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CLOSTRIDIUM DIFFICILE INFECTION AND IBD PATIENTS IN ONE CLINICAL CENTER

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ABSTRACT

In this article, a retrospective analysis of the incidence of Clostridium difficile CDI infection was performed among patients with inflammatory bowel disease (IBD)-ulcerative colitis (UC) and Crohn disease (CD). Factors that have a significant impact on the onset of the infection have been considered.

We used an immunochromatographic quantitative method for the determination of Clostridium difficile Glutamate Dehydrogenase Toxin A, B in the stool.

KEYWORDS: CDI, IBD, UC & CD

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) as part of inflammatory bowel disease (IBD), are chronic, lifelong, idiopathic, autoimmune inflammatory condition of the gastrointestinal tract [1]. CD and UC are characterized by relapsing and remitting courses with variable clinical manifestation and complications, requiring frequent hospitalizations and long-term therapy [2,3,4].

The incidence of IBD has increased worldwide, especially within the industrialized countries, as well as among young, fertile age people without pre-existing illnesses [5,6,7,8].

Clostridium difficile is a gram-positive rod-shaped bacterium belonging to the group of anaerobic spore-forming bacteria [4].

C. difficile has two exotoxins - A and B, the effect of which is related to the development of pseudomembranous colitis after prolonged antibiotic use. It occurs with increasing incidence in young people, following transplants, in immuno compromised patients and after antibiotic exposure [9].

The prevalence of CDI in IBD patients has increased rapidly over the past several decades and is associated with worse outcomes of IBD [7].

Because of insufficient data from developing countries, there are no exact global epidemiology records.

Ulcerative colitis and Chron's disease patients are at a significantly higher risk of developing active CDI. then the general population [10, 5].

It is difficult to distinguish the presence of CDI infection from an IBD flare-up. Very often CDI can be detected as

early as during the onset of the IBD disease. The infection itself can contribute to exacerbation and relapse of IBD, creating a higher mortality risk of and a high risk for colectomy [11].

Because of the high CDI incidence among IBD patients, it is important to always consider the possibility of a superimposed CD infection in this population. According to ECCO guidelines for the management of IBD (2017) all patients hospitalized with a disease flare should undergo testing for CD toxins [12].

When CDI is discovered, an immediate treatment must begin in order to minimize the complications that may occur [12].

The goal of the study is to examine the incidence of CDI in IBD patients hospitalized in a GE clinic at a referral IBD center.

MATERIALS AND METHODS

A retrospective, observational study in a referral center was performed to evaluate the incidence of Clostridium difficile among IBD patients.

For a 3 year period 202 consecutive IBD patients, 18 years old and above, with a confirmed IBD diagnosis were studied, after being admitted in a gastroenterology clinic, because of a disease flare-up; 105 of them have UC and 97 – CD. All patients with diarrhea and were tested for the presence of Cl. Difficile.

Demographic information, diagnosis, Montreal classification for IBD phenotype, IBD therapy including biologics, immune modulators, and 5-aminosalicylic acids (5-ASAs), antibiotic exposure, hospitalizations, and surgeries were obtained for all patients from their medical files.

The CDI diagnosis was confirmed with a stool toxin analysis. We used an immunochromatographic quantitative method for the determination of Clostridium difficile Glutamate Dehydrogenase Toxin A, B in stool samples.

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS for Windows, Version 20.0. (SPSS Inc., Chicago, IL, USA). For data analysis the following statistical methods were used: descriptive statistics for tabular and graphical presentation of results; Continuous variables were summarised using the mean ± standard deviation, Chi-squared test for categorical variables, we used calculated the odds ratio (OR) (95% confidence interval [CI]) for CDI in IBD, correlation and variance analysis. The level of significance used for all analyses was $p<0.05$.

RESULTS

A total number of 202 hospitalized IBD patients, including 105 with CD and 97 with UC, were enrolled in our study. The mean age of IBD patients was 43.4 ± 15.2 (18 - 73), 49.50% (100) of whom were male and 50.50% (102) female. The mean age of patients with UC was 43.7 ± 16.2 years, and of those with CD 43.0 ± 13.9. The male / female ratio is identical in both groups (CD 52 (49.5%) : 53 (50.5%) and UC 48 (49.5%) : 49 (50.5%)).

In CD patients, those with affected small intestine are predominant (n=40/ 41.70%), whereas, in UC patients, those with pancolitis are predominant (n=53/52.50%).

The demographic information, Montreal classification for IBD phenotype and disease activity of all IBD patients is listed in Table 1.

Table 1: Characteristics of IBD Patients

Characteristic		UC (n=105)	CD (n=97)
Age [mean± SD]		43.7 ± 16.2 years	43.0 ± 13.9 years
Duration of the disease [mean± SD]		83.4 ± 90.2 months	77.1 ± 83.6 months
Gender	Male, *n* [%]	52 [49.50]	48 [49.50]
	Female, *n* [%]	53 [50.50]	49 [50.50]
Location	Proctitis, *n* [%]	9 [8.90]	-
	Left colitis, *n* [%]	39 [38.60]	-
	Pancolitis, *n* [%]	53 [52.50]	-
	Terminal Ileum, *n* [%]	-	40 [41.70]
	Colon, *n* [%]	-	26 [27.10]
	Ileum and Colon, *n* [%]	-	28 [29.20]
	Colon and Upper GI modifier, *n* [%]	-	1 [1.00]
	Ileum and Colon and Upper GI modifier, *n* [%]	-	1 [1.00]
Severity of the disease	Remission, *n* [%]	5 [4.80]	17 [20.00]
	Mild disease, *n* [%]	21 [20.20]	16 [18.80]
	Moderate disease, *n* [%]	31 [29.80]	47 [55.30]
	Severe disease, *n* [%]	47 [45.20]	5 [5.90]

Clostridium difficile was identified in 28 (13.90 %) IBD patients. The results show that the incidence of CDI patients with UC is significantly higher than in patients with CD, respectively 18.1%(n=19) to 9.30% (n=9), (χ^2=3.28; p<0.05) (Fig. 1).

UC patients are at a higher risk of Clostridium difficile (OR=1.95 (0.927-4.102); p< 0.05). All patients positive for CDI have a clinical picture, which resembles a relapse of the disease (p < 0.05).

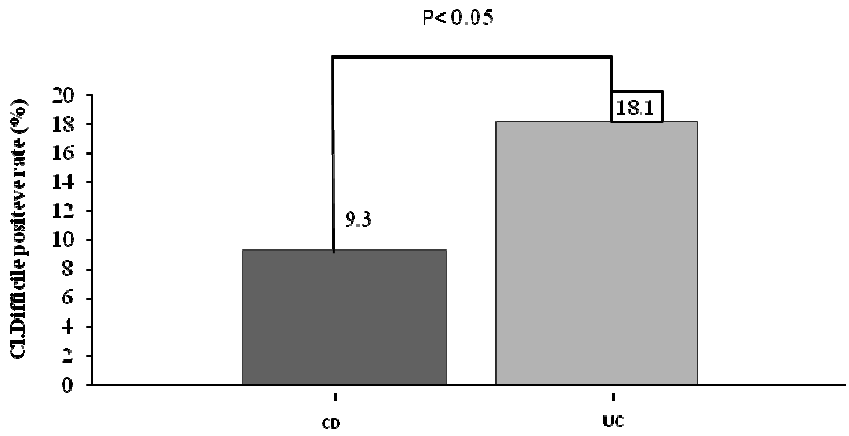

Figure 1: The incidence of Clostridium Difficile Infection in Patients with IBD (p < 0.05)

Data from the three-year follow-up of the overall CDI incidence among UC patients show a tendency towards increasing from 12.5% in 2014 to 13.5% in 2015, reaching 27.8% in 2016. The same upward trend in CDI incidence was also seen in CD patients from 5.9% in 2014, 7.7% in 2015, to 12.2% in 2016 (Fig. 2). Our results clearly demonstrate that the CDI incidence was significantly higher in UC patients within the study period, compared to the same results for CD patients (p<0.05).

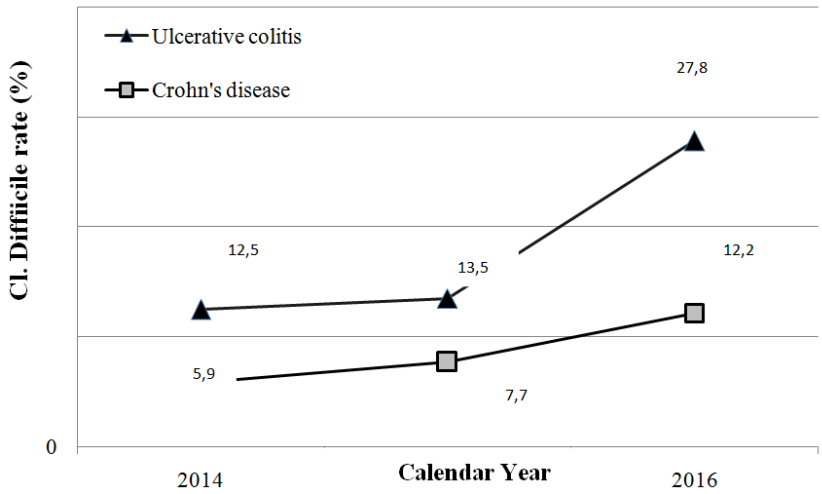

Figure 2: The incidence of Clostridium Difficile Infection in Patients with IBD for the 2014 – 2016 Period

The analysis of the CDI incidence results according to the disease activity shows a strong correlation between the CDI incidence in IBD patients and the severity of their disease (Tabl.2).

There is no significant correlation between the type of therapy and the presence of CDI (Tabl.2).

We did not find also significant difference and correlation between the value of C-reactive protein (CRP) and the presence of CDI. The analysis of our results shows mean CRP values at a negative CDI of 40.5 ± 53.7 (0.11-230) mgmol/ l, and in a positive CDI, the mean CRP was 57.8 ± 68.3 (0.13 -263). There is no correlation between the levels of CRP positive CDI in our study.

Table 2: Incidence of Clostridium Difficile Infection According to the Severity of the Disease (p < 0.05), According to Therapy (p>0.05) and According to Disease Extent

Characteristic		Positive CDI		Negative CDI	
		CD	UC	CD	UC
IBD therapy	Anti-TNF	2 [11.10]	2 [20.00]	16 [88.90]	10 [80.00]
	Immunosuppressive therapy	2 [6.50]	7 [16.70]	29 [93.50]	35 [83.30]
	5-ASA	3 [12.50]	7 [21.20]	21 [87.50]	26 [78.80]
	Without therapy	2 [11.10]	3 [17.60]	16 [88.90]	14 [82.60]
Disease extent	Proctitis, *n* [%]	-	1 [11.10]	-	8 [88.90]
	Left colitis, *n* [%]	-	9 [23.10]	-	30 [76.90]
	Pancolitis, *n* [%]	-	9 [17.00]	-	44 [83.00]
	Terminal Ileum, *n* [%]	5 [12.50]	-	35 [87.50]	-
	Colon, *n* [%]	1 [3.80]	-	25 [96.20]	-
	Ileum and Colon, *n* [%]	3 [10.70]	-	25 [89.30]	
Severity of the disease	Remission, *n* [%]	2 [11.80]	-	15 [88.20]	5 [100]
	Mild disease, *n* [%]	3 [18.80]	3 [14.30]	13 [81.20]	18 [85.70]
	Moderate disease, *n* [%]	4 [8.50]	3 [9.70]	43 [91.50]	28 [90.30]
	Severe disease, *n* [%]	-	13 [27.70]	5 [100]	34 [72.30]

DISCUSSIONS

With the increasing incidence of IBD worldwide, the interest in CDI among hospitalized IBD patients is also increasing. Different authors cite different incidence [13,14,15,16,17,18].

The incidence of CDI among our IBD patients, especially those with UC, is higher than that reported by some authors [4, 7, 19, 20, 21, 22] and is similar to that reported by others [11.]

Differences in results can be seen as a consequence of applying different CDI detection methods. The Enzyme immunoassay (EIA) for the detection of Toxin A and B is rapid and more frequent, but the sensitivity of single sample testing is low (72%) [14, 20] and may increase by 10% in second testing (84%) [23].

The tendency of increased CDI incidence among UC patients has been observed by other authors, who have reported results for the 1998 to 2004 period [24]. This trend has been preserved over the years.

Similar to other authors we have observed that CDI is more common among young patients [31]. In our study, the average age of UC and CD patients was 43 years.

One of the major risk factors is frequent antibiotic exposure [10,15,25]. Sometimes this use begins in ambulatory conditions due to an IBD flare-up. In other IBD patients, the required use of corticosteroids in combination with PPIs is related to controversial data in the literature on the risk of CDI development [10,22,25,26,27], which necessitates the need for new studies for identifying the risk factors that lead to CDI development.

There are a lot of studies confirming our results that the type of IBD treatment such as corticosteroids, biological drugs, immunosuppressive treatment does not increase the risk of CDI in IBD patients [22,25,26,27,28,29].

However, a large retrospective cohort study of 10,662 IBD inpatients recorded that the risk of CDI increases three times within 90d of corticosteroid initiation (RR= 3.4, 95% CI:1.9-6.1) but no increase in risk with preceding biologic therapy [4,30].

The lack of correlation between the IBD activity, measured by biochemical criteria like a value of CRP is contradictory, on one hand, but on the other, it could be explained by the fact that some of the patients with active UC and pancolitis could have normal CRP values and the presence of CDI.

If we look at IBD activity measured through the Montreal Classification and CDAI, data shows that the percentage CDI positive resultsis the highest inactive disease (CDAI > 150).

Interestingly, the result in CD patients in remission, which are at the same time CDI positive, requires the clinician to actively investigate patients for any superimposed infection during the follow-up of the disease.

It is generally difficult to differentiate IBD disease activity from CDI. For that reason, it is not clear if disease activity is an independent risk factor for the development of CDI [4.]

Some authors note that CDI is more often in UC patients and in patients with Crohn-colitis [14, 31]. This coincides with the data from our study on UC patients, but not in the case of CD patients. (Tabl.2)

Controversial data and literature results require prospective multicentre studies to investigate the risk factors for CDI occurrence among IBD patients and the connection between infection and the type of therapy, localisations, and disease severity.

CONCLUSIONS

CDI is a common infection among IBD patients. It is more common among UC patients and causes the disease flare-up with subsequent hospitalization and a need for treatment.

There is a strong correlation between the CDI incidence in IBD patients and the severity of their disease.

There is no significant correlation between the type of therapy and the presence of CDI.

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