

## ORIGINAL PAPERS

# Burden of *Clostridium Difficile* Infection in Inflammatory Bowel Disease

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## Abstract

**Objectives:** Over the past two decades has been a dramatic worldwide increase in both incidence and severity of *Clostridium Difficile* infection (CDI). Several studies showed worse clinical outcomes in Inflammatory Bowel Disease (IBD) patients with CDI, including longer hospital stay, higher colectomy and mortality rates than in those without CDI. The aim of our study was to evaluate the prevalence of *Clostridium difficile* infection in IBD patients and to evaluate the particularities of diagnosis and treatment. **Methodology:** We performed a retrospective study that included 15 patients from a group of 220 IBD patients admitted in the Gastroenterology Department of the Clinical Emergency Hospital Bucharest between 2013- 2016 having also *Clostridium Difficile* infection. **Results:** The patients mean age was 44.1 years. The prevalence of CDI in patients with inflammatory bowel disease was 6.81%. Patients with ulcerative colitis were more susceptible to CDI (86.6%), than those with Crohn's disease (13.3%). We studied also the response to treatment. Metronidazole alone was effective in 33.3% of cases. Vancomycin combined with Metronidazole was effective in 60% of cases. Refractory CDI unresponsive to 48 hours of conventional therapy appeared in 6.6% of cases. The eradication was achieved only with Tigecycline and fecal microbiota transplant. Immunosuppressive therapy was continued in all cases, concomitant with Metronidazole/Vancomycin. **Conclusions:** Patients with ulcerative colitis are at higher risk for CDI and have a poor prognosis than those with Crohn's disease. Average age of CDI in IBD patients significantly is lower than in general population. In IBD patients, presenting with diarrhea or a change in bowel habits, practitioners need to test for *C. difficile* and differentiate CDI symptoms from a disease flare. Special care to rule out *C. difficile* should be pursued prior to escalating or starting new immunosuppressive agents. Fecal microbiota transplant, probiotics, and newer antibiotics are good alternatives for refractory disease.

**Keywords:** *Clostridium difficile*, Inflammatory bowel disease, Ulcerative colitis, Crohn's disease, antibiotic associated diarrhea, Vancomycin, Metronidazole, Tigecycline, fecal transplantation.

## Rezumat

**Obiective:** În ultimele 2 decenii s-a observat o creștere dramatică a incidenței și severității infecției cu *Clostridium Difficile*. Câteva studii au arătat un prognostic clinic nefavorabil la pacienții cu boli inflamatorii intestinale incluzând spitalizare prelungită, lipsa răspunsului la tratament, rate de de colectomie și mortalitate mai crescute decât la cei fără infecție cu *Clostridium difficile*. Obiectivul studiului a fost de a evalua frecvența infecției cu *Clostridium Difficile* în rândul pacienților cu boala Crohn și Rectocolită ulcero-hemoragică și de asemenea de a evalua particularitățile de diagnostic și tratament. **Material și metodă:** Am efectuat un studiu retrospectiv ce a inclus 15 pacienți dintr-un total de 220 pacienți cunoscuți clinicii de Gastroenterologie a Spitalului Clinic de Urgență București cu Boală Inflamatorie Intestinală, internați în perioada 2013-2016, pentru suprainfecție cu *Clostridium Difficile*. **Rezultate:** Vârsta medie a fost 44,1 ani. Prevalența infecției cu *Clostridium Difficile* (ICD) în rândul pacienților cu boală inflamatorie intestinală a fost de 6,81%. Suprainfecția cu *Clostridium Difficile* a fost mult mai frecventă la pacienții cu Rectoco-

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lită ulcero-hemoragică (86,6%), comparativ cu pacienții cu boala Crohn (13,4%). Terapia cu Metronidazol 1,5 g /zi per os a fost eficace în 33,3 % din cazuri. La 60% din cazuri a fost necesară adăugarea vancomicinei 1 g /zi per os. La 6,7% din cazuri am avut formă refractară neresponsivă după 48h de terapie convențională. Eradicarea infecției a fost obținută numai după asocierea la terapia standard a Tigeciclinei 100 mg/zi iv și a transplantului de materii fecale. Terapia imunosupresivă a fost continuată în toate cazurile, concomitent cu Metronidazol/Vancomicina.

**Concluzii:** Pacienții cu rectocolită ulcero-hemoragică prezintă un risc mai mare de infecție cu *Clostridium difficile* și au un prognostic mai prost decât cei cu boală Crohn. Vârsta medie a pacienților cu infecție *Clostridium difficile* la pacienții cu boli inflamatorii intestinale este semnificativ mai scăzută decât în populația generală. Excluderea infecției cu *Clostridium Difficile* este obligatorie la pacienții cu boli inflamatorii intestinale veniți pentru o nouă exacerbare, având în vedere severitatea și managementul terapeutic dificil. Transplantul de materii fecale, probioticele și noile antibiotice reprezintă alternative favorabile la forma refractară.

**Cuvinte cheie:** *Clostridium difficile*, Boală inflamatorie intestinală, Colită ulcerativă, Boală Crohn, Diaree asociată consumului de antibiotic, Vancomicină, Metronidazol, Tigecilină, Transplant de materii fecale

## INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and Ulcerative Colitis (UC), is characterized by chronic inflammation of the gastrointestinal tract. There is epidemiologic evidence that in patients with IBD, *Clostridium difficile* infection (CDI) occurs more frequently than in the general population and that these rates have been increasing over the past several decades<sup>1,2</sup>.

*Clostridium difficile* is a Gram-positive anaerobic spore-forming bacterium that produces toxins and can lead to a clinically significant diarrhea. This can be difficult to treat and is associated with significant morbidity and mortality. The traditional risk factors for CDI have included hospitalization, antibiotic and proton pump inhibitors use, advanced age, chemotherapy, immunosuppression, multiple co-morbidities, hypoalbuminemia, renal insufficiency and the emergence of hypervirulent strain of the bacterium known as NAP1 (North American pulsed field type 1)<sup>2-4</sup>.

Several studies showed worse clinical outcomes in IBD patients with CDI, including longer hospital stay, higher colectomy and mortality rates than in those without CDI<sup>5</sup>.

Vancomycin and Metronidazole appear to have similar efficacy in patients with moderate disease, but Vancomycin is preferred in severe disease. For the disease recurrence or unresponsiveness to conventional treatment several alternative therapeutic approaches have been tried: fecal microbiota transplant, probiotics and newer antibiotics<sup>6</sup>.

The aim of our study was to evaluate the frequency of *Clostridium difficile* infection in patients with inflammatory bowel disease and to evaluate the response to treatment.

## METHODOLOGY

We performed a retrospective study that included 15 patients from a group of 220 IBD patients, hospitalized in the Gastroenterology Department of the Clinical Emergency Hospital of Bucharest, between September 2013–September 2015, for infection with *Clostridium Difficile*. All patients with IBD flare were tested for *C. difficile* infection. The laboratory diagnosis was established by a positive stool test for *C. difficile* (enzyme immunoassay (EIA) for *C. difficile* toxins A and B or Polymerase chain reaction for toxin gene detection).

Only one patient took antibiotics in the recent past and all of them were on maintenance therapy with 5-ASA drugs or immunosuppressants.

There are several diagnostic stool tests available for *C. difficile* including enzyme immunoassay (EIA) for *C. difficile* toxins A and B, EIA for *C. difficile* glutamate dehydrogenase (GDH), polymerase chain reaction (PCR) for the chromosomal genes encoding *C. difficile* toxin B (tcdB) or the toxin regulatory gene (tcdC), cell culture cytotoxicity assay (CTA), and selective anaerobic culture. For our study we used 2 laboratory stool tests for *C. difficile* detection: enzyme immunoassay (EIA) for *C. difficile* toxins A and B and Polymerase chain reaction for toxin gene detection.

EIA for *C. difficile* toxins A and B is rapid (results are available within a few hours), inexpensive, and widely available, being used as routine test in most countries (7). Testing should include both toxin A and B because some *C. difficile* strains produce only toxin A or B. EIA sensitivity for toxins A and B is 60-94%, with 75%-100% specificity. The false-negative rate may be high as a positive test requires 100-1000 pg of either toxin to be present. If the initial test is negative, the value of repeated stool testing in IBD patients is limited. Therefore, repeated EIA testing during one episode is not

recommended, but if clinical suspicion of CDI remains high a more sensitive assay is recommended.

PCR-based assays are highly sensitive and specific (8), commercially available, with results available within one hour, lately becoming in many laboratories the preferred test for CDI diagnosis. Nevertheless, real-time PCR is expensive and leads to false-positive results. In addition, it has poor accuracy in differentiating CDI from asymptomatic carriage of *C. difficile*, that should not be treated, and results in overtreatment in some patients.

## RESULTS

The patients mean age was 44.1 years.

We have also studied the response to treatment.

Metronidazole (500 mg orally 3 times a day for 10-14 days), the drug of choice for an initial episode of mild to moderate CDI, was effective in 33.3% of cases.

Vancomycin (500 mg orally 4 times a day) combined with Metronidazole was effective in 60% of cases.

Refractory CDI unresponsive to 48 hours of conventional therapy (Vancomycin + Metronidazole) ap-

peared in 6.6% of cases. The eradication was achieved only with Tigecycline and fecal microbiota transplant (FMT) (Figure 4).

## DISCUSSION

Although the proportion of elder IBD patients has increased in recent years, the average age of CDI in IBD patients is significantly lower than in general population.

IBD patients with CDI have several distinct characteristics including community acquisition, lack of antibiotic exposure and steroid use.

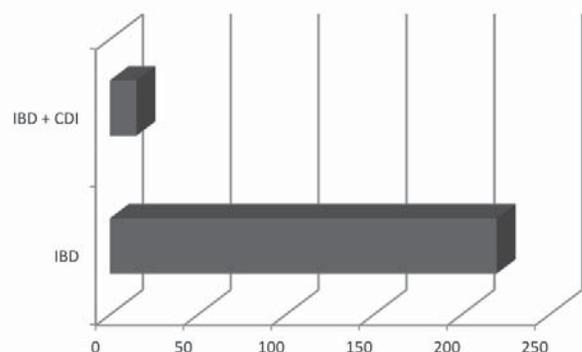
Patients with Ulcerative Colitis are at higher risk for CDI and have a poor prognosis than those with Crohn's disease.

In patients with IBD who present with worsening symptoms, CDI needs to be thought off and ruled out. Important treatment decisions regarding CDI in IBD patients include how to manage concomitant immunosuppression, initial choice of antibiotic for primary infection, and treatment of recurrent or refractory infections.

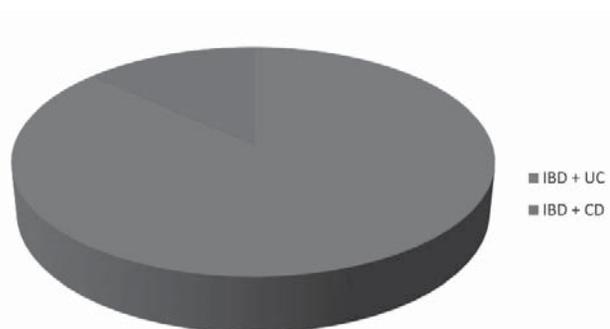
In most patients from our study, EIA for *C. difficile* toxins A and B was positive. In one patient with EIA negative and typical pseudomembrane on lower



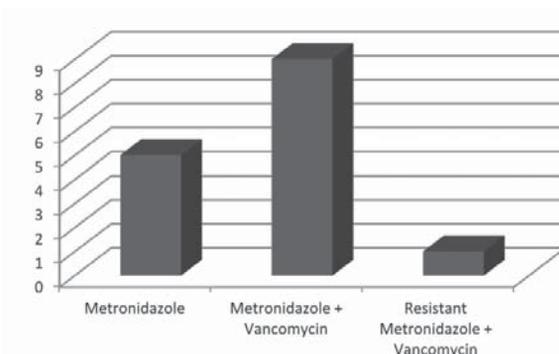
**Figure 1.** The distribution by gender: 9 (60%) men and 6 (40%) women.



**Figure 2.** The frequency of CDI in patients with inflammatory bowel disease was 6.81%. (Our IBD database includes 220 patients)



**Figure 3.** Patients with Ulcerative Colitis (UC) were more susceptible to CDI (86.6%), than those with Crohn's disease (13.3%).



**Figure 4.**

endoscopy we used PCR-based assays to confirm the infection.

Lower endoscopic visualization forms an important part in the evaluation of patients with CDI in IBD. Isolated CDI produces the classic endoscopic appearance of pseudomembrane formation which is described in 50% of patients<sup>9</sup>. However in patients with underlying IBD, classic endoscopic or histologic features of pseudomembranes may be absent, making it difficult to diagnose CDI in patients with worsening diarrhea.

Most patients respond to standard therapy. Mild/moderate disease is treated with Metronidazole 500 mg orally three times daily and severe disease with Vancomycin 125 mg PO four times daily for 10–14 days<sup>10,11</sup>. For complicated disease the recommended treatment is Vancomycin 500 mg four times daily<sup>12,13</sup> with or without Metronidazole 500 mg IV.

For recurrent disease, a repeat course of Metronidazole or Vancomycin is the recommended choice depending on disease severity. Metronidazole is not recommended beyond the first recurrence due to concerns for peripheral neuropathy following extended use, especially in the elderly. Prolonged, tapered, and pulsed-dose Vancomycin is the preferred approach for multiple recurrences of CDI<sup>14,15</sup>. Although there are several different protocols, one regimen is Vancomycin 125 mg four times daily for an initial 10–14 day course followed by 125 mg twice daily for 1 week, followed by 125 mg daily for 1 week and then 125 mg on alternate days for 2–8 weeks<sup>16</sup>.

For recurrent or refractory CDI several new antibiotics have been studied including Fusidic acid, Nitazoxanide, Teicoplanin, Rifampin, Rifaximin, Bacitracin, Fidaxomicin, and Tigecycline<sup>17–22</sup>.

Tigecycline, a broad-spectrum intravenous antibiotic with good fecal penetration, prevents protein synthesis and has been studied for refractory CDI. Case reports have suggested that Tigecycline may be successful for treatment of severe or complicated CDI when prior therapy has failed<sup>23</sup>.

Stool transplantation, also known as fecal microbiota transplantation (FMT), intestinal microbiota transplantation (IMT), or fecal bacteriotherapy has shown promise in numerous small reports as an effective treatment of recurrent or refractory CDI<sup>24–27</sup>.

Intestinal microbiota transplantation involves the transfer of stool from a healthy donor to the colon of

a sick recipient in an effort to reverse the recipient's colonic pathology.

The majority of our patients (89%) responded to conventional therapy (metronidazole +/- vancomycin). The fecal microbiota transplantation (FT) was necessary in one case of refractory CDI. In this case the antibiotic therapy (Metronidazole + Vancomycin+Tigecycline) was stopped two days before the procedure.

The donor (preferably a family member, in our case his brother) had been previously fully immunized against Hepatitis B and was HIV negative. Urgent investigations of his stools for toxin A/B, for pathogens on culture, and for ova and parasites on microscopy were all reportedly negative. The donor supplied a healthy stool specimen - the product of a full bowel evacuation produced less than three hours previously. The specimen was prepared and delivered into the recipient colon via the colonoscope in accordance with accepted practice. By the following day, the patient condition had improved. The diarrhea diminished to just about two stools per day with no blood and with no abdominal pain. After 3 days the antibiotics were reintroduced. The patient was discharged one week after FMT with normal stool and good appetite.

## CONCLUSIONS

*Clostridium difficile* infection when associated with inflammatory bowel disease (IBD) carries a higher mortality than in the absence of underlying IBD.

In IBD patients, especially those with colonic disease, presenting with diarrhea or a change in bowel habits, practitioners need to test for *C. difficile* and consider CDI with symptoms of a disease flare. Special care to rule out *C. difficile* should be pursued prior to escalating or starting new immunosuppressive agents.

Vancomycin and metronidazole are currently the two main antibiotic treatments.

For refractory disease or multiple recurrences, several alternative therapeutic approaches are available: fecal microbiota transplant, probiotics, and newer antibiotics.

Fecal microbiota transplantation is becoming increasingly accepted as an effective and safe intervention in patients with recurrent disease, likely due to the restoration of a disrupted microbiome. Cure rates of >90% are being consistently reported from multiple centers.

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