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Case Report

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Clostridium Difficile Infection in Hospitalized Patients Before and During Covid-19 Pandemic

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Abstract

Aims: Clostridium difficile infection (CDI), the leading cause of healthcare-associated diarrhea, has raised concerns during the COVID-19 pandemic due to its potential for severe outcomes. The aim of this study was to assess the incidence, severity, and treatment outcomes of CDI in hospitalized patients before and during the pandemic.

Methods: We analyzed 313 patients diagnosed with CDI between March 2017 and October 2022, divided into pre-pandemic (75 patients) and pandemic (238 patients) groups. CDI was defined by the presence of diarrhea and a positive stool toxin test.

Results: Our findings revealed a significantly higher incidence of CDI during the pandemic (54.2 vs. 14.6 per 10,000 hospital discharges, p<0.001), with a marked increase in both community-acquired (9.57 vs. 3.31 per 10,000 discharges, p=0.0522) and healthcare-associated cases (13.46 vs. 3.34 per 10,000 patient-days, p=0.0075). The pandemic group had more recurrent cases (17.6% vs. 6.7%, p=0.024), fewer diarrheal episodes at diagnosis (5.4 vs. 8.4, p=0.027), and a higher use of oral vancomycin (93% vs. 77%, p<0.001). However, severity, outcomes, and comorbidities were similar between groups.

Conclusion: This study shows a substantial rise in CDI incidence during the pandemic, attributed to factors such as increased antibiotic use and healthcare system strain. Despite its retrospective, single-centre design, this study offers robust data from a large sample size. In conclusion, the findings underscore the importance of refining antibiotic stewardship programs and infection control measures to mitigate CDI risks during public health crises.

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Introduction

The recent COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged from China in December 2019 [1] and spread worldwide imposing unprecedented challenges on hospitals and healthcare providers.

Initially, the primary focus was the management of viral outbreak. However, during the course of the pandemic the significance of other healthcare-associated infections was apparent. One of these infections is the Clostridium Difficile infection (CDI) which is the main cause of healthcare-associated infectious diarrhea [2]. It has a vast spectrum of clinical presentation ranging from mild diarrhea to severe life-threatening colitis [3]. The infection predominantly affects people in healthcare settings [4], particularly those with recent antibiotic exposure and prolonged hospital stay [5].

During the COVID-19 pandemic, hospitals faced great challenges in infection prevention and control, resource allocation, and overall management of patients. These hospital conditions along with the increased use of antibiotics, have raised concerns about the potential impact on CDI incidence and severity. Several conflicting studies are published showing either increased or decreased incidence during the pandemic [6-10]. To our knowledge, there are no published studies from Greece. It is important to establish the effect of COVID-19 pandemic on CDI incidence in order to implement targeted interventions, antimicrobial stewardship programs, and infection control protocols, ensuring the safety and well-being of hospitalized patients even during a pandemic.

The aim of our study was to investigate whether there was an increase in CDI incidence in patients hospitalized during the COVID-19 pandemic in a tertiary care hospital compared with those hospitalized before the pandemic. Furthermore, contributing factors which could explain possible increase such as antimicrobial agents used, previous COVID-19 infection and severity of the disease were investigated.

Materials and Methods

This is a case–control retrospective observational study conducted in a tertiary care teaching hospital, the Papageorgiou General Hospital, Greece. All adult patients (>18 years old) with CDI diagnosis who were hospitalized in our institution between 2017 and 2022 were included. Two groups were created: the control [patients hospitalized between March of 2017 and February of 2020 (pre-pandemic group)], and the case group [patients hospitalized during the pandemic (March 2020 - October 2022) (pandemic group)]. The CDI incidence was calculated within each group and compared between the pre-pandemic and the pandemic group. The incidence was calculated as cases per 10,000 hospital discharges. Furthermore, the incidence of healthcare-associated, community-associated, recurrent CDI and previous antibiotic use were compared between the two groups.

Data were extracted from patients' medical records and included: demographic information (sex, age), prior hospitalization or long term stay at healthcare facilities within the last three months, co-morbidities, prior medications used (mainly, antibiotic treatment), previous or concomitant diagnosis of Sars-Cov-2, laboratory data [white blood cell count

(WBC, cells/mm^3), creatinine levels (mg/dL), albumin levels (g/dL) and inflammation markers such as C-reactive protein (CRP, mg/L) and procalcitonin (PCT, ng/mL)], the treatment used for CDI, the severity of the disease as well as its outcome, including death. Throughout the study, patients' anonymity was ensured and the protocol was approved by the local Institutional Review Board.

The CDI was defined as presence of diarrhea and positive test for glutamate dehydrogenase (GDH) and/or positive test for toxins A/B. The Colored Chromatographic Immunoassay for the simultaneous qualitative detection of GDH, Toxin A and Toxin B in stool samples (CerTest Clostridium difficile GDH+Toxin A+B one step combo card test, CerTestBiotec S.L., Zaragoza, Spain) was used. We also included cases with CDI-positive biopsy samples obtained via colonoscopy. The Sars-Cov-2 infection was confirmed by means of real time-polymerase chain reaction (RT-PCR).

Healthcare-associated CDI (HA-CDI) was defined as cases presenting with a positive test 48 hours following hospital admission or those with documented overnight stay in a healthcare facility within the last four weeks.

Community-associated CDI (CA-CDI) was defined as cases with positive test within the first 48 hours of hospital admission and no prior hospitalization in any health care facility within the last four weeks.

Recurrent CDI was defined as CDI recurrence within eight weeks following the previous CDI episode, provided the symptoms from the previous episode resolved after completion of initial treatment.

The severity of the infection was evaluated according to the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA-SHEA) criteria [11]: 1. severe cases were deemed when WBC count >15,000/μL and/or creatinine >1.5mgr/dL, 2. fulminant infection were deemed the severe cases combined with hypotension, ileus or megacolon, 3. The rest cases were deemed mild/moderate.

The statistical analysis was performed with the statistical package SPSS v.28 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Continuous variables are described as mean ± standard deviation and categorical values as numbers and percentages. The baseline characteristics and the outcomes are presented for both groups (pre-pandemic and pandemic group). The comparisons between the 2 groups were performed by means of Student's t-test for the continuous and normally-distributed variables, Kruskal-Wallis test for the continuous non-normally distributed variables while Chi-square was used for the categorical variables. Statistical significance was set to $p<0.05$.

Results

During the period March of 2017 to October 2022, 313 hospitalized patients were discharged from our hospital with the diagnosis of CDI. The majority of whom were diagnosed during the pandemic [238 patients, 54.2/10,000 hospital discharges in the pandemic group vs 75 patients, 14.6/10,000 hospital discharges in the pre-pandemic group, $p<0.001$]. During this period, the incidence of both CA-CDI [9.57/10,000 hospital discharges pandemic group versus 3.31/10,000 discharges pre-pandemic group ($p=0.0522$) and HA-CDI (13.46/10,000 patient-days in the pandemic group versus 3.34/10,000 patient-days in the pre-pandemic (RR 4.67, CIs 1.3-25.3, $p=0.0075$) were increased.

Both groups were similar in age (75±15 years in the pandemic group vs 77±14 years in the pre-pandemic group, $p=0.783$) and presence of co-morbidities [arterial hypertension, diabetes, chronic kidney disease (CKD), cardiovascular diseases (CVDs), respiratory disease, nervous system disease, cancer, immunodeficiency] ($p>0.1$). Hypertension was the most prevalent co-morbidity in both groups [150 (63%) pandemic group vs 44 (59%) pre-pandemic group ($p=0.760$)], followed by the CVDs [115 (48.3%) pandemic group vs 33 (44%) pre-pandemic group ($p=0.767$)]. Similarly, in both groups only the minority of patients had no co-morbidities [13 (5.5%) pandemic group vs 9 (12%) pre-pandemic group, $p=0.141$]. However, there was significant difference between the two groups regarding the gender. The pre-pandemic group had less male representation than the pandemic group [25 (33%) pre-pandemic group vs 120 (50%) pandemic group ($p=0.010$)]. (Table 1)

Most of the studied patients were admitted in a hospital medical ward (96.6% pandemic group vs 100% pre-pandemic group, $p = 0.27$). During the pandemic, the minority of the patients diagnosed with CDI were discharged from an Intensive Care Unit (2%) or a Covid-19 Department (1%) ($p=0.274$).

Approximately 28% of the patients in each group were previously treated in a long-term healthcare facility ($p=0.853$). History of previous antibiotic use (penicillin, cephalosporins, quinolones, azithromycin, macrolides, clindamycin, glycopeptides) within the last 3 months, corticosteroid and proton pump inhibitor (PPI) use was similar in both groups ($p>0.05$). (Table 1)

The number of diarrheas recorded before CDI diagnosis was less in the pandemic group compared with the pre-pandemic group [5.4 (±4.26) diarrheas pandemic group vs 8.4 (±3.85) diarrheas pre-pandemic group, $p=0.027$] while the average days of symptom duration was similar in both groups [5.9 (±9.6) days pandemic group vs 7.5 (±8.7) days pre-pandemic group, $p=0.834$]. (Table 1)

There was no difference between the two groups regarding the studied laboratory parameters (WBC, serum creatinine, CRP, PCT, serum albumin) ($p>0.1$). (Table 1)

Table 1: Baseline characteristics of patients who were hospitalized between 2017 and 2022 and were discharged with the diagnosis of clostridium difficile. Two groups were created: the pre-pandemic [patients hospitalized between March of 2017 and February of 2020], and the pandemic group [patients hospitalized during the pandemic (March 2020 - October 2022)]. Data are presented as number of patients (percentage), unless otherwise stated.

Variable	Total (N=313)	Pandemic group (N=238)	Pre-pandemic group (N=75)	p-value
Demographics				
Age in years, mean (SD)		75(15)	77(14)	0.783
Gender	Male	120(50.4)	25(33,3)	0.010*
	Female	118(49.6)	50(66.7)	
Co-morbidities				
Arterial hypertension		150(63)	44(58.7)	0.760
CVD		115(48.3)	33(44)	0.767
Diabetes		87(36.6)	20(26.7)	0.279
CKD		33(13.9)	12(16)	0.830
Respiratory Disease		28(11.8)	17(22.7)	0.570
Nervous System Disease		93(39.1)	28(37.3)	0.903
Immunodeficiency		41(17.2)	8(10.7)	0.375
Cancer		49(20.6)	12(16)	0.644
Hospitalization				
ICU		5(2.1)		0.274
Ward		230(96.6)	75(100)	
Covid-dedicated Department		3(1.3)		
History				
Long term HCF		67(28.2)	21(28)	0.853
Previous Covid-19		56 (23.5)	0	NA
Diarrheas (number), mean (SD)		8.4(3.85)	5.4(4.26)	0.027*
Diarrhea onset (days), mean (SD)		5.9(9.56)	7.45(8.7)	0.834
Antibiotics-Other medication				
Penicillin/B-lactamase		97(40.8)	32(42.7)	0.882
Cephalosporin		92(38.7)	33(44)	0.644
Quinolones		126(52.9)	33(44)	0.389
Macrolides		21(8.8)	15(20)	0.027*
Azithromycin		20(8.4)	5(6.7)	0.831
Carbapenems		20(8.4)	6(8)	0.925
Glycopeptides		26(10.9)	5(6.7)	0.528
Clindamycin		4(1.7)	5(6.7)	0.072
Corticosteroids		21(8.8)	3(4)	0.369
PPIs		168(70.6)	42(56)	0.064
Treatment				
Vancomycin per os		222(93.3)	58(77.3)	<0.001*
Vancomycin enema		62(26.1)	15(20)	0.570
Fidaxomicin		17(7.1)	4(5.3)	0.861
Metronidazole per os		16(6.7)	23(30.7)	<0.001*
Metronidazole iv		110(46.2)	17(22.7)	0.001*
Teicoplanin per os		5(2.1)	0	0.449
Other antibiotics		164(68.9)	38(50.6)	0.514
Laboratory results, number, mean (SD)				
WBC (cells/mm^3)		14946(9529)	16224(7996)	0.840
Creatinine (mg/dL)		1.2(0.9)	1.3(1.13)	0.899
CRP (mg/dL)		12.43(10)	13.1(9.63)	1.000
PCT (ng/mL)		2.97(9.8)	2.07(6.6)	0.237
Albumin (g/dL)		2.72(0.61)	2.7(0.57)	0.227

*Statistical significance p<0.05

SD, standard deviation; CVD, cardiovascular disease; CKD, chronic kidney disease; ICU, intensive care unit; HCF, Health care facility; Covid-19, coronavirus disease of 2019; PPIs, proton pump inhibitors; iv, intravenous; Other antibiotics, other concomitant antibiotics; PCR, polymerase chain reaction; WBC, white blood cells; CRP, C-Reactive protein; PCT, procalcitonin

In our study, the pandemic group consisted of more recurrent cases compared with the pre-pandemic group [42 (17.6%) vs 5 (6.7%) patients, respectively, p =0.024].

More than half of the included patients in both groups had mild/moderate CDI [138 (59%) pandemic group vs (40 (53%) pre-pandemic group, p=0.478], followed by severe CDI [92 (38.7%) pandemic group vs 28 (37.3%) pre-pandemic group, p=0.837] while the minority of cases had fulminant CDI [13 (5.5%) pandemic group vs 5 (6.7%) cases pre-pandemic group, p=0.696].

Both groups had similar recovery [196 (82.4%) pandemic group vs 66 (88%) pre-pandemic group, p=0.430] and death rates [32 (13.4%) pandemic group vs 8 (10.7%) pre-pandemic group, p = 0.530]. The average length of hospital stay was approximately 11 days in both groups [12 (±10) days pandemic group vs 11 (±6) days pre-pandemic group, p=0.190]. (Table 2)

Table 2: The severity of clostridium difficile infection and its outcomes in patients who were hospitalized between 2017 and 2022 and were discharged with the diagnosis of clostridium difficile. The pre-pandemic group comprised of the patients hospitalized between March of 2017 and February of 2020, and the pandemic group comprised of patients hospitalized during the pandemic (March 2020 - October 2022)]. Data are presented as number of patients (percentage), unless otherwise stated.

Variable		Pandemic group (N=238)	Pre-pandemic group (N=75)	p-value
Mild - Moderate CDI		138(58.8)	40(53.3)	0.478
Severe CDI		92(38.7)	28(37.3)	0.837
Fulminant CDI		13(5.5)	5(6.7)	0.696
Recurrent CDI		42(17.6)	5(6.7)	0.255
Number of recurrences	0	196(82.4)	70(93.3)	0.024*
	1	30(12.6)	4(5.3)	
	2	8(3.4)	1(1.3)	
	3	1(0.4)		
	4	2(0.8)		
Recovery		196(82.4)	66(88)	0.430
Death CDI- associated		32(13.4)	8(10.7)	0.530
Death from other causes		13(5.5)	5(6.7)	0.793
Length of stay, days (SD)		11.8(9.9)	11.4(5.8)	0.190

*Statistical significance p<0.05
CDI, Clostridium difficile infection; SD, standard deviation

There was different approach regarding the choice of antibiotics used between the two groups. During the pandemic, CDI infection was primarily treated with vancomycin per os [222 (93%) pandemic group vs 58 (77%) pre-pandemic group, p=<0.001] and metronidazole per os was used infrequently compared with the pre-pandemic period [16 (6.7%) vs 23 (30.7%), respectively, p<0.001]. Furthermore, metronidazole iv was added in the therapeutic regime in about half of the patients (46.2%) in the pandemic group (p=0.001). Furthermore, the concomitant use of antibiotics for another infection during the treatment of CDI was similar in both groups [164 (68.9%) in the pandemic group vs 38 (50.6%) in the pre-pandemic group, p=0.514]. (Table 1)

Finally, within the pandemic group we examined whether the severity parameters and the outcomes were associated with previous Sars-CoV-2 infection but found no association (p>0.05).

Discussion

Our study showed an increased incidence of CDI during the pandemic. Specifically, there was significantly higher incidence of CDI in the pandemic group (54.2/10,000 discharges) compared with the pre-pandemic group (14.6/10,000 discharges). The observed increase could be associated to pandemic factors or better surveillance or evolution over time, as was previously reported and attributed to the emergence of particularly potent Clostridium difficile strains [12]. Indeed, both incidences are higher than the reported incidence of CDI at discharge (7.8/10,000) based on 2016 ECDC surveillance protocol in Greece [13].

The observed increase during the pandemic could be associated to either the COVID-19 infection or the conditions present during the pandemic. Accordingly, it was previously reported that there is increased incidence of CDI within the patients with COVID-19 infection [6, 8]. This could be attributed to antibiotic use as patients with COVID-19 infection were more likely to receive antibiotics, despite contrary advice [6, 14]. Indeed, during the pandemic we noticed an increase in quinolone usage which is in accordance to previously published data [15]. It is well known that antibiotics disrupt the gut's normal bacterial balance and increase the likelihood of CDI [16]. This raises the need to intensify physician awareness about unnecessary antibiotic usage by prioritizing organized surveillance of CDI, promoting measures for prevention and control and limiting antibiotic over-prescription through antibiotic stewardship programs implementation [17]. In contrast, several studies report decreased incidence of CDI during the pandemic in COVID-dedicated hospitals [7, 9, 10]. This has been attributed to patients' isolation and extensive use of personal protection measures. Nevertheless, it's worth noting that in most of these studies, the incidence of CDI in COVID-19 patients used for the denominator the total days of hospitalization for the entire population rather than solely focusing on COVID-19 cases.

According to our results, there was a 3- to 4-fold increase in both CA- and HA-CDI, respectively, in the pandemic group compared with the pre-pandemic group. This could be attributed to the overprescription of broad-spectrum antibiotics [6] in outpatients as an empirical therapy to prevent secondary bacterial infections or reflects the preference of the patients to

avoid hospital visits during the pandemic [18]. Furthermore, the increase in HA-CDI in the pandemic group could be attributed to the extreme working conditions of the overburdened medical personnel [19] and the limited healthcare resources due to inpatients overload that increased the risk of cross-contamination and transmission of CDI within healthcare facilities [20]. Data regarding the frequency of HA-CDI during the pandemic period remains limited and inconsistent [21-23]. Future studies could explore the impact of different infection control strategies to reduce the incidence of HA-CDI.

In our study, the pandemic group contained more recurrent cases compared with the pre-pandemic group [42 (17.6%) vs 5 (6.7%) patients, respectively, p =0.024]. Similarly, studies from the USA show increased incidence of recurrent cases of CDI [24]. This could be attributed to the emergence of more virulent strains of Clostridium difficile, such as the NAP1/BI/027 strain [25], the development of resistance to antibiotics used to treat CDI [26] or use of concomitant medications. For example, our results showed the majority of the cases were treated with PPIs in both groups. It was previously reported that PPI use is associated with higher likelihood of developing CDI [27, 28]. We suggest exercising greater caution in the routine utilization of PPIs as a prophylactic measure. The establishment of a PPI usage guideline could potentially assist in promoting more careful PPI utilization in the future. The recurring pattern of CDI also adds to the substantial load, as each subsequent occurrence raises the chances of requiring hospitalization [29].

The main limitation of our study was its retrospective design and data derived from one hospital. However, it was a hospital for both COVID and non-COVID cases, providing robust data about the pandemic period. Furthermore, it enabled the collection of follow-up data and the accurate calculation of recurrence rate as the hospital covers a specific city area. Another limitation was the lack of ribotyping data, primarily due to its infrequent utilization in our state hospitals. However, this method is typically limited to specialized research centers and we aimed at examining real-life data.

The study has several noteworthy strengths. To the best of our knowledge, our study represents one of the largest in sample size and surveillance period in Greece. Furthermore, we included samples from both COVID-19-positive and -negative patients hospitalized in a variety of wards (intensive care unit, medical ward, COVID-19 wards), comprising a representative patient sample [30].

Conclusion

In conclusion, we found an increased incidence of CDI, in both community-acquired and healthcare-associated CDI as well as recurrent CDI cases during COVID pandemic compared with the pre-pandemic period. The observed increase in CDI incidence mandates the inclusion of CDI in the differential diagnosis for inpatients and outpatients presenting with acute diarrheal syndrome. Future educational initiatives targeting healthcare workers should be implemented to enhance CDI prevention and management.

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Conflict of interest

All authors report no conflicts of interests relevant to this study.

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