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ORIGINAL ARTICLE

Epidemiological and Clinical Characteristics of Patients with Healthcare - Associated *Clostridioides Difficile* Infection Before and During the COVID-19 Pandemic

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Abstract

Background/Aim: Diarrhoea that occurs as a result of the presence of *Clostridium difficile* (reclassified as *Clostridioides difficile*) is usually manifested as a hospital infection, usually after antibiotic treatment. The study aim was to assess the incidence, characteristics and outcomes of hospitalised patients with healthcare – associated *Clostridioides difficile* infection (HA - CDI) before and during the COVID-19 pandemic.
Methods: This retrospective cohort study included patients older than 18, who met the HA - CDI case definition. The CDI diagnosis was made by demonstrating toxins A and B in stool samples using an immunochromatographic assay test and polymerase chain reaction (PCR).
Results: The incidence of HA - CDI has significantly decreased from the pre-COVID-19 period to the COVID-19 period (11.04 per 10,000 vs 6.49 per 10,000, $p < 0.001$). Before establishing the HA - CDI diagnosis, 41.4 % of patients used one antibiotic, 25.9 % used two and 11.2 % were treated with three or more antibiotics. Almost one half of the applied antibiotics were from the group that represents high risk for the development of HA - CDI. Multivariable logistic regression analysis showed that older age (OR = 3.4; 95 % CI = 0.9-12.4; $p = 0.038$) and complicated disease course (OR = 11.8; 95 % CI = 2.6-53.6; $p \leq 0.001$) were associated with a higher risk of death.
Conclusion: The incidence of HA - CDI has decreased during the observed period of the COVID-19 pandemic, however, no clear connection between the impact of the pandemic and incidence reduction was found. Due to unfavourable outcome of the treatment of HA - CDI patients during COVID-19 pandemic, the rational use of antibiotics is necessary.

Key words: *Clostridioides difficile* infections; COVID-19 pandemic; Risk factors; Disease outbreak.

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Introduction

Clostridium difficile (*Clostridioides*, according to the latest classification from 2016) is one of the leading causes of infections associated with healthcare (nosocomial infection), most often affecting the elderly and hospitalised. Colon infection with the Gram-positive bacterium *C difficile* (CDI) can be life-threatening and almost 20 % of patients are colonised with this bacterium during hospitalisation and more than 30 % of them develop diarrhoea.[1-3] After the spread of highly virulent strains, mostly ribotype 027 (ribotype 027, North American pulsed-field gel electrophoresis type 1 or restriction endonuclease analysis group BI, NAP1/027/B1), an increase in the number of severe cases was noticed, as shown by studies from Europe and of North America.[4,

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[5] Another problem is the recurrence of infection that occurs in 25 % (6 ± 42 %) of all CDI cases, endangering the health of patients even more.[6] These infections in hospitalised patients lead to prolonged hospital stays, adverse outcomes and increased costs. CDI has been present in the hospital environment for more than 50 years, but in the last two decades it represents one of the growing public health problems both worldwide and in the Republic of Srpska, Bosnia and Herzegovina. The USA Centre for Disease Control and Prevention (CDC) describes it as a "threatening infection due to the possibility of the manifestation of *C difficile* highly resistant to antibiotics".[7, 8] A research of the prevalence of diseases associated with healthcare and the use of antibiotics conducted by the European Centre for Disease Prevention and Control (ECDC) in acute care hospitals found that *C difficile* was the eighth most frequently reported microorganism.[9]

The COVID-19 pandemic had a pronounced negative impact on the outcome of patient treatment. The changes in the gut microbiota and immune response disorders can affect the development of healthcare – associated *Clostridioides difficile* infection (HA – CDI) in patients suffering from COVID-19. During hospitalisation, the majority of the infected with the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus received antibiotics, which can increase the risk of antibiotic-associated diarrhoea (AAD) and CDI. Uncontrolled use of antibiotics and disinfectants can lead to the selection of resistant strains of *C difficile* not only in hospitals but also in the community.[10, 11]

The aim of this study was to evaluate the frequency, characteristics and outcomes of HA - CDI patients treated in hospitals before and during the COVID-19 pandemic.

Methods

Study design and patients

This was a retrospective, cohort study in which all necessary variables were collected from the original laboratory and medical files of all hospitalised patients with HA - CDI from the beginning of July to the end of December 2019 (pre-COVID-19 period) and from the beginning of July to the end of December 2020 (COVID-19 period). The research was conducted at the University Clinical Centre of the Republic of Srpska (UCC RS) at the Clinic for General and Abdominal Surgery, Clinic for Internal Diseases, Clinic for Oncology, Clinic for Infectious Diseases and the Intensive Care Unit (ICU). For the purposes of the research, the consent of the Ethics Committee of UCC RS (No 01-19-612-2/19) was obtained.

A case in which symptoms appeared 48 h or later after admission to the hospital was considered a hospital CDI or if the case occurred outside the hospital within four weeks after the previous discharge from the health institution. Recurrent cases of CDI meet the case definition, with recurrent diarrhoea after the end of therapy, with a positive laboratory test, that occurred more than two and less than eight weeks after the beginning of the previous episode (regardless of the place of origin of the episode). CDI cases in which the symptoms started more than eight weeks after the onset of the previous episode were considered new CDI cases. Lethal outcome of treating patients was considered to be CDI-related when there were no other causes or it occurred within 10 days after establishing the CDI diagnosis or it was due to known CDI-related complications.

The study included all patients older than 18 years of age (total of 116 patients), who met the HA - CDI case definition: the date when the CDI symptoms started was during the study period, even if the patient was admitted before the start of the study; the patient was admitted to the hospital during the study period with signs and symptoms of CDI present at admission, even though this episode of CDI had already been diagnosed before admission (for example, in acute medical units) and these were repeated cases of CDI. The study did not include patients with CDI acquired in the community, as well as patients from outpatient clinics, for example same day surgery, haemodialysis patients and outpatients.

CDI was diagnosed by detecting toxin A and toxin B in stool samples using the VEDA LAB Toxin A+B (*C difficile*) DUO immunochromatographic test (*ZAT du Londeau - Rue de l'expansion, Cerisé - BP 181 - 61006 Alençon, France*) or using polymerase chain reaction (PCR) method for the detection of binary toxin in *C difficile* ribotype 027 (*Cefeid Xpert® C difficile BT, Röntgenvägen 5, SE-17154, Solna, Sweden*).

Variables

In order to compare the variables that could have contributed to differences in the frequency of CDI, the following patient data was obtained: age, sex (male/female), date and duration of hospitalisation, primary diagnosis, comorbidities antibiotics administered before and during hospitalisation (but before laboratory testing for *C difficile*), use of antacids, probiotics and corticosteroids during hospitalisation, previous medical history of CDI, date of laboratory testing for *C difficile*, previous admission to healthcare facilities in the last three months in relation to the occurrence of CDI (hospital or other healthcare facility, for example long-term treatment institutions, such as a nursing home, rehabilitation centre, long-term care home, etc), 24-hour-stool count, peripheral blood leukocyte count, serum creatinine and albumin value and C-reactive protein (CRP) value. To assess the severity of chronic disease and health status, the McCabe score was used, according to which patients were divided into three categories. The patient's treatment outcome was taken as the patient's status at hospital discharge or at the end of hospital follow-up.

Data and statistical analyses

For statistical data processing, the software package SPSS, version 25.0 was used with a 95 % confidence interval (CI) of statistical significance ($p < 0.05$). The incidence rate of HA - CDI was calculated as the ratio of the number of infections/10,000 patient days. Nominal variables were presented as number (percentage), whereas continuous variables were presented as mean (M) and standard deviation (SD). The Shapiro-Wilk test and histogram were used to analyse the normality of the distribution. If necessary, the Chi-square test or the Wilcoxon test for dichotomous variables and the Mann-Whitney test or Dependent t-test for constant variables were used to compare research groups. For the construction of the regression model, those variables that showed $p < 0.05$ using univariate analysis were used. Multivariable logistic regression analysis was performed to determine the combination of parameters predicting HA - CDI in patients with a fatal outcome.

Results

During the research period, a total of 116 patients with HA - CDI were treated, of which 74 (63.8 %) patients were treated in the period before COVID-19 and 42 (36.2 %) during the COVID-19 pandemic. In the second half of 2020, 17 (40.5 %) patients had COVID-19 as the primary disease for which HA - CDI patients were hospitalised. The incidence of HA - CDI between time periods is presented in Table 1. The incidence of HA - CDI has significantly decreased from the pre-COVID-19 period to the COVID-19 period (11.04 per 10,000 vs 6.49 per 10,000, $p < 0.001$). In the majority of observed clinics, there was a significant drop in the incidence during the pandemic period, except at the Clinic for Surgery, where there was a slight increase in incidence (4.56/10,000 vs 5.05/10,000) (Table 1).

Table 1: Trends in the incidence of healthcare – associated Clostridioides difficile infection (HA – CDI) in patients during study period

Variables	Pre-COVID-19 HA-CDI group n = 74		COVID-19 HA-CDI group n = 42		p-value
	Hospital inpatient (days)	New cases per 10,000 patient (days)	Hospital inpatient (days)	New cases per 10,000 patient (days)	
Internal medicine	33.994	8.53	30.486	5.90	0.041*
ICU	2.666	26.26	5.782	12.11	
General Surgery	9.069	1.10	8.718	4.59	
Oncology	13.144	5.05	9.896	4.56	
Infectiology	8.133	38.12	9.859	8.11	
Total	**67.006**	**11.04**	**64.741**	**6.49**	**< 0.001***

*HA - CDI, Healthcare - associated Clostridioides difficile infection; COVID-19, coronavirus disease 2019; ICU, Intensive care unit; *Chi-square test; p - value statistically significant (p < 0.05)*

Table 2: Demographic and epidemiological data, comorbidities, clinical characteristics of the patients with healthcare – associated Clostridioides difficile infection (HA – CDI) before and during COVID-19 pandemic and their differences

Variables	Pre-COVID-19 HA-CDI group n = 74	COVID-19 HA-CDI group n = 42	p-value
Male sex, n (%)	34 (45.9)	30 (71.4)	0.008 *
Women sex, n (%)	40 (54.1)	12 (28.6)	
Age in years (Median, IQR)	67 (21-75)	69 (63-74)	0.807 **
Previous hospital admission, n (%)	45 (60.8)	21 (50.0)	0.358 *
CDI case origin			0.041 *
Current hospital, n (%)	51 (68.9)	30 (71.4)	
Other hospital, n (%)	5 (6.8)	0 (0.0)	
LTCF, n (%)	6 (8.1)	0 (0.0)	
Not specified, n (%)	12 (16.2)	12 (28.6)	
Recurrent CDI, n (%)	16 (21.6)	11 (26.2)	0.464 *
Days of hospitalisation prior CDI, X ± SD	16.11 ± 12.46	16.88 ± 12.27	0.767 **
McCabe–Jackson disease classification, n (%)			0.352 *
Non-fatal	33 (44.6)	24 (57.1)	
Rapidly fatal	31 (41.9)	15 (35.7)	
Ultimately fatal	10 (13.5)	3 (7.1)	
ICU admission, n (%)	9 (9.5)	9 (16)	0.041 *
Mean duration of diarrhoea, days (range)	9.67 (5.36)	11.47 (6.46)	0.181 **
Leukocyte count ≥ 15 x 10^9/L, n (%)	25 (33.8)	17 (40.5)	0.205 **
Serum creatinine > 1.5 mg/dL, n (%)	30 (40.5)	5 (11.9)	0.001 **
Albumin, g/l, n (%)	18 (24.3)	14 (33.3)	0.297 ***
C-reactive protein ≥ 200 mg/L, n (%)	12 (16.2)	6 (14.3)	0.783 ***
Proton pump inhibitors, n (%)	49 (66.2)	38 (90.5)	0.020 *
Immunosuppressive condition, n (%)	7 (9.5)	19 (45.2)	< 0.001 *

*HA - CDI, Healthcare - associated Clostridioides difficile infection; COVID-19, coronavirus disease 2019; LTCF, long term care facility; ICU, Intensive care unit; *Chi-square test ** Wilcoxon test, *** Dependent t-test; p - value statistically significant (p < 0.05)*

Table 2 shows data on HA - CDI patients with specific characteristics during the 2020 wave of the COVID-19 pandemic and the same calendar period in 2019. A statistically significant difference (p = 0.008) in gender was observed between patients during the reporting period. Before the COVID-19 pandemic, men contracted HA - CDI significantly less frequently (45.9 %) compared to the pandemic period (71.4 %). The average age of HA - CDI patients before the study period (66.25 ± 13.12) and after (66.14 ± 12.56) was similar. During the reporting period in 2020, 17 (40.47 %) patients had COVID-19 as the primary disease for which CDI patients were hospitalised. In the ICU during the pandemic period, statistically significantly (p = 0.041) more patients were treated compared to the period before the COVID-19 pandemic (16.7 % : 9.5 %). During the surveillance period, the previous admission to healthcare institutions in the last three months in relation to the occurrence of HA - CDI was determined in 66 (56.9 %) patients and the largest number were acute care hospitals 59 (50.9 %). There were no differences in the frequency of HA - CDI symptoms present at admission, nor in the occurrence of repeated HA - CDI before and after the COVID-19 pandemic. There was no statistically significant difference in the severity of the underlying disease between the cohorts of HA - CDI patients (p = 0.352). Data analysis showed that patients with HA - CDI had a significantly higher number of leukocytes in peripheral blood, significantly elevated CRP values, lower serum albumin levels and higher serum creatinine levels compared to basal values. Table 2 also shows that proton pump inhibitors were significantly more often used in patients with HA - CDI (57.1 %) during the COVID-19 pandemic compared to patients examined before the pandemic (47.3 %) (p = 0.020). Before the pandemic, 90.5 % of patients were treated without corticosteroids, but in the observed period of the pandemic, that percentage was highly statistically significantly lower (p < 0.001) and amounted to 54.8 % (Table 2).

Drugs administered to patients before the onset of HA - CDI is showed in Table 3. Before establishing the diagnosis of HA - CDI, 48 (41.4 %) patients used one antibiotic, 30 of them (25.9 %) used two, 13 patients (11.2 %) were treated with

Table 3: Drugs administered to patients before the onset of healthcare – associated Clostridioides difficile infection (HA – CDI)

Variables	Pre-COVID-19 HA-CDI group	COVID-19 HA-CDI group	p-value
Antibiotic exposure n (%)	61 (82.4)	32 (76.2)	0.282 *
Number of received antibiotics			**0.424** *
One	33 (44.6)	15 (35.7)	
Two	17 (23.0)	13 (31.0)	
Three and more	10 (13.5)	3 (7.1)	
Beta-lactams	60 (81.1)	18 (42.8)	**0.033** **
Cephalosporins	40 (54.1)	13 (30.9)	0.008 **
Carbapenems	17 (23.0)	7 (16.7)	0.806 **
Quinolones	12 (16.2)	15 (35.7)	**0.197** **
Macrolides	2 (2.7)	8 (19.0)	0.007 **
Aminoglycosides	10 (13.5)	1 (2.4)	0.013 **
Colistin	5 (6.7)	4 (9.5)	0.594 **
Level of risk for CDI			**0.331** *
High risk	36 (48.6)	18 (42.9)	
Moderate risk	9 (12.2)	8 (19.0)	
Low risk	16 (21.6)	5 (11.9)	

*HA - CDI, Healthcare - associated Clostridioides difficile infection; COVID-19, coronavirus disease 2019; *Chi-square test; ** Mann-Whitney test; p - value statistically significant (p < 0.05)*

Table 4: Healthcare – associated Clostridioides difficile infection (HA – CDI) patient outcome

Variables	Pre-COVID-19 HA-CDI group (n = 74)	COVID-19 HA-CDI group (n = 42)	p-value
Discharged alive	62 (83.8)	28 (66.7)	
In-hospital death	12 (16.2)	14 (33.3)	0.04*
CDI-related death	5 (6.7)	9 (21.4)	

*HA - CDI, Healthcare - associated Clostridioides difficile infection; COVID-19, coronavirus disease 2019; *Chi-square test; p - value statistically significant (p < 0.05)*

three or more antibiotics, whereas 25 (21.6 %) patients did not use antibiotics in therapy. Almost half of the applied antibiotics 54 (46.6 %) were from the group representing a high risk for the occurrence of HA - CDI. Antibiotics from the group of beta-lactam antibiotics (54.97 %) were significantly more often used in patients before the COVID-19 pandemic (81.1 vs 42.8; p = 0.033). Macrolides (azithromycin) were used more often during the observed pandemic period in 2020 (2.7 vs 19.0; p = 0.007) as well as quinolones (16.2 vs 35.7; p = 0.197) (Table 3).

Mortality of HA - CDI patients before the COVID-19 pandemic was 16.2 % and during the observed pandemic period it was 33.33 %. The highest mortality rate was recorded in the ICU (71.4 %). The mean time period (in days) from establishing the laboratory diagnosis of HA - CDI to HA - CDI-related death was 12.56 ± 14.60 (Table 4).

Table 5: Risk factors for the HA - CDI-related fatal outcome

Parameter [a]	RR	95 % CI	p-value
Age > 65	3.426	0.944 - 12.437	0.038
Complicated course	11.850	2.622 - 53.642	< 0.001
Leucocytosis	3.794	1.193 - 12.066	0.024
CRP > 200 mg/L	3.635	1.143 - 11.562	0.029

[a]Reference category: HA - CDI, healthcare - associated Clostridioides difficile infection related fatal outcome; RR, risk ratio; CI, confidence interval; CRP, C-reactive protein; p-values were calculated by logistic regression analysis.

Multivariate logistic regression analysis showed that older age, complicated disease course, leucocytosis and elevated values of CRP (> 200 mg/L) were associated with a higher risk of death (Table 5).

Discussion

Surveillance of infections caused by *C difficile* is an important component of the prevention program. Understanding the determinants of HA - CDI incidence will allow for more meaningful comparisons of rates, the course and outcome of the disease for the planning of preventive programmes.[12] Treating a patient during the COVID-19 pandemic represents a challenge for hospital systems worldwide. UCC RS had to adapt to a greater influx of patients who requested healthcare, which led to the reorganisation of certain clinics. During the COVID-19 pandemic, many preventive procedures (personal protective equipment (PPE), regular use of hand sanitisers, cleaning the environment, disinfecting the objects, bio-medical waste management) were adopted to prevent the spread of microorganisms in the hospital environment.

The results of the present study showed that there was a significant decrease in the incidence rate of HA - CDI during the observed period. The studies conducted by Italian and Spanish authors showed similar results, where the incidence of HA - CDI during 2020 was significantly lower compared to the period before the COVID-19 pandemic.[13, 14] Contrary to these studies, Velev et al found a significant increase in the incidence of HA - CDI during the COVID-19 pandemic compared to the pre-pandemic period at one university hospital in Bulgaria.[15]

In the group of HA - CDI patients during the observed period in 2020, 40.5 % patients had COVID-19 as the primary disease. Departments where patients with COVID-19 were hospitalised had a higher incidence of HA - CDI than departments that were not. A study conducted at one Serbia university hospital from January 2019 to December 2021 showed that out of 547 patients with CDI, 62.3 % had COVID-19. The incidence of HA - CDI per 1000 patients-days was 1.33 in the non-COVID period and 4.53 in the COVID period.[16]

The most common risk factor for HA - CDI in the population compared to the period before and after the study was age ≥ 65 years. Numerous other studies have shown that due to frequent hospitalisations and a greater number of comorbidities, people older than 65 years of age have a higher risk of developing infections caused by *C difficile*.[17, 18] The basic mechanisms as to why CDI occurs more often and presents a more severe clinical manifestation in the elderly population, have not been sufficiently clarified. It is believed that several associated factors, such as comorbidities, polypharmacy and frequent hospitalisations may contribute to the observed outcomes. However, three possible biological factors may be critical for the development of CDI in the elderly: humoral response, innate immunity and gut microbiota.[19]

According to the study data during the surveillance period, previous admission to healthcare institutions in the last three months in relation to the occurrence of CDI was recorded in 56.9 % of patients and majority of these were acute care hospitals (50.9 %). The currently observed hospital had the highest proportion of HA - CDI cases.

In an ECDC research conducted in 20 EU/EEA countries, which included CDI surveillance in 593 hospitals in 2016, the overall results showed that in 85.6 % of hospital-associated cases, the source of CDI was the hospital where the patient was treated at that moment. Out of the total number of reported cases of CDI (3,042), in the previous 3 months, 62.6 % of cases were admitted to healthcare institutions; 87.0 % of these cases were admitted to hospital and 6.4 % to long-term care institutions.[20] On the contrary, in the report on the epidemiology of CDI in Belgian hospitals from 2019, the proportion of hospital-associated cases was 56 % and 29 % of community associated CDI (CA - CDI) and it represented an increase compared to the research conducted ten years before (22 %).[21] Similarly, Song et al observed decreasing trends for nosocomial CDI (- 0.03 % per year) and increasing trends for non-nosocomial CDI (+ 0.04 % per year).[22] Recognising the importance of these infections, in 2016, the ECDC developed a protocol and initiated active surveillance of *C difficile*-related infections. The Republic of Serbia initiated this surveillance at the end of 2018, whereas Bosnia and Herzegovina still has not. This surveillance would make it possible to estimate the frequency of infections in acute care hospitals, to compare rates with other hospitals in the country and in Europe, to assess adverse outcomes of infections, including death, to promote the introduction of diagnostic procedures with high diagnostic accuracy and to detect new ribotypes using PCR.[23]

In the present study, from the total number of HA - CDI cases, recurrent HA - CDI was recorded in 23.3 % patients. Based on the literature review

conducted by Finn et al, recurrent cases of HA - CDI occur in approximately 10-20 % of HA - CDI patients worldwide and the average recurrence rate from all included studies was 17 %. The highest rates were recorded in Canada (23.7 %), Poland (21.7 %) and the USA (20.2 %).[24] According to a study conducted in a tertiary care hospital in Romania, the recurrence rate of HA - CDI was 53.8 %.[25] On the opposite, in one study conducted in Tel Aviv, 12.7 % of patients had at least one confirmed recurrent case of HA - CDI.[26]

In the sample of patients with HA - CDI, the majority of patients had McCabe score (marker of co-morbidity in HA infection) 1 (49.1 %), while slightly fewer had score 2 (39.7 %) and score 3 had 10.3 % patients. In contrast to this data, it is notable that in the 2018 ECDC research, 13.9 % of 2,577 cases with a reported McCabe score were indicated to have had a 'rapidly fatal underlying disease', ie the patient was expected to survive for less than a year.[20]

The results of this study showed that proton pump inhibitors were significantly more frequently used in patients with CDI in the COVID-19 pandemic period of the research (p = 0.020). Proton pump inhibitors are most often prescribed by gastroenterologists due to the high success rate of symptom relief (such as heartburn, reflux esophagitis) and prevention of stomach ulcers and the first part of the small intestine. However, recently, there has been concern regarding the association between the use of proton pump inhibitors and several possible serious side effects, such as CDI.[27]

There have been several clinical studies that support the success of corticosteroids in patients with COVID-19 disease. A retrospective study by Wu et al from 2020, showed that the use of methylprednisolone significantly reduces the risk of death in patients with COVID-19.[28] However, other recently published research, such as the one conducted by Carlson et al from 2021 showed that patients who took corticosteroids in the last 90 days had a lower risk of CDI occurrence.[29] In one research conducted by Russian authors who examined the impact of CDI on the course of the COVID-19 disease, the use of glucocorticoids was not a predictor of death.[30]

Antibiotic therapy is the most important risk factor for the occurrence of CDI, which depends on the duration of their use, as well as the class and number of simultaneously administered antibiotics. Because of the fear of developing a bacterial infection, most patients infected with the SARS-CoV-2 virus received antibiotics during hospitalisation. According to the results of the present study, before the diagnosis of HA - CDI, 42.2 % of patients used one antibiotic, 25.9 % simultaneously used two antibiotics and 11.2 % used three or more antibiotics. Almost half of the applied antibiotics (46.6 %) were in the group representing a high risk of HA - CDI.

The COVID-19 pandemic had a negative effect on patient outcomes. Mortality from HA - CDI during the pandemic period was higher compared to the pre-pandemic period (16.2 % vs 33 %). The highest number of deaths was recorded in a period shorter than 10 days from the moment of the laboratory diagnosis of HA - CDI and in the ICU during the pandemic period of monitoring the outcome of treatment of HA - CDI patients.

Study by Filippidis et al have shown that there is a significant correlation between HA - CDI clinical failure (day 10) and mortality. These authors state that an all-cause mortality at week 8 was estimated at 15.3 %, with 50.9 % of these patients dying within 10 days from diagnosis.[31] The results of a research conducted by Maslennikov et al showed that HA - CDI was associated with an increased risk of death in COVID-19 patients, particularly after 20 days of illness onset. AAD patients with a positive test for *C difficile* infection had diarrhoea longer and more severely than those with a negative test. Unlike AAD patients with a negative test for *C difficile* infection, AAD patients with a positive test were admitted to the ICU and needed mechanical ventilation more often than patients without diarrhoea.[30]

The results of this study showed that older age, complicated course of the disease, leucocytosis and increased values of CRP (> 200 mg/L) were associated with a fatal outcome. Those predictors have also been identified in several other HA - CDI studies.[32, 33] HA - CDI patients aged over 65 are at particularly high risk for mortality. Also, high CRP values in patients with HA - CDI may be a repercussion of the presence of more serious concomitant infections of other aetiology, which puts these patients at additional risk of a poor outcome of the disease.[17]

Strengths and limitations

To according to authors' knowledge, this is the first study in the Republic of Srpska, Bosnia and Herzegovina examining several clinical and epidemiological features of HA - CDI patients before and during the COVID-19 pandemic. The importance of the results of the current study is that they contribute towards providing a means for identifying HA - CDI patients at risk for a fatal outcome, in order to reduce their exposure to such risk factors. One of the main limitations of this study is the small sample size and the intervention was conducted in a single centre. The total consumption of antibiotics in the hospital was not measured. Findings in single tertiary hospital in the Republic of Srpska, Bosnia and Herzegovina need to be confirmed in a well-conducted prospective study involving multiple sites.

Conclusion

The incidence of HA - CDI has decreased during the observed period of the COVID-19 pandemic, however, no clear association of the impact of the pandemic on the incidence reduction was found. Patients with COVID-19 and HA - CDI coinfection were significantly with more comorbidities and hospitalised in the ICU. Almost half of the patients with HA - CDI were treated with antibiotics from the group that represents a high risk for the development of CDI, mostly from the group of beta-lactam antibiotics, followed by macrolides and quinolones. Due to the unfavourable outcome of the treatment of HA - CDI patients during the COVID-19 pandemic, the rational use of antibiotics and disinfectants is necessary to prevent the emergence of resistant strains of *C difficile* in hospitals and in the community.

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Conflict of interest

None.

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