INCIDENCE AND RISK FACTORS OF CLOSTRIDIUM DIFFICILE INFECTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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INCIDENCE AND RISK FACTORS OF CLOSTRIDIUM DIFFICILE INFECTION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (Abstract). Recent changes in the epidemiology of Clostridium difficile infection (CDI) include the identification of patients with inflammatory bowel disease (IBD) as a group at risk in comparison to the general population. Aim: To identify the incidence and risk factors for CDI among patients with IBD. Material and methods: Case-control study of 78 patients diagnosed with IBD, hospitalized at the Iasi Institute of Gastroenterology and Hepatology between January 2012 and July 2014. Demographic data and clinical characteristics were reviewed for all patients. IBD patients with positive C. difficile toxins A and B tests were matched by sex, age and type of IBD with IBD patients hospitalized in the same period with negative C. difficile toxins tests. Results: Both groups were comparable for baseline characteristics. Of the 78 patients diagnosed with IBD included in the study, C. difficile was detected in 26 patients (33.33%). There was no statistical difference regarding length of hospital stay (10.42±7.34 vs. 8.01±6.14 days, p=0.129) between the two study groups. Risk factors for CDI in patients with IBD were: ulcerative colitis (OR=1.90, CI=1.320-2.720, p=0.001), use of proton pump inhibitors (OR=1.57, CI=1.133-2.032, p=0.012), previous antibiotic use (OR=2.3, CI=1.587-3.332, p<0.0001), and albumin<3g/dl (OR=1.78, CI=1.023-5.558, p=0.038). Immunosuppressive and anti TNF-α treatment were not risk factors for C. difficile development in patients with IBD. Conclusions: CDI in patients with IBD is a serious infection and should be treated aggressively with close clinical follow-up. Ulcerative colitis, previous treatment with antibiotics and proton pump inhibitors represent risk factors for CDI development in patients with IBD. Keywords: CLOSTRIDIUM DIFFICILE, RISK FACTORS, ULCERATIVE COLITIS, INCIDENCE.

Recently there has been an increase in both incidence and severity of Clostridium difficile infection (CDI) worldwide (1). Recognized risk factors for infection include advanced age, broad-spectrum antibiotic therapy, prolonged hospitalization, malignancies (2), immunosuppression, the use of proton pump inhibitors and the presence of multiple co-morbidities (3, 4).

Several studies demonstrated an increasing incidence of CDI in patients with underlying inflammatory bowel disease (IBD), with a more severe course of the disease compared with the non-IBD population (5-9). The incidence of CDI among hospitalized IBD patients increased from
1% in 1998 to 3% in 2007 (10). Both ulcerative colitis (UC) and Crohn’s disease (CD) present high-risk for CDI, but patients with UC are more susceptible than those with CD (11,12).

Besides traditional risk factors for CDI, IBD patients present specific risk factors, unique to IBD, in relation to colonic involvement and disease severity, and it seems that IBD itself is an independent risk factor for CDI. In a study by Issa et al., colonic involvement and pancolitis were associated with a threefold greater risk (5), concluding that the extent and severity of the disease may be considered independent risk factors for CDI development in patients with IBD.

CDI has a negative impact on IBD course and is associated with a significant increase in need for colectomy and mortality (13). Therefore, in the present study we aimed to evaluate the incidence and the risk factors associated with CDI in IBD patients admitted in a tertiary center.

MATERIAL AND METHODS

Patients. We conducted a prospective, case-control study on IBD patients admitted to the Iasi Institute of Gastroenterology and Hepatology in the interval January 2012- July 2014.

Demographic data and clinical characteristics like comorbidities, previous antibiotic use, immunomodulators, acid suppression, length of hospital stay, gastrointestinal surgery and outcome were assessed. Patients with indeterminate colitis, other infectious colitis and sepsis were excluded.

Diagnosis of CDI. All patients with flare activity were tested using immunochromatography assays for toxins A and B. Patients who tested positive for C. difficile toxins A and B were identified (n=26) and matched with IBD patients with negative C. difficile toxins (n=52) hospitalized during the same period of time.

Statistical analysis. The statistical analysis was carried out using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean ±SD and categorical data as percentage. The Kolmogorov-Smirnov test was used to determine whether the continuous variables were normally distributed. Analysis of variance and the chi-square test were used for continuous and categorical variables, respectively. The Student t test or Mann-Whitney U test were used to compare groups, with the chi-square test used for categorical variables. Risk factors for CDI in patients with IBD were determined using logistic regression for univariate analysis. A p value of less than 0.05 was considered statistically significant.

RESULTS

Incidence of CDI. Baseline demographic, clinical, and laboratory characteristics of the study population are outlined in Table I. There was no significant difference between the 2 study groups.

During the study period, a total of 78 patients were admitted with the diagnosis of IBD of whom 26 (33.3%) had concomitant CDI. Of the IBD patients, 43(55.1%) had UC, and 35(44.8%) had CD.

We assessed the annual incidence of CDI in patients with IBD and found that it increased from 2.01% in 2012 to 16% in 2014 (fig.1). Likewise, UC patients were more susceptible to CDI than CD patients (fig.2).
Incidence and risk factors of *Clostridium difficile* infection in patients with inflammatory Bowel disease

### TABLE I

Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th><em>C. difficile</em> n=26</th>
<th>Control n=52</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) (mean±SD)</td>
<td>50.96±18.16</td>
<td>44.60±16.57</td>
<td>0.126</td>
</tr>
<tr>
<td>Sex m/f</td>
<td>16/9</td>
<td>33/19</td>
<td>0.363*</td>
</tr>
<tr>
<td>UC/CD</td>
<td>21/9</td>
<td>22/30</td>
<td>0.001*</td>
</tr>
<tr>
<td>Albumin (g/dl) (mean ±SD)</td>
<td>3.63±0.67</td>
<td>4.36±0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Hemoglobin (g/dl) (mean ±SD)</td>
<td>12.46±2.25</td>
<td>12.88±2.28</td>
<td>0.450</td>
</tr>
<tr>
<td>Platelets (x10^9/mmc) (mean ±SD)</td>
<td>351±16.88</td>
<td>350±15.33</td>
<td>0.966</td>
</tr>
<tr>
<td>ESR (mm/h) (mean ±SD)</td>
<td>34.22±17.69</td>
<td>32.02±33.63</td>
<td>0.777</td>
</tr>
<tr>
<td>CRP (mg/dl) (mean ±SD)</td>
<td>4.81±6.26</td>
<td>4.81±6.26</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Abbreviations: UC, ulcerative colitis, CD, Crohn’s disease, SD, Standard deviation, ESR, erythrocyte sedimentation rate, CRP, C-reactive protein.

*test $X^2$
Risk factors for CDI. Antibiotic use prior to CDI was reported in 43 patients (55.1%), the most commonly used antibiotics being ciprofloxacin (36.1%) and ampicillin (19%) for urinary tract and upper respiratory tract infections. In our study, the length of hospital stay was not influenced by CDI (10.42±7.34 vs. 8.01±6.14, p=0.129) (tab. II).

C. difficile infection was more common among patients with a recent diagnosis of IBD. Likewise, patients with an IBD flare-up were more susceptible to CDI (8.07±4.48 vs. 3.94±3.13, p<0.0001) (fig. 3). Cardiovascular co morbidities and malignancies did not influence the risk for CDI in our study population.

In our study, IBD patients with CDI were treated with metronidazole 250 mg orally four times daily for 10 days. In case of metronidazole failure vancomycin treatment was initiated. This was required in 2/26 (7.69%) patients. In this study the rate of CDI recurrence was 16%.

### TABLE II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>IC 95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ulcerative colitis</td>
<td>1.90</td>
<td>1.320-2.720</td>
<td>0.001</td>
</tr>
<tr>
<td>proton pump inhibitors use</td>
<td>1.57</td>
<td>1.133-2.032</td>
<td>0.012</td>
</tr>
<tr>
<td>antibiotic use</td>
<td>2.3</td>
<td>1.587-3.332</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>albumin &lt;3g/dl</td>
<td>1.78</td>
<td>1.023-5.558</td>
<td>0.038</td>
</tr>
</tbody>
</table>

**DISCUSSION**

A dramatic increase in CDI has been documented over the last two decades (5-9). Today, CDI is recognized as the main cause of infectious nosocomial diarrhea associated with increased morbidity, mortality and healthcare costs (14).

Several studies have reported a significantly increased incidence of CDI among IBD patients, particularly in those with UC. Thus, a study using nationwide data showed that in US the incidence of CDI among hos-
pitalized UC patients has doubled over a 7-year period (15). Likewise, a Belgian study reported a nearly four-fold increase in CDI in both IBD and non-IBD patients between 2000 and 2008 (8). Our results showed that the incidence of CDI in IBD has increased during the study period for which data were available. Also, CDI is significantly more common in UC than in CD.

The classical risk factor for CDI is exposure to broad-spectrum antibiotics. Antibiotics disturb the normal intestinal flora, allowing *C. difficile* to proliferate (16). In this study, we found that previous antibiotic therapy and previous proton pump inhibitors treatment represent risk factors for CDI development in patients with IBD. Additionally, immunosuppressive and anti-TNF-α treatments were not risk factors for CDI.

Contrasting results have been reported regarding the length of hospital stay in IBD patients with CDI. Jodorkovsky et al. (11), reported a similar mean length of hospital stay for UC patients with and without superimposed CDI (11.7 vs. 11.0 days; p = 0.70), while Bossuyt et al. (8) found notably shorter stays in IBD patients with CDI (mean 15.2 days) as compared to non-IBD patients with *C. difficile* (mean 27.7 days) (p <0.001). Our data support that the length of hospital stay is not influenced by the presence of CDI.

Our findings suggest that CDI is more frequent in patients who present with IBD flare-ups. Therefore, clinicians should maintain a high index of suspicion for CDI in IBD patients, especially in those with UC. Recurrence of CDI is present in 10-30% of IBD patients (16). In this study the rate of CDI recurrence was 16%. This is in agreement with previous studies that reported similar findings.

A major limitation of our study may be the small number of patients and the fact that it was a single center study. This could have an influence on the conclusions regarding risk factors. Another limitation of this study is the absence of routine CDI testing in all patients with IBD as in other studies, and this could have influenced the annual incidence rate of CDI.

**CONCLUSIONS**

Our results show that the risk of CDI in IBD patients is extremely high and the incidence appears to be increasing at a faster rate. IBD patients who present with symptoms of a flare must be tested for *C. difficile* toxins. A rapid and adequate diagnosis and treatment may improve prognosis in IBD patients.

**REFERENCES**


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**THE STRUCTURE OF IBUPROFEN BOUND TO CYCLOOXYGENASE-2**

Cyclooxygenases (COX-1 and COX-2) catalyze the rate-limiting step in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes and are the pharmacological targets of non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 selective inhibitors (coxibs). One of the most commonly available over-the-counter pharmaceuticals in the world is ibuprofen. The anti-inflammatory and analgesic properties of ibuprofen are thought to arise from inhibition of COX-2 rather than COX-1. Ibuprofen occupies an area of the enzyme between the substrate channel opening and the apex of the active site. While an X-ray crystal structure of ibuprofen bound to COX-1 has been solved, no such structure exists for the cognate isoform COX-2. Almost all interactions formed between ibuprofen and the active site residues of COX-2 consist of hydrophobic interactions. A group of researchers have determined the crystal structure of muCOX-2 with a racemic mixture of (R/S)-ibuprofen and the study reveals that only the S-isomer of ibuprofen was bound resulting that the S-isomer possesses higher affinity for COX-2 than the R-isomer. The structure clearly reveals that S-ibuprofen is bound with full occupancy in both monomers of COX-2. The results provide the first atomic level detail of the interaction between ibuprofen and COX-2 (Orlando BJ, Lucido MJ, Malkowski MG. The structure of ibuprofen bound to cyclooxygenase-2. *J Struct Biol* 2015; 189: 62-66).

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