ONLINE FIRST

NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

MEDICAL RESEARCH JOURNAL

ISSN: 2451-2591

e-ISSN: 2451-4101

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DOI: 10.5603/mrj.102915

Article type: Original article

Submitted: 2024-10-02

Accepted: 2024-10-03

Published online: 2024-11-14

ORIGINAL ARTICLE

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The impact of the COVID-19 pandemic on the course of *Clostridioides difficile* infection in patients with inflammatory bowel disease

Short title: Aleksandra Jagura et al., CDI in IBD patients during the COVID-19 pandemic

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DOI: 10.5603/mrj.102915

ABSTRACT

Background: Patients with inflammatory bowel disease (IBD) are at high risk of *Clostridioides difficile* infection (CDI). The Coronavirus disease 2019 (COVID-19) pandemic was a special time, that had an impact on the course of many diseases. This study aimed to determine the influence of the COVID-19 pandemic on the course of CDI in patients with ulcerative colitis (UC) and Crohn's disease (CD).

Material and methods: A retrospective study involved a total of 61 patients and compared the course of CDI in IBD patients in the pre-pandemic period (2015–2020) and after the second wave of COVID-19 (2022–2023). The analysis included demographic, clinical, laboratory data, and CDI risk factors. The course of CDI was divided into benign, severe, and severe-complicated.

Results: In five years before the pandemic in IBD patients, there were 35 cases of CDI, whereas in 15 months after the first COVID-19 wave, there were 31 CDI. In the quartile comparison, the CDI incidence increased in the pandemic period ($p = 0.021$). The antibiotherapy wasn't a significant factor in increasing the CDI incidence. Patients with UC comprised 85.71% of the control group and 67.74% of the treatment group. The authors obtained a statistically significant higher rate of using an increased vancomycin dose ($p = 0.010$) and recurrences of CDI ($p = 0.045$) in the totality of IBD patients and only with ulcerative colitis ($p = 0.001$), ($p = 0.020$).

Conclusions: The COVID-19 pandemic contributed to an increase in CDI incidence in IBD patients. The infections require treatment intensification and are characterized by increased recurrence, especially in patients with UC.

Keywords *Clostridioides difficile* infection, COVID-19 pandemic, inflammatory bowel disease, Crohn’s disease, ulcerative colitis

Introduction

Ulcerative colitis (UC) and Crohn’s disease (CD) are chronic inflammatory disorders of unknown etiology, which are rated as inflammatory bowel disease (IBD). The relationship between environmental, immunological, and genetic factors interact in the pathogenesis of IBD. Chronic inflammation, gut microbiota disorder and drugs applied in the treatment of this condition predispose to gastrointestinal infections [1]. As a result of corticosteroid taking, chronic immunosuppressive therapy, more frequent antibiotic therapy, and repeated hospitalization, IBD patients are at high risk of CDI [1, 2]. *Clostridioides difficile* is one of the most common bacteria concurrent with exacerbation of the inflammatory bowel disease [3]. Course of the Coronavirus disease 2019 (COVID-19) pandemic, which was announced on 11 April 2020. by the World Health Organization (WHO), has modified the *Clostridioides difficile* infection (CDI) risk factors. On the one hand, social isolation, using personal protective equipment, and increased care about hygiene were constraining the transmission of *C. difficile* [4]. On the other hand, the application of wide-reaching antimicrobial therapy, which was often misused or prolonged, could have contributed to a higher incidence of CDI

[5]. Additionally, in the pandemic, the number of CDI could have been understated because of the attribution of the gastrointestinal symptoms to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and also through less frequent *C. difficile* testing [6].

Aim

This study aimed to determine the influence of the Coronavirus disease 2019 (COVID-19) pandemic on the course of *Clostridioides difficile* infection (CDI) in patients with ulcerative colitis (UC) and Crohn's disease (CD).

Material and methods

Study population

A retrospective study was conducted, in which it was compared two periods: the pre-pandemic period (from July 2015 to February 2020) and the period between January 2022 and March 2023. The pre-COVID-19 period started with the available data in the electronic documentation system and ended with the beginning of the pandemic in Poland. The period between March 2020 – December 2021 was excluded from the whole pandemic period, because of a reorganization in Clinic functioning (suspended admissions and hospitalizations for only the patients affected by SARS-CoV-2). Data were sourced from patient's medical records, that were hospitalized in the Gastroenterology Clinic in Central Teaching Hospital of the Medical University of Lodz. The analysis involved a total of 60 patients (29 male patients and 31 female patients). The pre-pandemic group consists of 34 patients, aged 42.7 ± 19.1 (range from 20 to 83 years old) including 15 men. aged 40.3 ± 19.7 (range from 20 to 78 years old) and 19 women aged 42.5 ± 19.1 (range from 20 to 83 years old). The pandemic group consists of 27 patients aged 45.1 ± 19.2 (range from 20 to 76 years old) including 14 men aged 46.4 ± 20.1 (range from 22 to 74 years old) and 13 women aged 47.5 ± 18.6 (range from 20 to 76 years old). Two patients were excluded from the second group because of a lack of laboratory data.

Inclusion criteria

Patients who suffered from IBD with confirmed CDI, age ≥ 18 were included in the study. IBD was diagnosed according to European Crohn's and Colitis Organisation (ECCO) criteria and confirmed by histopathological examination [7]. All patients with exacerbation of IBD underwent screening tests for Glutamate Dehydrogenase (GDH) on admission or during

the hospitalization. In case of a positive GDH test result, toxin A/B identification was conducted. In the case of a positive GDH test and the simultaneous absence of toxins A/B in feces, the polymerase chain reaction (PCR) test was ordered. The diagnosis of CDI was made based on a positive GDH test with the simultaneous presence of toxins A/B. In the case of a positive GDH test and the simultaneous absence of toxins A/B, the infection was confirmed by a positive PCR test. Patients had blood samples taken to determine laboratory parameters.

Analyzed parameters

We analyzed clinical data (type of inflammatory bowel disease, first episode or recurrence of CDI, body mass index (BMI), body temperature) and laboratory data (leukocytosis, creatinine clearance, albumin) on admission. CDI risk factors were also specified (antibiotic therapy in the last 3 months, steroid therapy in the past and currently, immunosuppressive therapy in the past and currently, proton pump inhibitors (PPIs) and selective serotonin reuptake inhibitors (SSRIs) intake, past hospitalization during last 6 months, parenteral/enteral nutrition during last 6 months). Additionally, the analysis involved the applied treatment of CDI (metronidazole, vancomycin and the necessity of enhancement of its dose, fecal microbiota transplantation, parenteral nutrition) and also demographic data (age, gender).

Comparison of the CDI course

The course of CDI was divided into benign, severe, and severe-complicated based on the 2021 update on the treatment guidance document on CDI in adults published by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [8]. Severe CDI was defined as one of the following factors: fever — core body temperature > 38.3°C, leukocytosis (leukocyte count > 15 000/mm^3 and serum creatinine > 1.5 mg/dL. This value substitute increases in serum creatinine > 50% above the level before CDI, because of lack of data about previous creatinine levels. Severe-complicated (or fulminant) CDI was defined by the presence of one of the factors, which was attributed to CDI: ileus, bowel perforation, toxic megacolon, or any fulminant course of disease (indispensability to hospitalization in intensive care unit (ICU), shock, death). The cases that didn’t require hospitalization in the ICU were treated in the department. Benign CDI was defined in case of absence of the criteria, that allow to classify the course of infection as severe or severe-complicated.

Statistical analysis

The data were analyzed using Statistica version 13.3. The Shapiro-Wilk test was used to check the normal distribution of the population. Pearson's Chi-square test was used to compare qualitative (categorized) variables. The quantitative data with normal distribution were analyzed using the Student's t-test (t-test), and the data without normal distribution were analyzed using the Mann–Whitney U-test. The level of p-value < 0.05 was approved as statistically significant. The standard deviations ($X \pm SD$) and arithmetical means were calculated.

Results

Incidence of CDI in IBD patients

In 34 IBD patients hospitalized between 2015 and 2020, there were 35 cases of CDI. Only one patient had a recurrence of CDI. Between January 2022 and March 2023, 27 patients had 31 cases of CDI. Two patients had single re-infections, and one patient had two recurrences. The rate of CDI in IBD patients was analyzed in particular quarters. The mean number of CDI in particular quarters is higher in the period after the first COVID-19 wave than in the pre-pandemic period ($p = 0.021$). The mean number of CDI in the first quarter of this period totaled 1.4 cases, in the second quarter 2.5 cases, in the third 2 cases, and the last one 1.6 cases. In the first quarter of the year 2022, it was 2 cases, in the second quarter, it was 7, in the third 5; in the fourth 9 and in the first quarter of 2023 – 8 cases. The detailed number of CDI cases in IBD patients during particular quarters is shown in Figure 1. There were no statistically significant differences in the mean incidence of CDI in IBD patients between particular quarters in the years 2015–2020 ($p = 0.616$).

Patient characteristics, applied treatment, recurrences, and risk factors of CDI

The comparison of all IBD patients with CDI in the pre-COVID-19 period with the period between January 2022–March 2023 is summarized in Table 1. In both analyzed periods, CDI was more often diagnosed in patients with UC than CD (85.71% and 67.74%). After the first COVID-19 wave in IBD patients was obtained statistically significant higher rate of applying increased vancomycin dose (OR = 4.89, Cramér's V = 0.525, $p = 0.010$) and recurrences of CDI (OR = 6.54, Cramér's V = 0.633, $p = 0.045$). The same associations were observed in patients with ulcerative colitis - increased vancomycin dose (OR = 1.47, Cramér's V = 0.685, $p = 0.001$), recurrences (Cramér's V = 0.717, $p = 0.020$). These differences didn't occur in patients with CD. There were no statistically significant differences in CDI risk

factors between the analyzed periods. Antibiotic therapy wasn't a significant factor in increasing the risk of CDI in all IBD patients (p = 0.487) or only with UC (0.801). The comparison of risk factors for CDI in both periods is presented in Table 2.

Severity of CDI in IBD patients

In 35 cases of CDI in the pre-pandemic group, 11 were severe course, and 3 were severe-complicated. 13 of 31 cases between January 2022 – March 2023 had a severe course, and 1 was severe-complicated. There was no statistically significant difference in severity between IBD patients in both periods (p = 0.676). The particular symptoms of a severe and severe-complicated course of CDI in IBD patients are presented percentage-wise in Figure 2.

Discussion

This study aimed to determine the influence of the COVID-19 pandemic on the course of CDI in patients with UC and CD. CDI is one of the most common infections, which can co-occur with exacerbation of the IBD [3]. The present study demonstrates an increased mean amount of CDI in particular quarters in the period after the first COVID-19 wave. Lewandowski K. et al. also observed an increased incidence of CDI from 2.6% before the COVID-19 pandemic to 10.9% during the pandemic period [5]. In the present study, antibiotic therapy wasn't a significant factor in increasing the risk of CDI. They observed a rise in antibiotic intake: daily antibiotic use per 100 person-days of hospitalization has grown from 57.2 before the COVID-19 pandemic to 105 in the COVID-19 period. They did not observe the effect of azithromycin [5]. This antibiotic was one of the most common in COVID-19 patients because of its potential therapeutic function [9].

In a Greek tertiary hospital, there was also a significant increase in monthly CDI from 0.00 to 11.77 infections per 10,000 bed-days ($p < 0.001$) and the rise was more intense during the pandemic ($r2 = +0.47$) compared to the pre-pandemic-period ($r1 = +0.16$) [10]. This elevation couldn't be solved by a rise in antibiotic intake because, in another study, it was demonstrated that there was a decrease in community antibiotic consumption in Greece of 6.043 defined daily dose (DDD) per 1000 inhabitants per day (18.6%) during the pandemic [11]. They suspect that the increase in CDI could result from more frequent testing of patients with COVID-19, which has gastrointestinal symptoms, to exclude CDI. Even 16% of confirmed COVID-19 cases presented only gastrointestinal symptoms; 37 % of them were diarrhea, and 25% were abdominal pain [12]. On the other hand, the number of CDI could have been underreported because of attributing the gastrointestinal symptoms to the SARS-

CoV-2 infection. As another probable cause of increased CDI incidence, Lewandowski K. quotes that it may be caused by direct microbiota alteration by SARS-CoV-2 [5]. Moreover, another study says that the coinfection of SARS-CoV-2 and CDI could increase the transmissibility of both pathogens through feces [13].

Other studies showed stable CDI incidence. Yadlapati S. et al. found no difference in the frequency of hospital-acquired *C. difficile* infection (HA-CDI) between COVID-19 and non-COVID-19 periods [6]. Also in a tertiary care hospital in Romania, the incidence of HA-CDI in the COVID-19 patients didn't change, but the antibiotic intake was the most important factor associated with HA-CDI [14]. They used the ATLAS severity score and guidelines of the Society for Healthcare Epidemiology of America (SHEA) to classify the severity of the CDI course. They also observed no difference between the pre-COVID-19 group and the COVID-19 group (40.4% *vs.* 45% severe CDI cases; $p = 0.6$).

In contrast to the results from the present study, Vendrik KE. et al. showed that the annual CDI incidence rate in 2020 was lower than in previous years, but there was a higher percentage of severe CDI cases in the second pandemic wave [15]. In the author's view, this could be caused by delayed diagnostics and reduced hospital referrals for patients with community-acquired (CA-CDI). Additionally, in contrast with the present study, they didn't observe differences in CDI recurrences in the COVID-19 waves versus the same periods in 2015–2019. Bentivegna E. et al. also demonstrated a significantly lower incidence of HA-CDI in the pandemic period (2020) in comparison to 2017 ($p = 0.002$), 2018 ($p = 0.023$), and 2019 ($p = 0.047$) [16]. Possible reasons for the decreasing incidence of CDI are social distancing, lower contact with medical services, increased care about hand hygiene, and using personal protective equipment (PPE) [4]. On the other hand, using alcohol-based disinfectants and PPE which were used to prevent the spread of SARS-CoV-2, may not have prevented CDI transmission, which could have caused an increase in CDI incidence in the present study [6]. Also, in a UK tertiary center was a significant decrease in the total CDI rate per 10,000 occupied bed days during the first and second quarters of 2021 compared to the same period in 2020; however, the CDI rate in 2020 was significantly higher in the quarter from July to September than the same quarter in 2019 [17]. In the present study, there were no differences in CDI rates between particular quarters.

It is relevant that none of the above studies relate to IBD patients. In the present study, 85.71% of the pre-pandemic group and 67.74% of the IBD patients after the second COVID-19 wave were patients with ulcerative colitis. Issa M. et al. also observed that patients with UC 1,5 times more frequently suffer from CDI, than patients with CD [18]. The IBD group is

especially at high risk of CDI through genetic and immunologic susceptibility as well as specific medication [1]. Razik R. et al. demonstrate that IBD patients have a 30% higher risk of CDI recurrence than the general population [19]. The CDI develops during exposure to C. difficile or its toxic spores during the disturbance of the right colonic microbiota. This disruption also facilitates *C. difficile* colonization and enhances the risk of CDI recurrence [20]. CP. Kelly says that the vancomycin and metronidazole that are used in CDI treatment can also modify the colonic microbiota, which can predispose to the recurrence of CDI [21]. Additionally, the anti-CDI antibiotics have no effect on the spores, which may also cause repeated CDI. The other group at high risk of recurrence is older adults [21]. With advancing age, immunological senescence may be insufficient to fight off CDI. That can also explain why undergoing a CDI at an older age predisposes to subsequent recurrences.

This study also has limitations. The analysis was retrospectively conducted and included only one center. This study didn't make a demarcation between HA-CDI and CA-CDI. The authors couldn't differentiate the type of antibiotic because of a lack of data. This study prompts further exploration of another cause of increased CDI incidence in IBD patients. The impact of SARS-COV-2 infection on vulnerability to CDI by microbiome dysfunction and other mechanisms should be considered.

Conclusions

In conclusion, the COVID-19 pandemic contributed to an increase in CDI incidence in IBD patients. The infections required intensification of treatment and were characterized by increased recurrence, especially in patients suffering from UC. The present study is interesting and significant because it covers a new health problem. The results and discussion point out the complexity of the grounds for increased CDI incidence in IBD patients after the pandemic and prompt further exploration of another cause of this conjuncture.

Article information

Ethics statement: *The study did not require ethics approval, because of its retrospective character and lack of interference in human and animal organisms.*

Author contributions: *study design — Aleksandra Jagura, Aleksandra Sobolewska-Włodarczyk; data collection — Aleksandra Jagura; statistical analysis — Aleksandra Jagura; data interpretation — Aleksandra Jagura, Aleksandra Sobolewska-Włodarczyk; manuscript preparation — Aleksandra Jagura, Aleksandra Sobolewska-Włodarczyk, Anita Gąsiorowska;*

literature search — Aleksandra Jagura, Aleksandra Sobolewska-Włodarczyk; funds collection — Anita Gąsiorowska.

Funding: *None.*

Acknowledgments: *Statutory funds of the Department of Gastroenterology in Central Teaching Hospital of the Medical University of Lodz.*

Conflict of interest: *None.*

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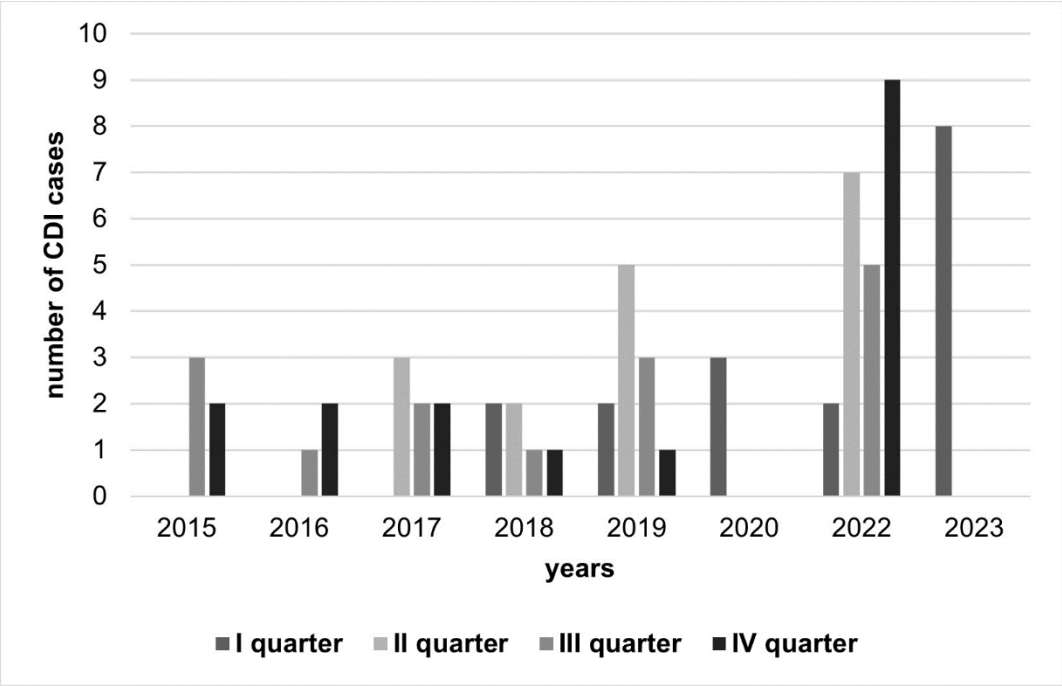

Figure 1. Number of CDI cases in IBD patients during particular quarters

CDI — *Clostridioides difficile* infection; IBD — inflammatory bowel disease

The number of CDI in IBD patients was higher in the particular quarters of the pandemic period (2022–2023) than the number of CDI in the same quarters of the pre-pandemic period (2015–2020), ($p = 0.021$)

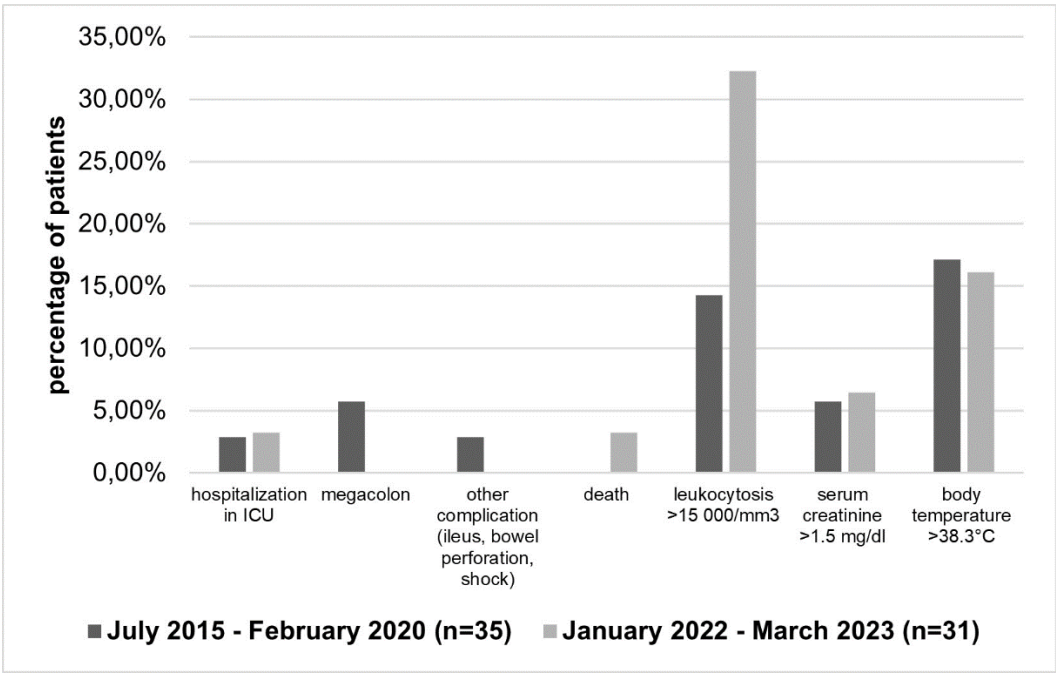

Figure 2. Percentage presentation of symptoms of severe and severe-complicated CDI in IBD patients with a distinction between the analyzed periods

CDI — *Clostridioides difficile* infection; IBD — inflammatory bowel disease

Table 1. The characteristics, laboratory data, applied treatment, and negative outcomes in both analyzed groups of patients

	Period between July 2015–February 2020 (n = 35)	**Period between January 2022–March 2023 (n = 31)**	**p-value**
Characteristic			
Age [years] median (min–max)	38 (20–83)	41 (20–76)	0.681
Sex [no (%)]			0.459
Female gender	19 (54.29%)	14 (45.16%)	
Male gender	16 (45.71%)	17 (54.84%)	
BMI			0.752
Mean	23	23,8	
SD	6.02	5.7	
Type of IBD [no (%)]			0.082
CD	5 (14.29%)	10 (32.26%)	
UC	30 (85.71%)	21 (67.74%)	
Laboratory data			
WBC [/μL] median (min–max)	10110 (4400–45300)	11390 (2240–30110)	0.355
Creatinine [mg/dL] median (min–max)	0.79 (0.43–1.82)	0.89 (0.49–6.94)	0.162
Albumin [g/dL]			0.607
Mean	3.41	3.51	
SD	0,65	0,72	
Treatment of CDI			
Metronidazole [no (%)]	21 (60%)	16 (51.61%)	0.495
Vancomycin [no (%)]	34 (97.14%)	29 (93.55%)	0.527
Increased dose of vancomycin [no (%)]	4 (11.43%)	12 (38.71%)	**0.010**
FMT [no (%)]	1 (2.86%)	4 (12.90%)	0.299
Parenteral nutrition [no (%)]	7 (20%)	10 (32.26%)	0.256
Negative outcomes			
Hospitalization in ICU [no (%)]	1 (2.86%)	1 (3.23%)	0.527
Megacolon [no (%)]	2 (5.71%)	0	0.527
Other complication (ileus bowel perforation shock) [no (%)]	1 (2.86%)	0	0.951
Death [no (%)]	0	1 (3.23%)	0.951
Body temperature >38.3°C	6 (17.14%)	5 (16.13%)	0.959

Recurrence of CDI [no (%)]	1 (2.86%)	5 (16.13%)	**0.045**

Note: $p < 0.05$ was considered significant. In the pandemic period, in IBD patients with CDI, it was obtained a statistically significant higher rate of applying increased vancomycin dose ($p = 0.010$) and recurrences of CDI ($p = 0.045$). The statistically significant differences were indicated in bold text

BMI — Body Mass Index; SD — standard deviation; IBD — inflammatory bowel disease; CD — Crohn's disease; UC — ulcerative colitis; WBC — white blood cells; FMT — fecal microbiota transplantation; ICU — intensive care unit; CDI — *Clostridioides difficile* infection.

Table 2. The comparison of risk factors for CDI in IBD patients in both analyzed periods

CDI risk factors	Period between July 2015–February 2020 (n = 35)	Period between January 2022–March 2023 (n = 31)	p-value
Antibiotics [no (%)]	10 (28.57%)	11 (35.48%)	0.487
Corticosteroids currently [no (%)]	24 (68.57%)	23 (74.19%)	0.615
Corticosteroids in the past [no (%)]	23 (65.71%)	20 (64.52%)	0.919
Azathioprine currently [no (%)]	10 (28.57%)	12 (35.29%)	0.383
Azathioprine in the past [no (%)]	17 (48.57%)	14 (45.16%)	0.878
PPIs [no (%)]	10 (28.57%)	13 (41.94%)	0.256
SSRIs [no (%)]	2 (5.71%)	2 (6.45%)	0.695
Past hospitalization [no (%)]	23 (65.71%)	19 (61.29%)	0.709
Parenteral/enteral nutrition [no (%)]	5 (14.29%)	4 (12.90%)	0.803

Note: $p < 0.05$ was considered significant. There were nonsignificant differences between the analyzed risk factors

PPIs — proton pump inhibitors; SSRIs — selective serotonin reuptake inhibitors