA-CDI may be a complication of hospitalization with a fatal outcome, during our surveillance, we did not see any case where the patient died due to *Clostridioides difficile*. Several patients with HA-CDI died during hospitalization, but *Clostridioides difficile* did not factor in the deaths. More than 90 % of patients were discharged alive. This is in line with other results of our research where CDI did not have a complicated course in most patients. The possible reasons are the absence of serious strains of *Clostridioides difficile* in health-care facilities in Martin District as well as in the quality of health care provided. Another possible reason is that the underlying diseases in most patients were categorized as non-fatal.

The age distribution in our surveillance shows that CDI is most common in patients over the age of 65 years. Due to the ageing of the population, it can be assumed that this trend will not change. Older patients are often polymorbid, being more subjected to a more frequent use of different types of antibiotics. Therefore, it is especially necessary to prescribe the antibiotic treatment only when necessary and for the necessary time duration.

Washing hands with soap and water is the most effective way to remove CDI spores from hands [16]. For this reason, the training of health professionals is important. If a hospital or other health care facility is equipped with in-room disinfectant dispensers, it is possible that healthcare workers will automatically disinfect their hands, even in patients with CDI, and will consider it to be sufficient. As

a result, in Slovakia the hand disinfection is supplemented with hand washing with soap in cases of contamination or suspected contamination by *Clostridioides difficile*.

It is important to repeat the practice of proper hand hygiene procedures regularly. In a study aimed to trace the knowledge of hand hygiene compliance in students of medical and non-medical study programs (Public Health, Nursing and Midwifery) in Martin, many students failed to carry out the hand hygiene procedure according to the WHO guidelines successfully. Although students showed some knowledge of hand hygiene, they did not consider hand washing to be an essential part of daily routines [17].

Our study shows that CDI is very serious hospital-acquired infection. Special treatment regime for infected patients, including correct hand washing and rational antibiotic treatment, may significantly affect the situation. Properly implemented surveillance of CDI will also prevent such diseases, especially in the risk group of the population.

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