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RISK FACTORS AND INCIDENCE FOR *CLOSTRIDIOIDES DIFFICILE* INFECTION IN COVID-19 AND NON-COVID-19 PATIENTS – OUR EXPERIENCES

Osmani Lloga Arlinda[1], Vidinikj Ivan[1], Georgievska Dajana[1], Demiri Ilir[1,2], Dimzova Marija[1,2], Hasipi Mesut[1], Milenkovikj Zvonko[1]

[1]University Clinic for Infectious Diseases and Febrile Conditions, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
[2]Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
e-mail: aosmani@infektivnaklinika.mk

Abstract

Introduction: *Clostridioides difficile* infection (CDI) is a major cause of healthcare-associated diarrhea. Identifying risk factors and evaluating treatment regimens are critical to reducing morbidity and mortality.

Aim: This study aimed to compare epidemiological and demographic features, risk factors, and treatment experiences in CDI patients with and without COVID-19 coinfection.

Material and methods: Data were collected from patients admitted at the University Clinic for Infectious Diseases, Skopje, North Macedonia (October 2020-June 2025). COVID-19 diagnosis was based on clinical criteria and PCR confirmation, while CDI was confirmed by culture and toxin detection, supplemented with molecular stool testing when available.

Results: Among 847 hospitalized patients, CDI was confirmed in 56(6.7%) cases: 24 (44.6%) with COVID-19 and 32(55.4%) without, with no significant statistical difference. The median age was 67 years with no significant differences in age, gender, or comorbidity distribution between groups. Proton pump inhibitor use was high in both groups (73.2%). Antibiotic and corticosteroid exposure prior to CDI onset was significantly more frequent in COVID-19 patients ($p<0.005$). Hospitalization was longer in the COVID-19 group ($p=0.005$), and mortality was higher ($p=0.03$). Treatment included oral metronidazole (31%), oral vancomycin (54%), combined parenteral metronidazole and oral vancomycin (10%), and vancomycin with rifaximin (5%).

Conclusion: CDI incidence appeared unchanged across periods, likely due to strict infection control measures. Age, comorbidities, hospitalization, and antimicrobial or steroid exposure remain key risk factors. Metronidazole and vancomycin remain effective first line treatments in our settings.

Keywords: CDI, risk factors, COVID 19, treatment regimens

Introduction

Clostridioides difficile infection (CDI) represents a major cause of healthcare-associated diarrhea, usually as a result of gut microflora disruption caused by antimicrobial therapy[1]. In 2019, the COVID-19 pandemic is thought to have fostered conditions conducive to CDI due to the extensive use of broad-spectrum antibiotics and prolonged hospitalizations in clinical care[2]. Patients hospitalized with COVID-19 experienced co-illnesses and superinfections with additional hospital pathogens, leading to other hospital-acquired infections

(HAI). Changes in gut microbiota resulting from empirical antibiotic therapies and experimental antiviral and immunomodulatory agents heightened the risk for hospital-acquired *Clostridioides difficile* infection (HA-CDI). Countries vary in their COVID-19 therapy approach, with some converting entire hospital facilities into COVID-19 centers[3-5]. In the Republic of North Macedonia, the University Clinic for Infectious Diseases in Skopje was the primary COVID-19 center. Our facility, which primarily treats one or two patients in one room, is dedicated to treating infectious diseases and preventing their spread between patients with different infectious diseases. The rooms are furnished with private bathrooms. There are doors separating the staff rooms from the patient area. Our facility serves patients from the capital and all around the country who require critical care treatment, recognizing that we are a tertiary institution with an intensive care unit and oxygen therapy available throughout the institution. This implies that patients during SARS-CoV-2 epidemy were transferred from other hospital facilities, or were admitted immediately in our hospital correlated with disease severity according protocols for diagnosis and treatment in our country. Patients with other primary infectious diseases during this period were not admitted for treatment in our facility. During the final stages of the pandemic, our hospital had designated yards for the treatment of patients with infectious diseases other than COVID -19.

Aim

This study aimed to identify and compare epidemiological and demographic features of patients with CDI, risk factors for developing CDI, as well as diagnostic methods and potential therapeutic regimens in patients with COVID-19 and those without COVID-19 infections.

Material and methods

Design

A single-center retrospective, descriptive longitudinal study was conducted at the University Clinic for Infectious Diseases, Skopje, Republic of North Macedonia, from October 2020 to June 2025. Upon admission, participants submitted an informed consent. All patients with CDI, as defined by ECDC, were included in the study. The first case of SARS-CoV-2 infection in our country was confirmed on 28 February 2020. In March 2020, WHO declared the beginning of the COVID-19 pandemic. This marked the onset of the upcoming epidemic period in our country, and the entire hospital became a COVID-19 center, meaning that only patients with confirmed SARS-CoV-2 infection were admitted (March 2020 till April 2022). With the last stages of the epidemic, our center began to treat patients with other infectious diseases rather than COVID-19, including CDI. Therefore, patients were categorized in two groups: CDI and COVID-19 coinfection and CDI in non-COVID-19 patients.

Diagnosis and definitions

The diagnosis of COVID-19 infection was based on clinical criteria and confirmed by positive polymerase chain reaction test on nasopharyngeal swab. [6,7] Patients with clinical criteria for CDI were tested for *Clostridioides difficile* infection according to ECDC and WHO guidelines, depending on diagnostic sources[8,9]. Stool samples were tested with standard microbiological methods for isolation of bacteria (culture for *Clostridioides difficile*) and toxin confirmation with immunochromatographic tests. Due to limited resources a small number of cases were confirmed with molecular or culture independent tests.

The case definition of CDI is based on the European definition approved by ECDC and CDC, and is divided as follows:

- First episode of CDI – the first episode of CDI ever experienced by the patient, or a new episode of CDI that occurs more than eight weeks after the diagnosis of a previous episode.
- Recurrent episode CDI (rCDI) – defined as an episode of CDI occurring within 2-8 weeks of a previous episode.
- The HOHA (Hospital Onset Healthcare-associated CDI) definition of *C. difficile* infection covers instances in which the positive sample falls within a period of >= 48 hours after healthcare contact was initiated until 48 hours after the healthcare contact concluded.
- COHA (Community onset health-care-associated CDI) covers instances in which infections are likely associated with hospital contact, but diagnosis occurs after hospital discharge or after outpatient courses and treatments have concluded. The COHA definition for *C. difficile* infection covers instances in which the positive sample was taken from 48 hours to 30 days after hospital contact. *C. difficile* infections also fall into this category if the positive sample was taken within 48 hours of admission and if the patient had any contact with a hospital in the 30 days leading up to admission.

Data collection

All participants in the study provided informed consent. Information regarding age, gender, comorbidities, prior hospitalizations, and antimicrobial or immunosuppressive therapy is documented in patients' history. The clinical diagnosis relies on patient medical history and physical examination. Patient follow-up or clinical progression is conducted continuously on a daily basis and is documented both electronically and manually in the record titled *decursus morbi*. Therapeutic regimens and laboratory findings are also gathered.

Statistical analysis

Statistical analysis of the data obtained from the survey was performed in the statistical program SPSS (version 25.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test and Shapiro Wilk's test were used to test the normality of the data distribution. Parametric and non-parametric tests for independent samples were used to compare groups, depending on the distribution of the data (Chi-square test, Fisher exact test, Student t-test and Mann-Whitney test). Statistical significance was defined at the $p<0.05$ level.

Results

We evaluated 847 hospitalized patients with diarrheal syndrome and risk factors for CDI. A total of 56 patients with confirmed CDI were included in the study, of whom 24 (44.6%) were diagnosed with COVID-19 coinfection and 32 (55.4%) comprised the non-COVID-19 or control group. The total number of tested patients in respective groups was 394 *vs*. 453. The incidence of *Clostridioides difficile* infection in COVID 19 cohort was 6.1% (24/394; 95% CI: 3.9-8.9%), while in non-COVID-19 cohort the incidence was 7.06% (32/453; CI: 4.7-9.4%). The average statistical difference in incidence between the two periods was not significant (P=0.57) (Table 1).

Table 1. Demographic features

	Total (n=56, 100%)	COVID-19 (n=25, 44.6%)	non-COVID 19 (n=31, 55.4%)	p value (<0.05)
Gender (n, %)				
Male	31 (44.6%)	13	18	0.650
Female	25 (54.6%	12	13	
Age (age, median IQR 25^{th}-75^{th})	67 (54-74.7)	67 (55-78)	64 (50.5-74)	0.760
Comorbidities (n, %)				
With comorbidities	45 (80.4%)	21	24	0.903
Without comorbidities	11 (19.6%)	4	7	

There was no statistically significant difference in gender distribution between the two groups (p=0.650). The median age of the entire cohort was 67 years (IQR: 54-74.7), with similar age distributions in the COVID-19 (67; IQR: 55-78) and non-COVID-19 (64; IQR: 50.5-74) groups (p=0.760). The majority of patients in both groups had at least one comorbidity, with no significant difference observed (80.4% overall; p=0.903).

Use of proton pump inhibitors (PPI) was reported in 73.2% of patients, with no significant difference between groups (p=0.672). A significantly higher proportion of patients in the COVID-19 group had received antibiotics prior to the onset of illness (88%) compared to the non-COVID-19 group (51.6%) (p=0.006). Similarly, pre-illness corticosteroid use was significantly more frequent in the COVID-19 group (52%) compared to the non-COVID-19 group (12.9%) (p<0.005). All patients in the COVID-19 group received parenteral antibiotics after diarrhea onset, correlated with underlying diseases such as respiratory illnesses, compared to only 38.7% of non-COVID-19 patients, revealing a statistically significant difference (p< 0.005) (Table 2).

Table 2. Risk factors for CDI

	Total (n=56, 100%)	COVID-19 (n=25, 44.6%)	non-COVID 19 (n=31, 55.4%)	p value (*<0.05)*
PPI (n, %)				
PPI used	41(73.2%)	19	22	0.672
PPI not used	15(26.8%)	6	9	
Antibiotics (n, %)				
Antibiotics used	38(67.9%)	22	16	0.006
Antibiotics not used	18(32.1%)	3	15	
Corticosteroids (n, %)				
Corticosteroids used	17(30.4%)	13	4	<0.005
Corticosteroids not used	39(69.6%)	12	25	
Systemic antibiotics during CDI (n, %)				
Antibiotics used	38(67.9%)	25	12	<0.005
Antibiotics not used	18(32.1%)	0	16	
Duration of hospitalization (days, Median IQR 25^{th}-75^{th})	12(10-26.2)	22(12-30)	11(9-16.5)	0.005

All cases with CDI in our study were nosocomial infections. Nine of the 24 patients in the COVID-19 CDI group had a history of previous hospitalization, while the remaining experienced CDI onset symptoms during hospital treatment at our facility. Among the 32 patients in the non-COVID-19 group, 19 had a history of prior hospitalizations or antimicrobial treatment and/or immunosuppressive therapy for other underlying conditions, while the remaining patients experienced diarrhea onset during their treatment in our hospital.

The median duration of hospitalization was significantly longer in the COVID-19 group (22 days; IQR: 12-30) compared to the non-COVID-19 group (11 days; IQR: 9-16.5) (p=0.005).

The overall mortality rate was 8.9% in the COVID-19 group. Only one mortality case was recorded among non-COVID-19 CDI, and a statistically significant difference was observed (p=0.030).

The therapeutic regimens administered included metronidazole oral monotherapy in 31% of patients, oral vancomycin monotherapy in 54%, a combination of metronidazole parenterally and vancomycin orally in 10%, and a combination of vancomycin and rifaximin in 5% of cases. The effectiveness of the drugs was assessed based on the alleviation of enteral symptomatology.

Discussion

Comparison of epidemiological differences between the two groups was challenging because of various approaches to diagnosis, treatment and data reporting - considering the primary preoccupation with respiratory symptomatology of medical staff and the possible burn out syndrome during the pandemic, as well as involvement of medical doctors from other profiles and experiences. However, we assume that diarrhea was a symptom that was reported continuously by our nursing staff. Reporting cases with CDI and diagnosing was affected by testing capacity and diagnostic methods used. Standard diagnostic stool tests, such as culture for *Clostridioides* and immunochromatographic tests for confirmation of toxins, are less sensitive compared to molecular testing and toxin A and B immunoassay (EIA). During COVID-19, our facility did not perform molecular or culture-independent testing of stool samples, possibly avoiding it, despite adhering to precautionary measures to minimize personnel infection risk or lacking available tests. Conversely, it is essential to emphasize the importance of clinically evaluating microbiological results in relation to clinical symptoms to reduce the risk of overdiagnosis stemming from molecular testing[10,11].

Our results revealed that the incidence rate was similar during the two periods and between the groups. The incidence of *Clostridioides difficile* infections rose in the mid-2000s, mainly due to the emergence of highly virulent strains such as ribotype 027[12]. In 2019, the Institute of Microbiology at the University Center Skopje, North Macedonia, conducted a study and they concluded that in the clinical center i.e, in our country ribotype 001/072 appeared endemic, unlike the hypervirulent 027 which dominated in many European countries[13].

In response to new strains, many countries prioritized infection prevention and control, focusing particularly on rational antibiotic use, supported by organized surveillance systems[14,15]. These measures proved effectiveness: in the USA, healthcare-associated CDI (HA-CDI) rates dropped by 36% between 2011 and 2017, primarily due to preventive strategies, including antibiotic stewardship programs that curtailed fluoroquinolone use[16-18]. Similar downward trends in CDIs incidence were also observed across European Union countries[14]. Effective prevention of *C. difficile* infection requires contact precautions, hand hygiene with soap and water, effective environmental cleaning, use of sporicidal agents and antimicrobial stewardship.

Regarding implementation of preventive measures on controlling spreading of infection in our facility, every patient with diarrhea and CDI-confirmed infection, undertook strong controlled multimodal intervention measures. The room of every patient was marked as '*C. difficile infection*' at the door, so that the medical staff was more precautious; hand hygiene of the medical staff or changing hand gloves after every intervention, disinfection with bleach was performed in the toilets and the inventory after patient's discharge.

There are studies reporting that elderly and patients with comorbidities have higher risk for CDI, and higher mortality rate[19].

Results regarding demographic characteristics of our patients showed similar gender distribution between groups. The mean age of patients was 67 years, with no differences in the CDI patients' age during COVID-19 pandemic and the period afterwards. In our study groups, there was no significant difference regarding comorbidities and coinfection with SARS-CoV-2.

It is well known that antimicrobial therapy leads to gut disruption predisposing post-antimicrobial diarrhea, one third of which are caused by *Clostridioides difficile*[20]. Meta-analysis of articles published up to June 2020 concluded that every three out of four COVID-19 patients worldwide received antibiotics even though bacterial co-infections were not diagnosed[21]. Similar picture is noted in our country where antibiotics are overprescribed from primary and secondary healthcare centers. As far as our center (a tertiary institution) is concerned, it was observed that with admission to hospital these patients received antibiotics related to the severe form of COVID-19 disease, usually pneumonia, whereas only 2/3 of patients with CDI without COVID-19 had to be treated with concomitant parenteral antimicrobial therapy related to other underlying diseases. We noted significant difference on prior CDI antimicrobial therapy usage in patients with COVID-19 coinfection. Similar results have been reported in studies conducted in our neighboring countries[22,23].

Corticosteroids were used as part of many versions of COVID-19 treatment protocols due to their anti-inflammatory role. Their use in COVID-19 patients, who did not require oxygen therapy or mild form of disease, were viewed negatively. [24] Furthermore, no definitive conclusion regarding their role in lowering disease progression and mortality in mild forms of disease was found, while in critically ill patients it reduced mortality compared to standard therapy[25]. One of the more common side effects of steroid therapy was post-antimicrobial diarrhea caused by *Clostridioides difficile*. Corticosteroid treatment contributes as CDI risk factor by compromising host immunity and altering microbial ecology, thereby facilitating *C. difficile* overgrowth and toxin production. In our study, corticosteroids combined with antimicrobial medication were predominantly utilized in the COVID-19 cohort, rendering them a risk factor for CDI.

Protein pump inhibitors, identified as a potential risk factor for CDIs in our patients, were utilized in about two-thirds of cases, irrespective of SARS-CoV-2 co-infection, and served as complementary supportive therapy. Due to their acid suppressive role, these medications provide conditions for survival of spores and growth of *C. difficile*. However, their direct link still needs to be further studied. PPIs and CDI did not significantly correlate, according to data from the EUCLID study, which examined CDI in hospitalized patients with diarrhea across 59 hospitals in seven European countries. On the other hand, a case-control study conducted at a university hospital in Germany validated this association[26,27].

Patients with COVID-19 had a significantly longer hospital duration treatment and all CDI cases were determined as 'healthcare onset associated CDI'. Non-COVID-19 CDI patients in approximately half of the cases were determined as 'community onset healthcare-associated *Clostridioides difficile* infection'[8,9].

IDSA (Infectious Disease Society of America) and SHEA (Society for Healthcare Epidemiology of America) recommend fidaxomicin over standard course for patients with first episode of CDI. However, cost and source availabilities might restrict its application. When fidaxomicin is not available, vancomycin is still a suitable substitute. On the other hand, American Society of Gastroenterohepatology supports therapy with oral metronidazole course for first episode non-severe CDI and low risk patients.

Therapy with metronidazole and vancomycin in our patients showed a good therapeutic result.

Since the mortality rate is much higher in COVID-19 patients, all of whom had a severe form of the disease and were treated in the intensive care unit, we assume that the primary cause of mortality was mainly influenced by the severity of pneumonia, although CDI as a nosocomial infection contributes to worsening of the patients' condition. In the non-COVID-19 group death was notified only in one patient admitted in intensive care unit with severe dehydration and clinical signs of acute bacterial gastroenteritis; and *Clostridioides difficile* was diagnosed with PCR stool test as coinfection with Shigella like producing E. coli.

The limitations of this study are: the study was retrospective and conducted at a single center; the absence of data on ribotyping and antimicrobial resistance. At the same time, we lack information and data on the incidence of CDIs that were not associated with SARS-CoV-2 coinfection during the pandemic period, as well as data on rCDI cases. During the pandemic, medical staff collaborated with professionals from other specialties; however, the hospital facilities remained consistent, facilitating the implementation of precautionary measures.

Conclusion

We assume that the CDI incidence rate remained consistent between periods due to accurate SARS-CoV-2 prevention measures, such as masks, gowns and gloves. Comorbidities, older age, previous hospitalizations, steroid and antibiotic use represent risk factors for CDI regardless of COVID-19 coinfection. Treatment regimens with metronidazole and vancomycin still remain therapy of choice in our settings related to availability and good therapeutic results.

Conflict of interest statement. None declared.

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