doi: 10.7251/ZSAN2302439K **Original scientific paper**

INCIDENCE OF *CLOSTRIDIUM DIFFICILE* INFECTION IN PATIENTS WITH DIARRHEA IN A TERTIARY CARE HOSPITAL

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Apstract: *Clostridium difficile infection (CDI) is one of the most common healthcare-associated infections. Establishing an accurate diagnosis of CDI, apart from the patient, is important for controlling the spread of infection and is a prerequisite for collecting reliable surveillance data, so that infections can be monitored, compared and the effectiveness of interventions evaluated. A retrospective study was conducted to determine the incidence of C. difficile in patients with a history of prior hospitalization and/or antibiotic treatment who developed diarrhoea in a tertiary care hospital. The etiological diagnosis of CDI was established by an immunochromatographic rapid test for the qualitative detection of toxin A and toxin B antigens from stool samples using VEDA LAB Toxin A+B (Clostridium difficile). Because of the comparison of variables that could have contributed to the differences in CDI incidence, clinical data on patients were also taken. During the five-year surveillance period, the incidence rate was 4.2 cases per 10,000 patient-days. A total of 5,538 stool samples were laboratory tested for the detection of C. difficile toxin A + B. There were 590 (10.7%) positive samples for toxin A and/or B, while CDI was not laboratory confirmed in 4,948 (89.4%). The dominance of C. difficile toxin A over toxin B or toxin AB was observed ($p < 0.001$). The largest number of cases positive for C. difficile toxin were from stool samples of patients hospitalized at the Internal Medicine Clinic, and then at the Infectious Diseases Clinic. Of the total number of CDI cases, in 430 (87.6%) patients it was a nosocomial infection, and repeated CDI was recorded in 34 (6.9%) patients. CDI is the most important cause of nosocomial diarrhoea, and timely laboratory results of C. difficile testing can influence decisions regarding antibiotic therapy and infection control measures. Due to the large number of negative results, immunoassays alone cannot be used to prove C. difficile in the stool. It is necessary to improve reference methods for laboratory diagnostics of C. difficile.*

Keywords*: Clostridium difficile infection, epidemiological surveillance, laboratory tests*

Introduction

Clostridium difficile, recently reclassified as *Clostridioides difficile* is an anaerobic, Gram-positive bacterium that causes infection in patients with altered intestinal microbiota due to the use of antimicrobial or chemotherapy drugs (dysbiosis). Establishing an accurate diagnosis of *C.difficile* infection (CDI), apart from the patient, is important to control the spread of infection, and is a prerequisite for the collection of reliable surveillance data, so that infections can be monitored, compared and the success of interventions evaluated [1]. The optimal method for laboratory diagnosis of *C.difficile* is still questionable [2]. The laboratory methods used to detect *C.difficile* at the beginning of the CDI era took a long time, which limited their application in routine diagnostics. Several laboratory tests are currently available to detect *C.difficile*: tests to determine toxins in the stool (Enzyme Immuno Assay, EIA; Cytotoxin Test /Cell Culture Cytotoxicity Assay, CCCA), tests for *C.difficile* common antigen, EIA for glutamate dehydrogenase (GDH) or proving of a toxic strain of *C.difficile* (toxigenic stool culture / Nucleic Acid Amplification Test, NAAT) [3]. The sensitivity of these tests is different and ranges from 53 to 60% for EIA, up to 95% for NAAT. The average specificity of these methods is >90%. However, the positive predictive value (PPV) depends on the prevalence of the disease, meaning that lower reported CDI rates are associated with lower PPV [4]. American guidelines for the diagnosis and treatment of CDI recommend toxigenic culture as the standard against which the results of other clinical tests should be compared [5]. However, toxigenic culture is usually used as a reference method and not as a diagnostic one due to technical problems and long duration [6]. The reference methods according to some authors for the detection of *C.difficile* toxins are the cell culture neutralization test (CCCA) and EIA. CCCA is used to detect free toxins (mainly toxin B) in feces. EIAs generally detect both toxins A and B (with or without differentiation), using monoclonal or polyclonal antibodies [7-9]. GDH is an enzyme, which is present in both toxigenic and non-toxigenic strains of *C.difficile*, and can be determined by EIA (ELISA or immunochromatographic assays; GDH EIA), where the results are usually shown as a color change, which is determined visually or photo-spectrometrically or visually on the membrane [10]. Various guidelines now suggest GDH EIA as a CDI screening method. A positive GDH result must be confirmed by another more specific toxin test [11]. Amplification of *C.difficile* DNA is carried out using Polymerase Chain Reaction (PCR), which determines the genes that code for toxins, the tcdA gene for toxin A and the tcdB gene for toxin B. NAAT and binary toxin (cdt) genes and nucleotide deletions 117 to tcdC, so they represent a possible advantage of detecting PCR ribotype 027 [10]. Although NAAT is more expensive than other methods, it is widely accepted as a laboratory diagnostic tool due to its high sensitivity and speed of sample processing [2]. It is important to choose a representative sample of feces, because currently available laboratory tests do not distinguish symptomatic CDI from asymptomatic. Laboratories can apply appropriate criteria for inappropriate test samples [12]. Continuous education of doctors and nurses, as well as monitoring of feedback, are necessary to reduce the percentage of unnecessary testing [13]. Literary data have shown that among patients with diarrhea,

there is a significant number of those with false positive or negative tests for *C.difficile*, due to incorrect laboratory processing of samples [14]. One stool is sufficient for analysis, as multiple stools do not increase the likelihood of detecting *C.difficile*. Repeated testing increases the likelihood of false positive results due to the lack of specific methods [11].

The aim of the study is to determine the incidence of *C.difficile* infections in a tertiary care hospital, as well as to examine the current application of laboratory-diagnostic methods for the detection of *C.difficile*.

Methods

The hospital surveillance study was retrospective, and CDI case definitions based on CDI surveillance recommendations from the European Center for Infection Prevention and Control (ECDC) were used [15]. Demographic data on CDI patients were collected from original laboratory and medical records. The research included the records of patients who met the inclusion criteria from January 1, 2018 to December 31, 2022. The inclusion criteria were: patients older than two years; hospitalized in the University Clinical Center of the Republic of Srpska (UKC RS) who meet the definition of CDI; that the patient was admitted to the hospital during the study period with signs and symptoms of CDI present on admission, although this episode of CDI had already been diagnosed before admission (e.g. in the admission clinic), that these were repeated cases of CDI and only the first positive *C .difficile* laboratory tests were included in the study. The research did not include patients of day hospitals, e.g. one-day surgery, hemodialysis patients and outpatients, as well as repeated positive laboratory tests for *C. difficile*, i.e. two or more stool samples from the same patient during the current hospitalization. The etiological diagnosis of CDI was made at the Department of Clinical Microbiology UKC RS by an immunochromatographic test for the detection of toxin A and toxin B from stool samples using VEDA LAB Toxin A and/or B (*Clostridium difficile*) DUO (ZAT du Londeau - Rue de l'expansion, Cerisé - BP 181 - 61006 Alençon, France). The PCR method for proving the binary toxin in *C.difficile* ribotype 027 (Cefeid Xpert® C. difficile BT, Röntgenvägen 5, SE-17154, Solna, Sweden) has been used in the Institute of Clinical Microbiology UKC RS since 2019, and since 2022. and a gastrointestinal (GI) panel (BioFire Diagnostics, LLC, Salt Lake City, United States), that is, tests for common GI microorganisms (viruses, bacteria, and parasites) that cause diarrhea, including *C. difficile*.

The software package SPSS, version 25.0 with a 95% confidence interval of statistical significance was used for statistical data processing. The incidence rate of intrahospital CDI was calculated as the ratio of the number of infections/10,000 patient days. The Kolmogorov-Smirnov and Shapiro-Wilks tests and the chi-square ($\chi 2$) test were used to compare research groups. Values of $p<0.05$ were considered statistically significant.

Results

During the five-year surveillance period, the overall incidence of CDI was 4.20 per 10,000 hospital-days. The annual CDI rate ranged from 2.86 per 10,000 patient-days recorded in 2020 to 3.94 per 10,000 patient-days in 2018 (3.36±0.50). The highest number of CDI cases (147) was recorded in 2019 (Figure 1).

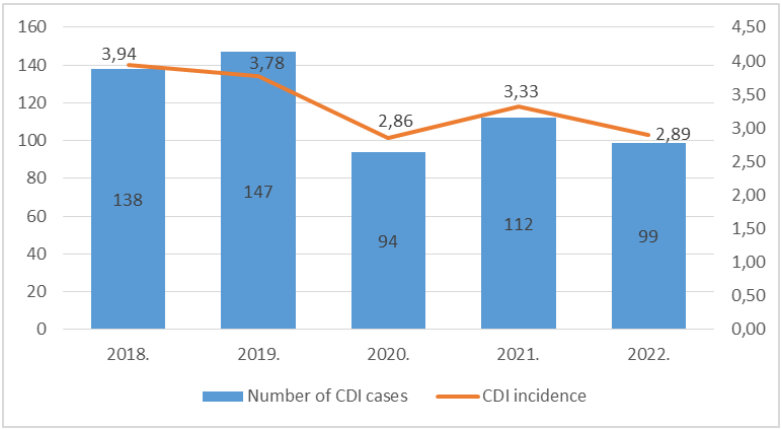

Figure 1. Number of CDI cases and annual CDI incidence rates per 10.000 patient-days.

During the study period, a total of 5,538 stool samples were sent to the microbiology laboratory for determination of *C. difficile*. There were 590 (10.7%) positive samples, and 4,948 (89.4%) negative samples ($p<0.05$) (Table 1). As of 2019, *C. difficile* isolates from 65 stool samples were sent for ribotyping (GeneXpert), and in the population of analyzed patients, ribotype 027 was proven in 23 (35.4%). Using the PCR method (FilmArray, GIT panel) to prove the tcdA gene for toxin A, the tcdB gene for toxin B and the tcdC gene for the binary toxin, 121 stool samples were processed during 2022, of which 9 samples were positive.

Table 1. Results of microbiological testing for *C. difficile* by year

The time of examination	**Microbiological analyses**						**χ^2 p-value**
	Positive		**Negative**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	
2018.	138	11.4	1,077	88.6	1,215	21.9	
2019.	147	14.2	890	85.8	1,037	18.7	
2020.	94	9.9	859	90.1	953	17.2	**23,709 p<0.05**
2021.	112	10.1	994	89.9	1,106	20.0	
2022.	99	8.1	1.128	91.9	1,227	22.2	
Total	**590**	**10.7**	**4,948**	**89.4**	**5,538**	**100.0**	

χ^2, Chi square test; p, statistical significance

Table 2 shows the results of microbiological testing using rapid immunochromatographic tests to prove toxin A and/or B. The dominance of toxin A in *C. difficile* positive patients (68.8%) was observed compared to toxin B in *C. difficile* (21.4%). ie toxin AB *C. difficile* (9.8%).

Table 2. Differences in the frequency of microbiological diagnostic results of rapid immunochromatographic tests

The time of examination	Immunochromatographic tests						χ^2 p-value
	Toxins A		Toxins B		Toxins A/B		
	n	%	n	%	n	%	
2018.	106	76.8	32	23.2	0	0.00	
2019.	100	68.0	47	32.0	0	0.00	
2020.	69	73.4	4	4.3	21	22.3	**160,544 p<0.001**
2021.	57	55.9	41	40.2	4	3.9	
2022.	67	67.7	0	0.00	32	32.3	
Total	**399**	**68.8**	**124**	**21.4**	**57**	**9.8**	

χ^2, Chi square test; p, statistical significance

Table 3 shows the clinics where there were the most patients with CDI in the observed hospital. Statistically significant (p<0.001) more patients were treated in the Clinic for internal medicine (37.1%) compared to other clinics (Table 3). Of the total number of CDI cases, in 430 (87.6%) patients it was a nosocomial infection, repeated CDI was recorded in 34 (6.9%) patients, and for 126 (21.4%) cases there was no data on the origin CDI.

Table 3. Differences in number of positive cases between clinics with hospitalized CDI patients

Clinics	The time of examination						χ^2 p-value
	2018.	2019.	2020.	2021.	2022.	Ukupno	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Internal medicine	38 (22.8)	48 (28.7)	30 (18.0)	29 (17.4)	22 (13.2)	167 (37.1)	
Infectology	45 (34.1)	43 (32.6)	14 (10.6)	15 (11.4)	15 (11.4)	132 (29.3)	
Medical ICUs	13 (22.0)	9 (15.3)	8 (13.6)	16 (27.1)	13 (22.0)	59 (13.1)	
Oncology	5 (15.6)	11 (34.4)	6 (18.8)	5 (15.6)	5 (15.6)	32 (7.1)	**47,914 p<0.001**
Pulmonology	3 (8.8)	4 (11.8)	6 (17.7)	13 (38.2)	8 (23.5)	34 (7.6)	
General Surgery	4 (15.4)	4 (15.4)	9 (34.6)	5 (19.2)	4 (15.4)	26 (5.8)	
Total	**399 (24.0)**	**119 (26.4)**	**73 (16.2)**	**83 (18.4)**	**67 (14.9)**	**450 (100.0)**	

ICU, Intensive care medicine; χ^2, Chi-square test

Discusion

Surveillance of infections caused by C. difficile is an important component of the prevention program. Calculation of annual CDI incidence rates provides a useful analysis of CDI risk factors, disease course, and outcome for planning prevention programs [16].

The results of the research presented here showed that the average annual incidence of CDI was 3.94 per 10,000 patient-hospital days.

According to currently available ECDC data published in 2018, the average incidence of CDI was highest in tertiary care hospitals (5.8 cases/10,000 patient-days) and lowest in primary care hospitals (2.8 cases/10,000 patient-days). days). Estonia (12.93 cases/10,000 patient-days), Lithuania (7.88 cases/10,000 patient-days) and Poland (6.18 cases/10,000 patient-days) had the highest incidence rates of nosocomial CDI. The lowest incidence rate of nosocomial CDI was in Austria (1.64 cases/10,000 patient-days), followed by Lithuania (1.71 cases/10,000 patient-days) and England and Scotland (1.99 cases/10,000 patient-days) [17].

In the observed time period during 2020, there was a significantly lower number of patients with laboratory-confirmed CDI, which could be explained by the fact that due to the COVID-19 pandemic, samples were sent less often for CDI testing. In addition, most of the UKC RS clinics were organized into COVID-19 clinics during the COVID-19 pandemic. The employed staff wore personal protective equipment and the hospital environment was disinfected more often, and visits to patients were prohibited. Similar results were shown by a study by Spanish authors conducted in two tertiary level hospitals in the period from January 2019 to February 2021. During the COVID-19 pandemic, the incidence rate of CDI was 2.6 per 10,000 hospital days in one hospital, which was lower from the incidence before the pandemic (4.1 per 10,000 hospital days). In another hospital, the incidence of CDI was 3.9 out of 10. 000 hospital days and was not significantly different from the rate before the COVID-19 pandemic (3.7 per 10,000 hospital days) [18]. Contrary to these studies, Lewandowski et al. [19] found a significant increase in the incidence of CDI during the COVID-19 pandemic compared to the pre-pandemic period in a university hospital in Warsaw.

Some recently published studies have shown results similar to ours when it comes to the proportion of laboratory-proven CDI compared to all tested patients with suspected CDI. The results of the research by Hawes et al. [20] from January 2019 to June 2020 showed that there was no change in CDI incidence rates, but testing decreased statistically significantly during the first wave of the COVID-19 pandemic despite increased antibiotic use. The decrease in the incidence rate of CDI may be due to a decrease in the rate of CDI testing, possibly due to diarrhea as a symptom in both COVID-19 and CDI, less interest in infectious diseases other than COVID-19, or the lack of PCR diagnostics due to the priority of SARS-CoV-2 tests and an insufficient number of laboratory staff. In the Netherlands, the lack of PCR

diagnostics and laboratory staff has led to the use of other types of laboratory tests to detect C. difficile. such as EIA [21].

During the research period, from the total sample of patients with a post-antimicrobial diagnosis, 5,538 stool samples were laboratory tested to prove antigen positive for C. difficile. There were 10.65% positive patients for toxin A and/or B, while in 89.35% CDI was not laboratory confirmed. The dominance of C. difficile toxin A in positive patients (62.9%) was observed compared to C. difficile toxin AB (31.1%) and C. difficile toxin B (6%).

The results of ribotyping showed that ribotype 027 was isolated from patient samples, which is in accordance with the data of the research that was conducted on samples from several countries in Southeast Europe [22]. That the incidence of CDI infections in the Clinical Center of Serbia and throughout Serbia is constantly increasing was confirmed by the research of Jovanović et al. [23] where of 6,164 stool samples sent to a bacteriological laboratory for C. difficile culture and toxin determination from 2009 to 2013, 28.8% were positive, showing a linear upward trend. Of the 96 isolates, the majority (88.54%) belonged to PCR ribotype 027.

Because of the lack of confidence in the sensitivity of the EIA test for C. difficile, some clinicians assume that an initial negative result may represent a false negative result and therefore often send samples for retesting. If the first C. difficile EIA stool toxin test was negative, retesting is unnecessary and not cost effective. This was confirmed in their research by Mohan et al. [24] where of the total number of patients in the study group (396), 474 samples were tested for C. difficile toxin A and toxin B EIA. 78 were retested, and of these only 1 tested positive for C. difficile on retest (1/78) after initially being negative.

In contrast to these studies, some others showed a small participation of positive tests for C. difficile. Thus, in the research by Allawi et al. [25] during a five-year period (2013-2018), a test for toxins A and B was performed in 1,885 hospitalized adult patients. Only 129 patients had positive test results and were diagnosed with CDI.

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) has recommended that CDI testing should not be limited to samples with a specific request from a physician. Also, all submitted unformed stool samples from patients older than 3 years should be tested for CDI [10].

There is still no reference laboratory diagnostics for C. difficile because the exact characteristics of the tests and the success of different combinations of tests have not been proven. In addition, no single commercially available test can be used as a stand-alone test for diagnosing CDI due to inadequate PPVs at the low prevalence of CDI. ESCMID's recommendation is not to use one rapid test as an independent test due to inadequate PPV. Currently, the References based on published evidence for diagnosing C. difficile, i.e. the presence of toxins or genes, supports the use of GDH//NAAT or GDH/toxin/NAAT algorithms [3,10].

Conclusion

CDI is the most important cause of nosocomial diarrhoea, and timely laboratory results of *C.difficile* testing can influence decisions regarding antibiotic therapy and infection control measures. Due to the large number of negative results, immunoassays alone cannot be used to prove *C.difficile* in the stool. It is necessary to improve reference methods for laboratory diagnostics of *C.difficile*.

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INCIDENCIJA INFEKCIJA SA *CLOSTRIDIUM DIFFICILE* KOD PACIJENATA SA DIJAREJOM U BOLNICI ZA TERCIJARNU NJEGU

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Sažetak: *Infekcija sa Clostridium difficile (CDI) jedna je od najčešćih infekcija povezanih sa zdravstvenom njegom. Postavljanje tačne dijagnoze CDI, osim za pacijenta važna je za sprečavanje širenja infekcije, a i preduslov je za prikupljanje pouzdanih podataka nadzora, kako bi se infekcije mogle pratiti, porediti i procjenjivati uspjeh intervencija.Provedena je retrospektivna studija kako bi se utvrdila incidencija infekcija sa C.difficile kod pacijenata sa anamnezom prethodne hospitalizacije i/ili liječenja antibioticima koji su razvili dijareju u bolnici za tercijarnu njegu. Etiološka dijagnoza CDI je postavljana imunohromato-grafski brzim testom za kvalitativno utvrđivanje antigena toksina A i toksina B iz uzoraka stolice pomoću VEDA LAB Toxin A+B (Clostridium difficile). Radi upoređivanja varijabli koje su mogle da doprinesu razlikama učestalosti CDI, uzeti su i klinički podaci o pacijentima. Tokom petogodišnjeg perioda nadzora, stopa incidencije iznosila je 4,2 slučajeva na 10.000 pacijent-dana. Laboratorijski je testirano ukupno 5.538 uzoraka stolice radi dokazivanja antigen pozitivnih na C.difficile. Pozitivnih uzoraka na toksin A i/ili B bilo je 590 (10,7%), dok je 4.948 (89,4%) bilo negativno. Primjećena je dominacija toksina A C.difficile u odnosu na toksin B odnosno toksin AB (p<0,001). Najveći broj slučajeva pozitivnih na toksin C.difficile bio je iz uzoraka stolice pacijenata hospitalizovanih na Klinici za unutrašnje bolesti, a zatim na Klinici za infektivne bolesti. Od ukupnog broja CDI slučajeva, kod 430 (87,6%) pacijenata radilo se o bolničkoj infekciji, a ponovljena CDI je zabilježena kod 34 (6,9%). CDI je najvažniji uzročnik bolničke dijareje, a pravovremeni laboratorijski rezultati testiranja na C.difficile mogu da utiču na odluke u vezi sa antibiotskom terapijom i mjerama kontrole infekcije. Zbog velikog broja negativnih rezultata, za dokazivanje C.difficile u stolici ne mogu da se koriste samo imunski testovi. Neophodno je poboljšati referentne metode za laboratorijsku dijagnostiku C.difficile.*

Ključne riječi*: Intrahospitalna infekcija, Clostridium difficile, dijareja, epidemiološki nadzo*