Clostridium Difficile Infection in Patients with Inflammatory Bowel Disease

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Scientific Study
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Patients with inflammatory bowel disease (IBD) are at increased risk for developing symptomatic *Clostridium difficile* infection (CDI) with worse clinical outcomes, including mortality, as compared with the general population. IBD-patients are also more susceptible to have recurrences of CDI. At present, predisposing factors for CDI in IBD-patients are poorly established. To characterize IBD-related CDI, a retrospective cohort from HUS register was gathered. Patient characteristics were compared with two control groups: IBD-patients with CDI and CDI-patients. According to our results, there was no statistically significant difference in mortality rate between IBD- and CDI-patients in contrary to previous reports. We detected corticosteroid consumption in IBD patients with CDI to be greater than in patient with IBD alone. It could be considered as a risk factor for CDI. Clarifying risk factors for CDI could lead to better understanding of optimal treatment for CDI in IBD patients.

**Avainsanat – Nyckelord – Keywords**
IBD, CDI, recurrent infections, risk factors

**Säilytyspaikka – Förvaringställe – Where deposited**

**Muita tietoja – Övriga uppgifter – Additional information**
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1 Introduction

The incidence of Clostridium difficile infection (CDI) in patients with inflammatory bowel disease (IBD) has increased over the past few decades [1, 2]. IBD patients are more susceptible to develop CDI and severe outcomes than non-IBD patients [3, 4]. Moreover, the recurrences of CDI seem to occur more frequently in IBD patients and the risk for recurrences increases after every CDI episode [5, 6].

Currently the risk factors for CDI in IBD patients have only poorly established. IBD patients with CDI are on average younger than other patients with CDI [7]. Some evidence suggests that IBD-related medications and colon limited disease could predispose to CDI although more studies are needed to define these factors more clearly [5, 7, 8].

Our study paid interest on the differences between IBD and CDI patient characteristics. We compared in our study IBD patients with CDI to two control patients groups; CDI patients without IBD and IBD patients for clarifying the predisposing and prognostic factors. The study could offer a way to better understanding for the risks of CDI in IBD patients, diagnosing and optimal treatment strategy in IBD patients with CDI. At the moment, diagnosis of CDI in IBD patients may be difficult due to overlapping clinical symptoms of CDI and IBD flare up. Moreover, asymptomatic colonization of the bacterium and lack of the traditional pseudomembranes on the mucosa of the colon may also mislead the clinician.
2 Review of literature

2.1 Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract. There are two principal IBD types: Crohn’s disease (CD) and ulcerative colitis (Colitis ulcerosa, CU). Sometimes it may be difficult for a specialist to distinguish CD and CU from each other at the colonoscopy or afterwards in the colonoscopy biopsies. When the diagnosis cannot be clearly made after these processes, the condition is defined as an inflammatory bowel disease unclassified (IBD-U). IBD is a lifelong idiopathic autoimmune condition with relapsing and remitting courses. The incidence of IBD varies geographically and has increased worldwide especially within the industrialized countries [1, 2]. The prevalence of CU in Europe is 500 per 100000 persons and for CD 320 per 100000. In the United States corresponding values are 250 per 100000 individuals for CU and 200 per 100000 for CD [1]. In Finland the incidence of IBD has increased approximately three fold since the 1990s. In 2008 the prevalence was 595 per 100000 individuals [9]. The onset of disease has two age peaks: the well-defined first peak seems to arise between the ages of 20 to 39, and the second between the ages of 50-70 [10]. However, the emergence of second peak is under dispute and poorly established [9].

Although the exact cause of inflammatory bowel disease remains poorly understood, some genetic and environmental predisposing factors have been identified. Current opinion on the course of disease is that genetically susceptible individuals develop an inadequate immune response when in contact in environmental factors (Figure 1) [2]. The result is enhanced immune reaction against gut’s microflora. Previous studies have shown that the composition of normal flora in IBD-patient’s gut is altered, although some age-related changes also exist [11]. Altered microbiota in the intestine is also called dysbiosis and it has thought to play a critical role in the pathogenesis of inflammatory bowel disease [12]. It is not yet clearly demonstrated if dysbiosis plays a part in development of IBD or vice versa. There are also over 163 genetic loci associated with susceptibility to develop IBD [13].
2.1.1 Crohn’s disease

The prevalence of Crohn’s disease has increased in the past few decades, especially in the younger generation. CD is a progressive chronic inflammatory disease that can affect the entire gastrointestinal tract from mouth to anus. Usually inflammation persists in the terminal ileum or colon. It is characterized by segmental transmural lesions and granulomas on the intestinal wall. Smoking is strongly associated with CD [15]. There are also some genetic factors that predispose to CD. The most often associated gene variant with CD is NOD2 (encoding nucleotide-binding oligomerization domain-containing protein 2). The hallmarks of clinical symptoms include bloody diarrhea, abdominal pain, fatigue and weight loss. Complications may also occur, especially in more severe disease. These complications include fibrosis, intestinal
obstruction and perianal manifestations such as fistulae and abscesses [16]. Some studies have shown that most of the CD patients will sooner or later require a surgery depending on the site and activity of the disease [17].

2.1.2 Ulcerative colitis
The inflammation in the ulcerative colitis is limited to the mucosal layer of the colon and rectum. The most common symptom of UC is bloody diarrhea. In an active state of disease there may form some ulcers in a mucous membrane of the colon or rectum. The disease can occur at any age, but most commonly it arises later in life or in early adulthood [18]. The incidence of CU has increased over the world in the recent decades and it is more frequent than Crohn’s disease [5]. A few predisposing factors for CU have found including usage of NSAIDs, family history and some nutritional factors [18]. The effect of smoking history in patients suffering from UC is different compared to CD patients. It is now known that smoking is a protective agent in CU [18]. There is also some conflicting data according to the gender predominance in CU. Some sources have reported male gender to be more common among patients with CU, but recent studies have published some data in which female gender predominates [19-21].

2.1.3 Treatment strategy for IBD
A conventional treatment strategy for mild to moderate IBD is based on anti-inflammatory drug 5-aminosalicylate (5-ASA). 5-ASA is occasionally combined with corticosteroids for patients who otherwise fail to achieve remission [22]. Immunomodulators, such as thiopurines or methotrexate, may be required for maintenance of remission in certain patients or in patients with more severe disease [13]. Thiopurines and methotrexate are effective in maintenance of remission and lessen the need for corticosteroid intake. Indeed, a moderate corticosteroid sparing impact makes these immunomodulators an important option, especially for steroid
dependent IBD patients [23]. One remarkable disadvantage of therapy with immunomodulators is a risk of leukopenia which increases susceptibility to infectious complications [24].

While systemic corticosteroids are beneficial in short-term treatment of IBD, especially in patients under acute IBD flare [25, 26], the long-term treatment with corticosteroids is limited due to vast array of adverse effects. [25]. Drawbacks of corticosteroid therapy are different side effects including bone loss and poor wound healing, which may occur particularly in prolonged use. However, among IBD patients the most adverse complication due to corticosteroids is that they predispose to infections which seem to increase the mortality rate in elderly, hospitalized IBD patients [27]. The risk of infection seems to depend on dose and duration of corticosteroid therapy, usage of immunosuppressive medication or immunomodulators and the patient’s underlying disease state [28] [24]. Most of the patients respond acutely to treatment with corticosteroids but the therapy becomes problematic in patients who fail to respond appropriately or become dependent on the usage of corticosteroids [13, 29]. In corticosteroid dependent patients, clinical relapses occur upon steroid withdrawal. These conditions are difficult to treat and may lead to a need of escalation of medical therapies from corticosteroids to biologic agents including anti-TNF or vedolizumab [22, 30].

Biological therapy has shown efficacy in IBD patients. Treatment with antibodies targeting tumor necrosis factor alpha (anti-TNFα agents), such as infliximab and adalimumab, have been established in treatment of more severe IBD [13]. Previous studies have reported these medications to be effective especially for patients who have not achieved a clinical remission with conventional therapies. Furthermore, these therapeutics have been demonstrated to induce mucosal healing and cure fistulizing disease in CD patients [31]. Negative effects of TNF-alpha have also been reported. They include formation of autoantibodies against the medication, especially when used as monotherapy, eczema and the ability to reactivate latent tuberculosis which further can cause a serious infection [13, 32].
There is no known cure for CD or CU but different medications can be used to relieve the symptoms and prevent complications [12]. Immunosuppressants and biologic agents are the cornerstones of Crohn’s disease treatment [12]. Certain antibiotics can be used for maintaining remission in CD or as a treatment for complications and post-operative wound infections [12]. A lifelong medication is needed in a majority of patients with CU. The medication is largely the same which are used in CD including immunosuppressants, biologic agents and 5-ASA. Steroids are commonly used as a treatment to induce clinical remission in the cases of acute exacerbation in both CD and CU. However, steroids are not recommended to use as a maintenance therapy probably due to the side effect and inefficiency in prolonged use [25]. Some patients, who have contraindications or who do not respond to medical therapy have to undergo surgery [33].
2.2 Clostridium difficile Infection

Clostridium difficile is an anaerobic, spore-forming gram-positive bacterium. It is the most common cause of antibiotic-associated diarrhea, especially among hospitalized patients. Healthy infants may be asymptomatic carriers of Clostridium difficile but usually the colonization of this bacterium decreases with age [34]. Germs can be transmitted through food, human and environmental sources. Clostridium difficile can spread from one person to another as a heat resistant spore through fecal-oral route and colonize the colon. Infection disease can be caused by production and further secretion of two pathogenic toxins (toxin A and B).

Rates of Clostridium difficile infection (CDI) have increased since 2000, especially among elderly hospitalized patients [35]. However, the increase in the prevalence of CDI is not as great in countries, which have paid much attention on prophylactic effects against hospital infections (Figure 2). CDI is classically considered a nosocomial concern but the prevalence of the infection in community has increased worldwide over the past two decades [36]. Many previous studies have identified risk factors for hospital-acquired CDI. These include advanced age, antineoplastic chemotherapy, co-morbidities and usage of multiple medications most importantly antibiotics and proton pump inhibitors (PPIs). Patients with community-acquired CDI seem to be not associated with these traditional risk factor [36]. As compared to nosocomial CDI, community-acquired infection appears to occur in younger patients who have not received antibiotics recently [36, 37].
Clostridium difficile infection (CDI) rarely arises spontaneously as antibiotic usage usually precedes it. The most important antibiotics associated with CDI are ampicillin, amoxicillin, cephalosporins, clindamycin and fluoroquinolones [37]. Antibiotics have negative impact on the gut flora. They affect the diversity and composition of the gut normal microbiota and disturb colonization resistance of the colon. Weakening of this resistance allow C. difficile to colonize the colon and cause infection. The spectrum of infection may range from asymptomatic carriage and mild diarrhea to life-threatening pseudomembranous colitis and even bowel perforation. Clinical symptoms include abdominal pain, vomiting, green diarrhea, fever, leukocytosis, hypoalbuminemia and raised C-reactive protein [11]. There have been identified a hypervirulent strain of Clostridium difficile (BI/NAP1/027). In addition to toxin A and B, this 027-ribotype is also able to produce binary toxin, which is associated with more severe disease.
2.2.1 Treatment for CDI

The first-line and conventional treatment of CDI consist of antibiotic therapy including metronidazole and vancomycin [37, 38]. These antibiotics have been used since 1970s and no resistance against these two medication has been reported [37]. The latest antibiotic against Clostridium difficile is fidaxomicin, which is recommended to use especially in recurrent infections [39]. However, great costs limit its usage. Despite the effective treatment with these drugs, relapses occur. The risk of recurrence for symptomatic CDI increases with each successive episode. It increases from 20% after the first episode up to 60% after multiple recurrences [37, 38]. It is still recommended to treat recurrences of Clostridium difficile infection with repeated course of antibiotics. Infections may be difficult to permanently cure probably because of re-exposure to or reactivation of spores in the intestine, diminished antibody response to infection or weakened colonization resistance in the colon [37]. One way to prevent the recurrence of CDI (rCDI), especially in patients with mild symptoms, is to avoid antibiotic intake that allowed the infection to develop [37].

There is strong evidence of efficacy of fecal microbiota transplantation (FMT) as a treatment for rCDI, however, little is known of the exact mechanisms of this treatment. Recent studies have reported effectiveness of FMT preventing relapses of CDI. It is thought that FMT reconstitute the normal gut flora and so a subsequent colonization resistance in the gut is created again [40, 41].

2.3 CDI in IBD patients

The incidence of CDI and its related complications in IBD-patients has increased rapidly over the past decades in North America and Europe [42]. These patients are at significantly higher risk of developing active infection than the general population [3]. Patients with UC have been reported to be even more susceptible to CDI than CD patients [6]. Previous studies have shown that IBD patients are more likely to have severe CDI and worse outcomes than the IBD patients without CDI. [3, 4]. These patients not only had a longer length of hospital stay but also higher rates of IBD flare,
colectomies and mortality [7, 8]. According to Nguyen et. al. the length of hospital stay was 65% longer in CD patients with CDI and 46% longer in UC patients with CDI [4]. Likewise IBD patients with CDI were found to have approximately 1.2 to 3 times higher risk of undergoing gastrointestinal surgery as compared to patients with IBD alone [43].

The incidence of CDI is higher in IBD patients and IBD has been shown to be an independent risk factor for CDI [6]. IBD patients are also likely to have additional risk factors that differ from conventional risk factors of non-IBD patients [6]. In fact, IBD-related CDI patients seem to be younger than non-IBD CDI patients. These IBD patients usually have a disease affecting the colon and a community acquired CDI [8, 44, 45].

There is some evidence about IBD-associated medical factors such as steroids and immunosuppressants which seem to be remarkable risk factors for CDI among these patients. Moreover, initiation of corticosteroids in IBD-patient increased the CDI rate threefold compared with other immunosuppressant agents [42]. Unlike the common risk factor for CDI in non-IBD patients, exposure to antibiotics does not seem to play a critical role in triggering CDI probably because of the gut dysbiosis in patients with IBD [7, 42].

In addition to disease susceptibility, IBD-patients are documented to have 33% higher risk to develop recurrence of CDI compared with non-IBD patients [5]. Factors that increase the risk for recurrence include 5-ASA use, steroid use, antibiotic and biologic therapy and non-ileal CD [5].
2.3.1 Treatment of CDI in IBD patients

Usually both infectious disease specialists and gastroenterologists participate in the treatment strategy for IBD patients with CDI. According to ECCO and ACG guidelines metronidazole and vancomycin should be used as a first-line treatment for patients with mild to moderate CDI in general. The CDI in patients suffering from IBD is considered as a serious condition which should be treated even more aggressively than generally [46]. Further, treatment strategy for CDI in patients with IBD should not only be based on the severity of the infection but also the risk factors for poor outcome. One interesting consideration is the usage of immunosuppressants in IBD-CDI patients. As previously mentioned, patients who have been using these medications have documented to be more susceptible to develop CDI. It can cause confusion whether to decrease or increase the dose of immunosuppressant in IBD patients during CDI. Further, Ben-Horin et. al. reported negative impacts of antibiotics and immunosuppressants on IBD-patients with CDI when using as a combination therapy [47]. They noticed that worse outcomes were achieved by patients who received both antibiotics and immunosuppressants compared to patients who were cured with antibiotics alone [47]. For now, ACG recommended continuation of immunosuppressants with same doses as already used during ongoing therapy.

The exact course in the pathogenesis of CDI in IBD remains unclear. It is not known whether the CDI triggers an IBD flare up or if the flare up occurs independently from CDI and further predisposes to C. difficile colonization. It may be difficult for the clinicians to differentiate CDI from IBD flare because they often co-exist, the symptoms resemble one another and the classic pseudomembranes are rarely found. It is recommended to screen for CDI in every flare up in IBD [48]. It is important to diagnose CDI because the negative impacts on IBD.
3 Methods

The study was approved by the institutional review board of Helsinki University Hospital. In this retrospective cohort study, 167 IBD patients with CDI were enrolled from medical records of HUS register. These patients were registered between years of 2008 and 2013 and data from records collected between June and July in 2016. The patient selection based on the clinician’s diagnosis of that time. Thus, following variant forms of IBD were also included in our study: Ulcerative colitis (n=105, 63% of all), Crohn’s disease (n=48, 29% of all) and unspecified IBD (IBD-U, n=14, 8% of all).

Different clinical parameters including age, gender and mortality were collected. Exposure to commonly used medications among these patients was also investigated. Usage of IBD-related drugs, antibiotics, NSAIDs and PPIs during the last 3 months before a toxin positive CDI test were recorded.

A control group of non-IBD related CDI patients was gathered from HUS register to compare the patient characteristics with the patients in IBD-CDI cohort. The cohort was age- and gender-matched with our study cohort. The number of CDI recurrences was matched to our study cohort, thus differences in recurrence rates between these patient groups are not compared.

A second control age- and gender-matched cohort of IBD-patients was gathered from the IBD cohort studied in the Doctoral thesis of Johanna Haapamäki [49].

3.1 Statistical methods

Patient characteristics between groups were analyzed using the chi-square test, the Fisher exact test and the Bonferroni multiple comparison test. One-way analysis of variance was used for continuous variables. A p value of <0.05 was considered statistically significant. All calculations were accomplished with NCSS-2000 software.
4 Results

4.1 Patient characteristics
A total of 167 IBD patients with CDI were included in our IBD related CDI (IBD-CDI) study cohort. All the patient suffered from IBD (Figure 3) and variable number of CDI episodes. Patient characteristics are represented in table one. In the study cohort, the mean age was 46.1 (range 6.4-91.9 years). Age and gender matched control cohorts of non-IBD related CDI (CDI cohort) and IBD (IBD cohort) were gathered also (Table 1).

Figure 3. Different types of IBD. Most of the patients in the IBD-CDI cohort suffered from CU.
Table 1. Characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>IBD* and CDI n=167</th>
<th>CDI** and no IBD n=166</th>
<th>IBD* n=157</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (Males n (% of total)</strong>)</td>
<td>85 (50,9)</td>
<td>78 (47,0)</td>
<td>77 (49,0)</td>
</tr>
<tr>
<td><strong>Age (average±SD yrs)</strong></td>
<td>46,1±21,0</td>
<td>47,4±21,5</td>
<td>45,9±19,8</td>
</tr>
</tbody>
</table>

*IBD group includes patients with Crohn’s disease, colitis ulcerosa and unspecified colitis. These groups include age and sex selected control patients for IBD and CDI patients. **CDI=Clostridium difficile infection.

Table 2. The overall count of CDI episodes in IBD patients with CDI and patients without IBD.

<table>
<thead>
<tr>
<th></th>
<th>One episode</th>
<th>Two episodes</th>
<th>Three episodes</th>
<th>Four episodes</th>
<th>Five episodes</th>
<th>Seven episodes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD+CDI (n)</td>
<td>116</td>
<td>26</td>
<td>15</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>167</td>
</tr>
<tr>
<td>CDI+no IBD (n)</td>
<td>115</td>
<td>24</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td>1</td>
<td>166</td>
</tr>
</tbody>
</table>

4.2 Recurrence of CDI (rCDI)

The overall count of CDI episodes are shown in Table 2. In both cohorts the range of rCDI was between two to seven episodes and no significant difference in recurrence rate was evident between two patient groups (IBD-CDI and CDI cohorts).

4.2.1 Genders

We compared the recurrence rate of CDI between genders (Figure 4). A total of 524 episodes in IBD-CDI and CDI cohorts were initially analyzed. Together these cohorts showed CDI recurrences to occur more often in females than in men (p=0.0367). A similar trend was seen within the IBD-CDI cohort alone although statistical significance was not reached.
4.2.2 IBD forms

In our study cohort, the most common form of IBD was CU (Figure 3). The recurrence of CDI was most rarely seen in patients with CD as compared to other forms of IBD (Figure 5).

Figure 4. Clostridium difficile episodes in males and females (IBD-CDI and CDI cohorts merged). *p= 0.0367 male vs female in three or more episodes.

Figure 5. Clostridium difficile episodes (%) in variant forms of IBD patients.
4.2.3 Medical therapy

Drug usage in the IBD-CDI cohort was recorded for three months preceding an infection episode for available cases (Table 3). Corticosteroids were the most commonly used medication in the IBD-CDI cohort. The proportion of 5-ASA and PPI users was also high. About half of the patients had been exposed to systemic corticosteroid and few to local corticosteroid before CDI. Proportionally the usage of systemic corticosteroid was higher in patients with two or more CDI episodes, although statistical significance was not reached. Patients with no corticosteroid intake were not as susceptible to have a recurrent infection. Despite the usage of 5-ASA and PPIs, other medications in our study did not appear to have a similar impact on the rate of recurrence of CDI within the IBD-CDI cohort.

Table 3. Clostridium difficile-infection episodes in IBD patients using different treatments.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Once</th>
<th>Twice</th>
<th>Three or more episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA users % (n/total)</td>
<td>65.8% (73/111)</td>
<td>73.1% (19/26)</td>
<td>75.0% (18/24)</td>
</tr>
<tr>
<td>Corticosteroid users</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systemic % (n/total)</td>
<td>52.3% (57/109)</td>
<td>56.0% (14/25)</td>
<td>58.3% (14/24)</td>
</tr>
<tr>
<td>local % (n/total)</td>
<td>5.5% (6/109)</td>
<td>8.0% (2/25)</td>
<td>8.3% (2/24)</td>
</tr>
<tr>
<td>both % (n/total)</td>
<td>5.5% (6/109)</td>
<td>20.0% (5/25)</td>
<td>4.2% (1/24)</td>
</tr>
<tr>
<td>Tiopurines users % (n/total)</td>
<td>36.4% (40/110)</td>
<td>38.5% (10/26)</td>
<td>29.2% (7/24)</td>
</tr>
<tr>
<td>Infliximab users % (n/total)</td>
<td>12.7% (14/110)</td>
<td>11.5% (3/26)</td>
<td>4.2% (1/24)</td>
</tr>
<tr>
<td>Adalimumab users % (n/total)</td>
<td>3.6% (4/110)</td>
<td>0/26</td>
<td>0/24</td>
</tr>
<tr>
<td>Vedolitsumab users (n/total)</td>
<td>0/110</td>
<td>0/26</td>
<td>0/24</td>
</tr>
<tr>
<td>NSAID users % (n/total)</td>
<td>28.2% (31/110)</td>
<td>15.4% (4/26)</td>
<td>25.0% (6/24)</td>
</tr>
<tr>
<td>PPI users % (n/total)</td>
<td>47.3% (52/110)</td>
<td>53.8% (14/26)</td>
<td>45.8% (11/24)</td>
</tr>
</tbody>
</table>
Examining the potential predisposing medical factors for CDI in IBD patients, we compared the usage of different IBD-related drugs between IBD-CDI and IBD cohorts. The systemic corticosteroid usage was twice as high in IBD-CDI as in IBD cohort alone (p<0.01). The usage of 5-ASA was lower in IBD-CDI cohort. Other medications presented in the table did not appear to affect in the same way (Table 4).

Table 4. Use of drugs in IBD-CDI and IBD patients.

<table>
<thead>
<tr>
<th></th>
<th>IBD and CDI</th>
<th>IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5-ASA users % (n/total)</strong></td>
<td>68.3% (110/161)</td>
<td>75.2% (118/157)</td>
</tr>
<tr>
<td><strong>Corticosteroids (systemic) users % (n/total)</strong></td>
<td>61.4% (97/158)***</td>
<td>28.0% (44/157)</td>
</tr>
<tr>
<td><strong>Tiopurines users % (n/total)</strong></td>
<td>35.6% (57/160)</td>
<td>30.6% (48/157)</td>
</tr>
<tr>
<td><strong>Infliximab users % (n/total)</strong></td>
<td>11.3% (18/160)</td>
<td>8.3% (13/157)</td>
</tr>
</tbody>
</table>

***p<0.01

IBD patients in IBD-CDI cohort had also frequently received antibiotic therapy during the previous three months before a CDI episode as shown in Table 5. The use of broad spectrum antibiotics seem to be common in IBD patients during the diagnosis of CDI, but CDI can appear without any predisposing antibiotics. No significant difference was found in different antibiotics and different types of IBD.
Table 5. Antibiotic use of IBD patients during three months before the diagnosis of CDI.

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease (n=6)</th>
<th>Colitis ulcerosa (n=8)</th>
<th>IBD unclassified (n=2)</th>
<th>Total % of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antibiotic</td>
<td>66.7%</td>
<td>0%</td>
<td>0%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>16.7%</td>
<td>37.5%</td>
<td>0%</td>
<td>25.0%</td>
</tr>
<tr>
<td>Ciprofloxacin and metronidazole</td>
<td>0%</td>
<td>12.5%</td>
<td>100.0%</td>
<td>18.8%</td>
</tr>
<tr>
<td>Cephalosporin, clindamycin or meropenem etc</td>
<td>33.3%</td>
<td>12.5%</td>
<td>0%</td>
<td>12.5,3%</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>3.3%</td>
<td>12.5%</td>
<td>0%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Metronidazole or vancomycin</td>
<td>3.3%</td>
<td>25.0%</td>
<td>0%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

4.3 Mortality

We identified no statistically significant difference in the rates of CDI-related mortality between IBD-CDI and non-IBD patients in our study. IBD patients had even less mortality compared to non-IBD patients with following rates: 1 of IBD-CDI patients (0.6%) died during the next 7 days and 3 (1.8%) during the next 30 days. The rates among non-IBD patients were slightly higher with 3 (1.9%) patients during the next 7 days and 9 (5.6%) during the next 30 days. Altogether, short-term survival (30 days post-infection) after CDI episode was 97.6% in IBD-related CDI and 91.9% in non-IBD related CDI.
5 Discussion

At present, IBD-related CDI is a poorly understood entity associated with dismal outcome. Previous studies have shown that the recurrence of CDI is more common in IBD patients and is related to poorer prognosis. Different risk factors of CDI have been investigated to enhance the prognosis of IBD patients. However, little is known about the risk factors for increased incidence of rCDI in IBD patients.

Razik et. al. demonstrated in their retrospective cohort study that recurrences are likely to occur 33% more frequently among IBD patients as compared to non-IBD CDI patients. However, conflicting data about the rCDI and its risk factors in IBD patients exists.

In our IBD-related CDI cohort the recurrence rate of CDI was lowest in patients with CD. Recurrences seemed to occur more often in other forms of IBD, such as in CU and IBD-U. The manifestation of the disease in these variant forms usually is limited to the colon where the Clostridium difficile bacterium colonizes in contrast to CD which can affect any parts of the dietary tract. Hypothetically, one would expect that a colon-manifesting process could set up the premises for CDI colonization, which could explain the greater prevalence of recurrent infections in other forms of IBD [5]. The greater prevalence of CDI episodes in the colon manifesting disease could also be derived from the antimicrobial effects of 5-ASA on the gut microflora. It has been hypothesized that 5-ASA seems to develop dysbiosis which together with the colon affecting disease could make the patients even more susceptible to recurrence of CDI [50].

Comparing genders in IBD-CDI and CDI cohorts together, our study revealed females to be more susceptible to recurrence of CDI than men. The reason for a greater susceptibility to CDI may lie on the female’s greater tendency to suffer urinary tract infections. The cure and prevention of urinary tract infection may lead to a greater consumption of antibiotics, which are potential predisposing factors for CDI in general.
Previous studies have reported antibiotics not to be a critical risk factor for CDI in IBD patients. These studies have found antibiotic exposure to occur only 40-60% of IBD patients with subsequent CDI [7]. In our study cohort, majority of the patients (75.0%) were exposed to antibiotics in the past three months before CDI diagnosis. Interestingly, some of the antibiotics were given to patients due to other reasons than underlying IBD while others due to a flare up of IBD. While almost all antibiotics have been associated to CDI-related diarrhea, the most common association have been noticed to be with only certain antibiotics including fluorokininolones, which are commonly used, as in our cohort, to relieve the symptoms in IBD [6]. So, some of the same antibiotics which most often cause CDI-related diarrhea are used as a treatment in IBD patients who already have increased risk to develop CDI. The indications for antibiotics usage should be investigated more specifically in the future in order to clarify the effects of IBD-related antibiotics on CDI.

In addition to antibiotics, other IBD-related medications have also been associated with recurrent episodes of CDI. IBD patients with rCDI have often received recent therapies with 5-ASA, corticosteroids, and biologic therapy more frequently than IBD patients without rCDI. However, these medications, especially corticosteroids are usually used by IBD-patients with active disease. Since both immunosuppressants and IBD itself have been reported to increase the risk for CDI more studies are needed to define the independence of these predisposing factors [5].

Corticosteroids have been used for a long time as a conventional treatment of IBD due to its effectiveness in a rapid resolution of IBD symptoms. However, previous studies have shown steroid usage to cause even three-fold increase in a risk to develop CDI and also worse clinical outcomes in patients with concomitant IBD and CDI [51] [7]. In our study, the most striking finding was the difference in the usage of corticosteroids in the IBD-CDI and IBD cohorts. In our IBD-CDI cohort as much as 61.4% of all patients had used systemic corticosteroids during the previous three months preceding a CDI. The proportion of systemic corticosteroid users in the IBD cohort was only 28.0%. In addition to greater consumption of systemic corticosteroids the usage was even
greater when examining the recurrence infections in the IBD-CDI cohort (Table 3). So, the use of corticosteroids seems not only to increase the risk for CDI but also for recurrence infections. However, predisposing characteristic could as well arise due to an inadequate host immune response, which already exists because of the underlying disease. Thus corticosteroids could as well make the IBD patients even more susceptibility to CDI. So, our results about the corticosteroid’s predisposing effects to infections could support previous studies well.

To avoid complications of steroid use and optimize the therapy in IBD patients, other medications have been gaining popularity as a second-line therapy among clinicians. These therapeutic opportunities include immunosuppressants and biologics. Zhang et. al. suggest that causes for the increased incidence of CDI in IBD patients may lie on the therapies of these drugs. Some findings show that immunosuppressants may have a mild predisposing effect on CDI but conflicting data also exist [42]. Moreover, Infliximab but not adalimumab have been noticed to elevate the risk for CDI among IBD paient. The usage of immunosuppressants and biologics, such as vedolizumab or anti-TNF-α antibodies, is not related to increased risk for CDI in patients in accordance to our study. However, these therapies were not used by many patients in our cohort.

In our IBD-CDI cohort the consumption of 5-ASA and PPIs was quite high. The proportion of PPI and 5-ASA users in the IBD-CDI cohort was 48.1% and 68.3%, respectively. The usage of PPIs has long been known to increase the risk for CDI in general. Thus, a great consumption of PPIs detected in our data could further support its predisposing effect to CDI shown in previous studies. Previous studies have recorded 5-ASA to be associated with rCDI [5]. However, correlation between 5-ASA and recurrence infections cannot be directly detected. The consumption of NSAIDs was not common in our study and it seemed not to directly influence to development of CDI (Table 3).

Many previous studies have been considering the effects of CDI in IBD patient outcomes, such as in mortality. They have shown mortality rates to be twice higher in IBD patients with CDI as compared to non-IBD patients with CDI, and even four-fold
higher than in an inpatient with IBD alone [52]. However, there are also other studies which have found mortality rates to be equal or non-significantly difference between these patients [8]. In our study, significant differences between these two groups were not noticed. Moreover, IBD patients with CDI seem to have even less mortality compared to non-IBD CDI patients. This favorable mortality rate among IBD-related cases may arise due to traditional risk factors, including other co-morbidities, for non-IBD related CDI. IBD may often be the only underlying disease among patients with IBD alone, while non-IBD CDI patients are having more frequently co-morbidities.

One of the most important advices for all clinicians is to avoid using unnecessary antibiotics. It is also important for the clinicians to be able to differentiate CDI from IBD flare. Sometimes it may remain unclear whether the IBD flare occurs independently from CDI or has CDI triggered the flare up. Clinicians should accurately document each case with rapid diagnosis and subsequent adequate therapy. Routine stool sample screening for CDI in each case with characteristics of IBD exacerbation or infectious colitis is recommended before giving any antibiotics.

Since evidence based studies are disputable, there are no clear guidelines for the treatment of rCDI in IBD patients. So far, it is recommended to treat IBD patients with CDI in a similar way than the non-IBD patients with CDI alone. Here we have gathered and analyzed a retrospective cohort of Finnish IBD patients with CDI and compared patient characteristics, risk factors and CDI recurrence with IBD patients and non-IBD related CDI patients derived from medical records. Our study provides more insight into the poorly characterized CDI recurrence nature, rate and prognosis among IBD patients. The strengths of our study were a large IBD-CDI cohort (167 patients) with two different control cohorts (CDI and IBD cohorts). The weakness of our study was ignorance of IBD cohort’s history of CDI infections and our inability to compare disease activity between the IBD-CDI and IBD cohort.
6 Conclusions

According to our study, the recurrence of CDI is more common among female patients with or without underlying IBD. We highlight systemic corticosteroid-intake as a major risk factor for CDI between IBD patients. Moreover, higher corticosteroid-intake was associated with higher risk of recurrence. However, we identified no significant difference in the mortality rate between these groups. More prospective studies are required to evaluate different risk factors for CDI in IBD patients.
7 References


