ORIGINAL ARTICLE

Clostridioides difficile infection in coronavirus disease 2019 (COVID-19): an underestimated problem?

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KEY WORDS

acute diarrhea, *Clostridioides difficile* infection, COVID-19, pseudomembranous colitis, SARS-CoV-2

EDITORIALS

by Cammarota, Giambò, and Ianiro, see p. 116 and Spigaglia, see p. 118

ABSTRACT

INTRODUCTION The use of antibiotics and possibility of microbiota disruption during the coronavirus disease 2019 (COVID-19) pandemic have raised questions about the incidence of *Clostridioides difficile* infection (CDI).

OBJECTIVES This study aimed to assess the frequency of and risk factors for CDI in patients with COVID-19.

PATIENTS AND METHODS We conducted a retrospective, single-center evaluation study on the frequency of and risk factors for CDI in patients with COVID-19 and in the prepandemic era. The analysis included 441 patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and 2961 patients hospitalized before the pandemic.

RESULTS A significant increase in the incidence of CDI was noted during the COVID-19 pandemic compared with the prepandemic period: 10.9% versus 2.6%, $P < 0.001$. Risk factors for CDI in patients with COVID-19 included: age, length of hospital stay, occurrence of diarrhea during hospitalization, use of antibiotics other than azithromycin, and coexistence of nervous system disease or chronic kidney disease—all of these factos had a weak association with CDI development. The multivariable logistic regression model indicated other unassessed variables that had an impact on the CDI incidence rate.

CONCLUSIONS We observed a higher incidence of CDI in patients with COVID-19. Antibiotic therapy was a relevant risk factor for CDI, although its effect was weak. Other drugs used during the pandemic were not found to have an impact on disease development. Possible causes of CDI may include fecal microbiota disruption by SARS-CoV-2 infection, but further research is needed to validate this hypothesis.

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INTRODUCTION On March 11, 2020, the World Health Organization announced a pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1-3] The most common symptoms of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 include fever (83%–99%), cough (59%–82%), fatigue (44%–70%), and diarrhea (2%–50%).[2,4-6] The diagnosis of COVID-19 is established by detecting SARS-CoV-2 RNA in a reverse transcription–polymerase chain reaction test. The treatment of COVID-19 is mainly symptomatic and based on international research and guidelines.[7,8] Recommended drugs include chloroquine, hydroxychloroquine, azithromycin, and lopinavir / ritonavir.[9] The use of tocilizumab and remdesivir can be considered in severely ill patients.[10,11] As the rates of bacterial coinfections are high, empiric antibiotic therapy is often necessary.[7] It has been estimated that over

WHAT'S NEW?

The present paper is, to our knowledge, the first one to reveal a significant increase in the incidence of *Clostridioides difficile* infection in hospitalized patients during the coronavirus disease 2019 (COVID-19) pandemic. Antibiotic therapy was found to be a relevant risk factor, although the effect was weak. Other drugs used at the time of the pandemic, such as chloroquine or lopinavir/ritonavir, did not show any impact on disease incidence. Apart from widespread antibiotic use, altered microbiota, which might be directly affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can constitute another possible reason for disease development.

70% of patients with COVID-19 have been treated with antibiotics.[12]

Frail elderly individuals with multiple comorbidities are most severly affected by COVID-19.[13] The extensive use of broad-spectrum antibiotics in a predisposed population raises questions about the occurrence of *Clostridioides difficile* infection (CDI). Fecal microbiota disruption caused by SARS-CoV-2 infection (the alterations are associated with SARS-CoV-2 fecal levels and COVID-19 severity) might constitute another crucial risk factor for CDI.[14] As diarrhea is a symptom of both CDI and COVID-19, the problem might sometimes be overlooked.

On March 16, 2020, Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland, was turned into a single-purpose hospital dedicated solely to caring for patients with COVID-19. Patients with confirmed SARS-CoV-2 infection were hospitalized between March 15 and June 15, 2020. According to 2009 European Society of Clinical Microbiology and Infectious Diseases guidelines, each hospitalized patient with acute diarrhea (defined as 3 or more loose stools within 24 hours) was tested for CDI. In this study, we aimed to analyze the incidence of CDI in the population of hospitalized patients with COVID-19 and compare it with the respective figures for the hospitalized population from 2019, the year preceding the pandemic.

PATIENTS AND METHODS We conducted a retrospective, single-center analysis of the frequency of CDI among 441 consecutive patients aged 18 years and older who had confirmed COVID-19 and were hospitalized between March 15 and June 15, 2020 in the Department of Internal Medicine and Gastroenterology with Inflammatory Bowel Disease Unit, Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland. The diagnosis of COVID-19 was confirmed by the positive result of reverse transcriptase–polymerase chain reaction test (gene targets: RdRp, E, and N) for SARS-CoV-2 in a nasopharyngeal swab specimen.

Every patient with acute diarrhea (defined as 3 or more loose stools within 24 hours) was evaluated for CDI (240 out of 441 patients met this criterion). The diagnosis was established based on initial enzyme immunoassay screening for glutamate dehydrogenase antigen and toxins A and B; selective anaerobic culture was performed when necessary.

The group of patients with COVID-19 and confirmed CDI was then compared with a prepandemic cohort with CDI. That group consisted of 2961 consecutive patients aged 18 years or older, hospitalized between January and December 2019 in the Department of Internal Medicine and Gastroenterology with Inflammatory Bowel Disease Unit of the same hospital. The 2 study groups could be compared, since, according to a large European study, CDI is not a seasonal disease[15] and we included all patients hospitalized in a given period of time, living in the same geographical region, and treated in a single center offering patients the same standard of care and testing strategy, a predictable range of services, and identical antimicrobial stewardship programs. We excluded from the analysis all patients with inflammatory bowel diseases, as the rate of CDI is known to be higher in that population.[16] We ran a special inflammatory bowel disease subunit where numerous severely ill patients were hospitalized and, on the other hand, many single-day hospitalizations occurred (eg, for biologic treatment), all of which ended during the pandemic. Therefore, the inclusion of those patients would make the study groups incomparable. Apart from single-day hospitalizations, 3 other patients were excluded.

The primary study endpoint was to assess the frequency of and risk factors for CDI in patients with COVID-19. The secondary endpoint was to compare the frequency of and risk factors for CDI between patients treated before the pandemic and those with COVID-19 who were hospitalized in our hospital as well as to assess the effects of drugs used during the COVID-19 pandemic on the frequency of CDI.

Statistical analysis Statistical analysis was conducted with the use of the R package, version 3.5.4 (R project, Vienna, Austria). Nominal variables were presented as number (percentage), whereas continuous variables, as mean (SD) or median (interquartile range), depending on distribution. The normality of distribution was verified with the Shapiro–Wilk test and based on the visual assessment of histograms. The study groups were compared with the χ^2 test or the Fisher exact test for dichotomous variables, and with the *t* test or the Mann–Whitney test for continuous variables, as appropriate. The effect size was evaluated with Cramer V for dichotomous variables, and with a mean or median difference with 95% CI for continuous variables. Additional analysis (multivariable logistic regression) was performed to identify a combination of parameters predicting CDI in patients with COVID-19. Variables that significantly differed between the study groups based on the results of the analysis described above were

included in the models as predictors. As logistic regression was used, model coefficients were presented as log odds. For ease of interpretation, log odds were exponentiated into odds ratios (ORs), so that when the continuous predictor increased by a single unit or a dichotomous predictor was present, the expected risk in the outcome variable was described as odds (percentage). Model validation included the χ^2 test, Nagelkerke R^2 coefficient, and the Hosmer–Lemeshow goodness-of-fit test. All tests were 2-tailed, with $\alpha = 0.05$.

Ethics The study protocol was approved by the Bioethics Committee of the Central Clinical Hospital of the Ministry of the Interior and Administration in Warsaw, Poland. Anonymized data were analyzed.

RESULTS There was a significant increase in the incidence of CDI during the COVID-19 pandemic compared with the prepandemic period: 10.9% (48 cases of CDI among 441 patients) versus 2.6% (77 cases of CDI among 2961 patients); $P < 0.0001$.

Age, hospitalization time, treatment with antibiotics other than azithromycin, some comorbidities (cardiovascular disease, chronic kidney disease [CKD], and nervous system disease), and onset of abdominal symptoms during hospitalization costituted risk factors for CDI development during the COVID-19 pandemic. All variables had a significant yet weak effect (Cramer V, 0.1–0.3).

Antibiotics were administered in 354 patients (80.3%) with COVID-19, including 42 (87.5%) with CDI and 312 (79.4%) without CDI (V = 0.06, $P = 0.18$). Surprisingly, no effect of azithromycin was observed—it was used in a total of 214 patients (48.5%), including 28 (58.3%) with CDI and 186 (47.3%) without CDI (V = 0.07, $P = 0.15$). Antibiotics other than azithromycin were administered in 300 patients (68%)—more frequently in those with CDI (39 [81.3%]) than in those without CDI (261 [66.4%]), (V = 0.1, $P = 0.037$). There was an increase in antibiotic use, expressed as daily antibiotic intake per 100 person-days of hospitalization, from 57.2 before the pandemic to 105 during the pandemic. Due to the lack of data on the effects of drugs used in COVID-19, the effects of chloroquine and lopinavir / ritonavir were also examined. We showed that they did not impact the development of CDI. Detailed data are presented in TABLE 1.

Parameters that differed between COVID-19 patients with CDI and those without were included as predictors in a multivariable logistic regression model with CDI as the outcome variable. Hospitalization time ($P = 0.01$), stay in an intensive care unit (ICU) ($P = 0.006$), and onset of abdominal symptoms during hospitalization ($P = 0.001$) represented significant variables in the model. Prolongation of hospitalization time by a single day increased the risk of CDI by 3% (OR, 1.03; 95% CI, 1.01–1.05). In patients staying in the ICU, the risk of CDI was 76% lower (OR, 0.24; 95% CI, 0.08–0.61), while it was 3.4-fold higher in patients with abdominal symptom onset during hospitalization (OR, 3.38; 95% CI, 1.71–6.72). Other variables were nonsignificant in the model (TABLE 2). Model evaluation with the use of the χ^2 test confirmed that all variables were jointly significant ($P = 0.001$). The R^2 Nagelkerke coefficient was low (22%), which indicated the presence of other unassessed variables that had an impact on the occurrence rate of CDI in patients with SARS-CoV-2 infection. An additional assessment with the Hosmer–Lemeshow goodness-of-fit test ($P = 0.13$) confirmed the good fit of the model to the data.

The comparison of CDI incidence before and during the COVID-19 pandemic showed a significant relationship between the occurrence of SARS-CoV-2 infection and sex, antibiotic use, the presence of CKD, and the presence of nervous system disease in patients with CDI. Men with SARS-CoV-2 infection were more frequently affected by CDI than before the pandemic (45.8% vs 28.6%; V = 0.18; $P = 0.049$). Antibiotics were taken by 87.5% of SARS-CoV-2-infected patients with CDI vs 67.5% of patients with CDI before the pandemic (V = 0.22; $P = 0.012$). There was no significant difference in terms of age, hospitalization time, and frequency of proton pump inhibitor (PPI) use between SARS-CoV-2-infected patients with CDI and those treated before the pandemic. Chronic kidney disease and nervous system disease were more frequent in SARS-CoV-2-infected patients with CDI than in those with CDI before the pandemic, with a stronger effect for nervous system disease (31.3% vs 15.6%; V = 0.19; $P = 0.038$ for CKD and 11.7% vs 39.6%; V = 0.33; $P < 0.001$ for nervous system disease). No significant relationship was confirmed between CDI in patients with SARS-CoV-2 infection and those with CDI before the pandemic in terms of other comorbidities. Detailed data are presented in TABLE 3.

DISCUSSION *Clostridioides difficile* is an anaerobic gram-positive bacterium that forms spores capable of causing colitis. It is most commonly detected in the elderly hospitalized individuals or in those with a positive history of antibiotic use. An increased number of CDI cases has been observed in recent years in younger patients after transplant, with inflammatory bowel disease, with immunodeficiency, and in those on dialysis.[17] The discovery of a new hypervirulent strain of *Clostridioides*, called NAP1/B1/027, has been associated with an increase in CDI frequency and posed a significant burden on the healthcare system over the past 10 years. According to data published in the last decade, the annual cost of treating CDI in the United States ranges between 436 million and 3 billion dollars.[18] Similarly to other authors, we wondered about the impact of the COVID-19 pandemic on the CDI rate, as some of risk factors for both diseases are similar

TABLE 1 Risk factors for *Clostridioides difficile* infection in patients with coronavirus disease 2019

Variable		All (n = 441)	With CDI (n = 48)	Without CDI (n = 393)	Cramer V or MD (95% CI)[a]	*P* value
Age, y, mean (SD)		66.76 (18.43)	74.94 (15.68)	65.76 (18.51)	9.18[a] (3.7–14.66)	0.001
Hospitalization time, d, median (IQR)		16 (10–24)	21.5 (15–33)	15 (9–22)	–6.50[a] (–12 to –4)	<0.001
Death		148 (33.6)	16 (33.3)	132 (33.6)	0.01	0.97
Antibiotics	Any	354 (80.3)	42 (87.5)	312 (79.4)	0.06	0.18
	Azithromycin	214 (48.5)	28 (58.3)	186 (47.3)	0.07	0.15
	Other than azithromycin	300 (68)	39 (81.3)	261 (66.4)	0.1	0.037
Chloroquine		321 (72.8)	40 (83.3)	281 (71.5)	0.08	0.08
Lopinavir/ritonavir		60 (13.6)	4 (8.3)	56 (14.2)	0.05	0.26
PPIs		197 (44.7)	26 (54.2)	171 (43.5)	0.07	0.16
Comorbidities		385 (87.3)	46 (95.8)	339 (86.3)	0.09	0.1
Cardiovascular disease		269 (61)	36 (75)	233 (59.3)	0.1	0.035
Respiratory system disease		61 (13.8)	10 (20.8)	51 (13)	0.07	0.14
Diabetes		111 (25.2)	16 (33.3)	95 (24.2)	0.07	0.17
Chronic kidney disease		89 (20.2)	15 (31.3)	74 (18.8)	0.1	0.043
Nervous system disease	Any	108 (24.5)	19 (39.6)	89 (22.8)	0.12	0.01
	Dementia syndrome	47 (10.6)	10 (20.8)	37 (9.4)	0.11	0.016
	Stroke	42 (9.5)	8 (16.7)	34 (8.7)	0.08	0.07
	Epilepsy	16 (3.6)	3 (6.3)	13 (3.3)	0.05	0.30
	Parkinson disease	6 (1.4)	2 (4.2)	4 (1)	0.08	0.08
	Schizophrenia	6 (1.4)	2 (4.2)	4 (1)	0.08	0.08
	Other	7 (1.6)	0	7 (1.8)	0.04	0.35
	>1 disease	18 (4.1)	6 (12.5)	12 (3.1)	0.14	0.002
Cancer		75 (17)	10 (20.8)	65 (16.5)	0.04	0.46
Onset of abdominal symptoms before hospitalization		142 (32.2)	17 (35.4)	125 (31.8)	0.02	0.61
Onset of abdominal symptoms during hospitalization		113 (25.6)	25 (52.1)	88 (22.4)	0.21	<0.001

Data are presented as number (percentage) of patients unless otherwise indicated.

a Groups compared with the χ^2 test or the Fisher exact test for dichotomous variables and with the *t* test (age) or the Mann–Whitney test (hospitalization time)

Abbreviations: CDI, *Clostridioides difficile* infection; IQR, interquartile range; MD, mean or median difference; PPIs, proton pump inhibitors

TABLE 2 Multivariable logistic regression model for *Clostridioides difficile* infection in patients with coronavirus disease 2019 (ß coefficient of logistic regression)

Characteristic	Coefficient	SE	*P* value	OR	95% CI
Age, y	0.02	0.01	0.13	1.02	0.99–1.04
Hospitalization time, d	0.03	0.01	0.01	1.03	1.01–1.05
Intensive care unit stay	–1.44	0.52	0.006	0.24	0.08–0.61
Use of antibiotics other than azithromycin	0.58	0.41	0.16	1.79	0.82–4.24
Cardiovascular disease	0.24	0.41	0.56	1.27	0.58–2.94
Chronic kidney disease	0.46	0.38	0.23	1.58	0.74–3.29
Nervous system disease	0.29	0.35	0.41	1.34	0.66–2.66
Onset of abdominal symptoms during hospitalization	1.22	0.35	0.001	3.38	1.71–6.72
Constant	–5.04	0.9	<0.001	–	–

Abbreviations: OR, odds ratio

(advanced age, hospitalization, and immunodeficiency). Antibiotics are more frequently used in patients with COVID-19 and also a direct alteration of microbiota by SARS-CoV-2 has been observed.[13,14] A single research letter on 9 CDI cases has been published recently.[19] The study cohort from Detroit Medical Center hospitalized from March 11 to April 22, 2020 included elderly women with SARS-CoV-2 infection. Two other reports[20,21] presented contradictory findings: a decreased number of cases and a stable number of cases compared with the prepandemic era, respectively. It is possible that the problem of CDI in patients with COVID-19 is underestimated.

Our study showed, for the first time, that the incidence of CDI during the current pandemic is much higher than before—10.9% versus 2.6%. There are numerous reasons for this observation: advanced age of patients, prolonged hospitalizations, and widespread antibiotic use.

TABLE 3 Risk factors for *Clostridioides difficile* infection before and during coronavirus disease 2019 pandemic

Variable	Total (n = 125)	Patients with CDI before the SARS-CoV-2 pandemic (n = 77)	Patients with CDI and SARS-CoV-2 infection (n = 48)	Cramer V or MD (95% CI)[a]	*P* value
Female sex	81 (64.8)	55 (71.4)	26 (54.2)	0.18	0.049
Age, y, mean (SD)	72.19 (16.89)	70.48 (17.48)	74.94 (15.68)	–4.46[a] (–10.58 to 1.66)	0.15
Hospitalization, d, median (IQR)	21 (13–31)	19 (12–26)	21.5 (15–33)	–2.5[a] (–8 to 1)	0.11
Any antibiotics	94 (75.2)	52 (67.5)	42 (87.5)	0.22	0.012
PPIs	58 (46.4)	32 (41.6)	26 (54.2)	0.12	0.17
Comorbidities	115 (92)	69 (89.6)	46 (95.8)	0.11	0.36
Cardiovascular disease	86 (68.8)	50 (64.9)	36 (75)	0.11	0.24
Respiratory system disease	19 (15.2)	9 (11.7)	10 (20.8)	0.12	0.17
Digestive system disease	40 (32)	22 (28.6)	18 (37.5)	0.09	0.3
Diabetes	36 (28.8)	20 (26)	16 (33.3)	0.08	0.38
Chronic kidney disease	27 (21.6)	12 (15.6)	15 (31.3)	0.19	0.038
Nervous system disease	28 (22.4)	9 (11.7)	19 (39.6)	0.33	<0.001
Cancer	18 (14.4)	8 (10.4)	10 (20.8)	0.14	0.11

Data presented as number (percentage) of patients unless otherwise indicated.

a Groups compared with the χ^2 test or the Fisher exact test for dichotomous variables and with the *t* test (age) or the Mann–Whitney test (hospitalization time)

Abbreviations: see **TABLE 1**

Several studies have presented data on antibiotic use in patients with COVID-19. A single-center study from Wuhan, China, has reported that 94% of critically ill patients received antibiotics.[22] Another study of 799 moderately-to-severely ill patients provided similar numbers: between 89% and 93% of patients were treated with antibiotics. In our cohort, antibiotics were administered in 80.3% of the patients—a lower proportion—but there was still an increase in antibiotic use, expressed as daily antibiotic intake per 100 person-days of hospitalization, from 57.2 before the pandemic to 105 during the pandemic. In our analysis, we considered all the antibiotics together and also azithromycin separately (as for some time its use was more widespread due to the unpublished French data[23]) and, surprisingly, we found that it is antibiotics other than azithromycin that are mainly associated with CDI development. This might be due to the fact that azithromycin carries a comparatively lower risk of CDI.[24]

Due to the lack of data on the effects of drugs used for COVID-19, we also examined the effects of chloroquine and lopinavir / ritonavir and showed that they did not impact CDI development. Proton pump inhibitor therapy was not used more often in our cohort that developed CDI, which is not entirely surprising, as numerous observational studies and meta-analyses have reported conflicting results regarding the association of PPI therapy with the risk of CDI.[25] Glucocorticoids were not included in the analysis, because, at the time when the study was conducted (March 15–June 15, 2020), they were scarcely used for COVID-19 treatment (the results of the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial were published on June 17, 2020).[26]

In our multivariable logistic regression model, hospitalization time ($P = 0.01$), stay in an ICU ($P = 0.006$), and onset of abdominal symptoms during hospitalization ($P = 0.001$) were associated with CDI development. Antibiotic use was not related to CDI development in this model—we suspect that it was due to the presence of a weak association (V = 0.1 for antibiotics other than azithromycin) and might be an indicator of an unknown variable associated with CDI. The duration of hospitalization is often reported as a risk factor for CDI,[27] so this finding is not surprising. We cannot explain why ICU stay seems to be a protective factor—in our view, a confounding factor may exist here—probably, ICU stays were short, since it has been known that the prognosis of patients with COVID-19 who require mechanical ventilation is poor.[28] A more liberal CDI testing strategy might be another possible explanation, which would suggest that the true number of patients with CDI during the pandemic is even higher.

The clinical manifestations of CDI range from mild diarrhea to life-threatening fulminant colitis. Patients usually present with leukocytosis, malaise, abdominal cramping, pain, and watery diarrhea.[29] Unfortunately, isolated gastrointestinal symptoms might be present in the course of COVID-19 in up to 10% of patients.[30] For this reason, sometimes it is difficult to differentiate between the 2 diseases. Strict protocols for the diagnosis of CDI are therefore needed. Our finding that an onset of abdominal symptoms during hospitalization is a risk factor for CDI seems to be of importance and might help hospitalists who take care of patients with COVID-19.

The evaluation of our model indicated the presence of other unassessed variables that had an impact on the occurrence rate of CDI in patients with SARS-CoV-2 infection. The following hypothesis is, obviously, purely speculative, but it might confirm the direct alteration of microbiota by SARS--CoV-2 and requires further research. In a pilot study of 15 patients with COVID-19 compared with controls, persistent alterations in the fecal microbiome were found during hospitalization.[14] Yet, another study of 30 patients showed significantly reduced bacterial diversity, a higher relative abundance of opportunistic pathogens, and a lower relative abundance of beneficial symbionts,[31] so the issue of microbial alterations seems fascinating and remains a potential treatment target in both diseases. Furthermore, there has been evidence on the role of probiotics in the treatment of COVID-19. Lactobacilli and bifidobacteria have shown a promising beneficial effect and their administration might overcome gut dysbiosis induced by SARS-CoV-2 infection.[32] However, the role of probiotics, although interesting, remains unproven. Since, according to guidelines, adjunctive probiotics are not recommended for CDI treatment,[33] they were not used in our cohort of patients.

We also examined whether the factors responsible for CDI in our study population during the pandemic differed from those present in the prepandemic period. There was no significant difference in terms of age, hospitalization time, or frequency of PPI use between patients with CDI during the SARS-CoV-2 pandemic and those treated before the pandemic. The most striking difference was seen in antibiotic use, which is probably a relevant factor in SARS-CoV-2 / CDI coinfection. Other factors included nervous system disease and CKD, of which CKD carries a known risk of CDI.[27]

Strengths and limitations Some limitations of our study should be acknowledged: lack of characteristics of a large cohort of prepandemic patients (although we did obtain the characteristics of the prepandemic patients with CDI) and different timespans for the analysis of the 2 study cohorts. However, as explained above, since (according to a large European study) CDI is not a seasonal disease[15] and we included all hospitalized patients in a given time interval, living in the same geographical region, and treated a single center offering the same standard of care, the same testing strategy, a predictable range of services, and identical antimicrobial stewardship programs to all patients, the 2 groups could be compared.

Moreover, the major strength of our study is the fact that, to our knowledge, it is the first report on a considerably higher rate of CDI in hospitalized patients during the pandemic. Even though the probability of coinfection has always been regarded as high and speculated upon,[34] the high rate of CDI and SARS-CoV-2 coinfection has not been confirmed yet. We acknowledge that the findings of our study are in contrast to other recent publications, one of which reported a lower incidence of CDI,[21] while another one showed a similar incidence of CDI[20] among patients with SARS-CoV-2 infection. The universal use of personal protective equipment, including gowns and gloves, can account for a lower rate of CDI coinfection. Unfortunately, studies performed in the prepandemic era did not confirm that improving hospital cleaning procedures[35] or moving patients to new locations or single rooms influenced the rate of CDI.[36] In our hospital, all preventive measures were implemented, including personal protective equipment, patient isolation, visit restrictions, reinforcements, and continuous education of the cleaning staff, but the rate of CDI still remained high. Therefore, although we are convinced that our data hold true, we cannot explain why the results obtained in various centers vary so considerably. In a retrospective cohort from New York, described by Luo et al,[20] there was a trend towards a larger percentage of positive tests yet a smaller percentage of tests sent as compared with the prepandemic era. Similarly, in a report from Madrid,[21] there was a 9.8% reduction in the rate of requests for CDI tests. One might speculate that, perhaps, as abdominal symptoms of COVID-19 are common, in the heat of the pandemic and with the subsequent shortage of healthcare staff, CDI was not often considered in differential diagnosis. Further prospective observational data will be needed to solve this conundrum.

Conclusions In this study, we observed a significant increase in the incidence of CDI among hospitalized patients during the pandemic compared with the prepandemic period. The widespread antibiotic use constituted a crucial risk factor for CDI, although its effect was weak. Direct microbiota alteration by SARS-CoV-2 may be another possible explanation for the increased CDI incidence. A question should be raised whether we are facing an increase in the expected number of CDI cases. And since the answer might be positive, strict antibiotic stewardship programs and further research on microbiota alteration in COVID-19 are needed. The appearance of abdominal symptoms during hospitalization might be a relevant signal of CDI development. Clinicians should be aware of the risk of coinfection and remain vigilant—following protocols for CDI screening during the pandemic are of great importance.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT GR conceived the concept of the study. KL, MR, MK, and PK contributed to study design. KL, MR, MK, PK, and AM were involved in data collection. MR analyzed the data. GR and WW coordinated funding for the project. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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