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TOPIC HIGHLIGHT

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Clostridium difficile and inflammatory bowel disease: Role in pathogenesis and implications in treatment

Orna Nitzan, Mazen Elias, Bibiana Chazan, Raul Raz, Walid Saliba

Orna Nitzan, Bibiana Chazan, Raul Raz, Infectious Disease Unit, Ha'emek Medical Center, Afula 18101, Israel
Orna Nitzan, Mazen Elias, Bibiana Chazan, Raul Raz, Walid Saliba, Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa 31096, Israel
Mazen Elias, Walid Saliba, Department of Internal Medicine C, Ha'emek Medical Center, Afula 18101, Israel
Author contributions: Nitzan O, Elias M, Chazan B, Raz R and Saliba W equally contributed to this paper.
Correspondence to: Walid Saliba, MD, MPH, Department of Internal Medicine C, Ha'emek Medical Center, 21 Rabin street, Afula 18101, Israel. saliba_wa@clalit.org.il
Telephone: +972-4-6495132 Fax: +972-4-6495134
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Abstract

Clostridium difficile (*C. difficile*) is the leading cause of antibiotic associated colitis and nosocomial diarrhea. Patients with inflammatory bowel disease (IBD) are at increased risk of developing *C. difficile* infection (CDI), have worse outcomes of CDI-including higher rates of colectomy and death, and experience higher rates of recurrence. However, it is still not clear whether *C. difficile* is a cause of IBD or a consequence of the inflammatory state in the intestinal environment. The burden of CDI has increased dramatically over the past decade, with severe outbreaks described in many countries, which have been attributed to a new and more virulent strain. A parallel rise in the incidence of CDI has been noted in patients with IBD. IBD patients with CDI tend be younger, have less prior antibiotic exposure, and most cases of CDI in these patients represent outpatient acquired infections. The clinical presentation of CDI in these patients can be unique-including diversion colitis, enteritis and pouchitis, and typical findings on colonoscopy are often absent. Due to the high prevalence of CDI in patients hospitalized with an IBD exacerbation, and the prognostic implications of CDI in these patients, it is recommended to test all IBD patients hospitalized with a disease flare for *C. difficile.* Treatment includes general measures such as supportive care and infection control measures. Antibiotic therapy with either oral metronidazole, vancomycin, or the novel antibiotic-fidaxomicin, should be initiated as soon as possible. Fecal macrobiota transplantation constitutes another optional treatment for severe/recurrent CDI. The aim of this paper is to review recent data on CDI in IBD: role in pathogenesis, diagnostic methods, optional treatments, and outcomes of these patients.

Key words: *Clostridium difficile*; Diarrhea; Inflammatory bowel disease; Pathogenesis; Treatment

Core tip: In this review we focus on the role of *Clostridium difficile* (*C. difficile*) in inflammatory bowel disease pathogenesis, the unique clinical aspects of *C. difficile* infections and prognosis in patients with inflammatory bowel disease. We also present the implications of *C. difficile* infections in these patients and review the most recent literature concerning diagnostic methods and treatment.

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INTRODUCTION

The human gut microbiota contains about 10^{14} bacterial

cells from more than 1000 different bacterial species[1,2] that play an important role in conservation of mucosal innate and adaptive immune function, integrity of the epithelial barrier and nutrient absorption[3-6]. Disruption of the gut microbiota (dysbiosis) has been linked with many gastrointestinal conditions[7,8]. Accumulating evidence suggests that inflammatory bowel disease (IBD) results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host[9-11]. Dysbiosis in IBD may also contribute to disease severity, and is correlated with the occurrence of abscesses in patients with Crohn's disease (CD) and need for surgery at a younger age[12,13].

Clostridium difficile (*C. difficile*) is an anaerobic gram-positive, spore-forming, toxin-producing bacillus that causes intestinal disease varying from a mild diarrheal illness to severe colitis[14-16]. The burden of *C. difficile* infection (CDI) has increased dramatically over the past decade and it is now recognized that *C. difficile* is responsible for 20%-30% of cases of antibiotic associated diarrhea and 50%-75% of cases of antibiotic associated colitis[17,18]. *C. difficile* is also the leading cause of nosocomial diarrhea, with incidence ranging from 1:100-1:1000 hospitalized patients[19,20]. Loss of intestinal microbial equilibrium, most commonly following antibiotic use, creates an environment susceptible to colonization of *C. difficile* and subsequent CDI[21,22].

IBD has been found to be associated with *C. difficile*[23-26]. Patients with IBD are at increased risk of developing CDI, have worse outcomes of CDI-including higher rates of colectomy and death, and experience higher rates of recurrence[27-30]. However, it is still not clear whether *C. difficile* is a cause of IBD or a consequence of the inflammatory state in the intestinal environment. The association between IBD and *C. difficile* may be due to different factors, such as drugs that are used for the treatment of IBD that might alter the intestinal flora and promote colonization (including repeat courses of antibiotics), altered immune and nutritional status, frequent hospitalizations, and even genetic predisposition[31,32].

In this review we will try to focus on the role of *C. difficile* in IBD pathogenesis, the unique aspects of *C. difficile* infections in patients with IBD, and the implications for testing and treatment.

The role of C. difficile in IBD

The initial trigger responsible for the onset of IBD is not yet known. A complex interplay between the immune system, environmental factors, such as stress and diet, enteric infections, and genetic factors play a role in the pathogenesis of IBD[33-35]. Gut microbiota interacts with both the innate and adaptive immune systems, playing a pivotal role in maintenance and disruption of gut immune quiescence[36]. Different bacteria have been implicated in the pathogenesis of IBD, including *Mycobacterium avium paratuberculosis,* enterotoxigenic *Bacteroides fragilis,* adherent/invasive *Escherichia coli*, *Campylobacter jejuni*, *Listeria monocytogenes*, *Chlamydia sp.*, *Aeromonas hydrophila*, *Salmonella typhi*, and *C. difficile*[37-39]. However, to date there is no conclusive evidence that a specific pathogen is responsible for IBD onset or relapse.

C. difficile has been found to be associated with IBD. Different studies found that patients with IBD, including ulcerative colitis (UC) and CD, are at increased risk of developing CDI. A study based on a large cohort of IBD patients in the United States found that CDI was more common in UC patients (2.8%) as compared to the general inpatient population (0.4%), and another study reported an adjusted odds ratios for CDI in all IBD, CD, and UC admissions from 1998-2004 to be 2.9, 4.0, and 2.1 respectively[40,41]. Since 2003 there has been a dramatic rise in the incidence of CDI with severe outbreaks described in Canada, United States and England, which have been attributed to a new and more virulent strain designated BI/NAP1/027, that has also been found in patients with IBD[18,42,43]. A parallel rise in the incidence of CDI in patients with IBD has also been noted. During 1998-2004 CDI rates approximately doubled in CD (9.5 to 22.3/1000 admissions) and tripled in UC (18.4 to 57.6/1000)[41]. A retrospective observational study found that the rate of CDI in IBD patients increased from 1.8% in 2004 to 4.6% in 2005, with the majority of patients having colonic IBD[29]. More recent studies, found that 5.5%-19% of patients with an IBD exacerbation, tested positive for *C. difficile* infection, and as many as 3.5% of children hospitalized due to IBD, were diagnosed with CDI[44,45]. Furthermore, analysis of a registry database suggests that 10% of IBD patients will develop a *C. difficile* infection at some point, and approximately 10% of CDI occur at the time of IBD diagnosis[46]. Patients with IBD also have higher rates of asymptomatic carriage of *C. difficile* 8.2% (9.4% in patients with UC and 6.9% in patients with CD), versus 1% in healthy volunteers[47]. It is possible, though, that the seemingly increased risk of CDI in patients with IBD is due to increased surveillance of this population for CDI. There are studies that question the role of CDI in IBD. A recent prospective Dutch study found a low prevalence of *C. difficile* in IBD patients and did not find any association of *C. difficile* with disease activity, disease subtype (CD or UC), gender, antibiotic, and immunosuppressive therapy[48].

Though it is still not clear if *C. difficile* causes IBD, it is understood that *C. difficile* can cause an infectious colitis superimposed on IBD, or may precipitate an IBD flare leading to simultaneous inflammatory processes, and it is nowadays considered a risk factor for IBD exacerbation. The association between *C. difficile* and IBD is mediated by a chain of events, including- recurrent hospitalizations, that are a known risk factor for acquisition of *C. difficile* and CDI, medications administered to patients with IBD (including immunomodulatory and antimicrobial agents) that disturb the intestinal flora, thus allowing for *C. difficile* colonization and adherence, and a decreased nutritional status that promotes *C. difficile* infection[31,32]. Thus, *C. difficile* can colonize the intestines of these patients and produce its two potent exotoxins: toxin A ("enterotoxin") and toxin B ("cytotoxin") that bind to receptors on intestinal epithelial cells. This activates a cascade of proinflam-

Table 1 Unique features and clinical implications of Clostridium difficile infection in patients with inflammatory bowel disease

Risk factors
Colonic IBD
Immunomodulatory drugs
In comparison to patients with no IBD: younger age, more community acquired cases, less prior antibiotic exposure
Clinical characteristics
Diarrhea (can be bloody), often mimics a flare of IBD
In patients with ileostomies: acute enteritis(an increase in ileostomy output, nausea, fever and leukocytosis)
In patients with ileal pouch anal anastomosis: pouchitis
Often no pseudomembranes on colonoscopy
Outcomes and complications
Higher rates of toxic megacolon and colonic perforation
Higher rates of colectomies
Longer length of hospital stay
Increased mortality
Diagnosis:
Test for CDI in all IBD patients hospitalized with a disease flare
As in patients with no IBD-one step molecular assays or two step algorithms: screening with EIA for GDH, followed by EIA for toxins and/or a molecular assay
Treatment:
1 Escalation of immunosuppression should be avoided during CDI
2 Antibiotics treatment as in non IBD patients
Mild to moderate disease: oral metronidazole
Severe disease: oral vancomycin + intravenous metronidazole
Fidaxomicin-less recurrences (no data in IBD patients)
3 Fecal macrobiota transplantation
Limited data in IBD patients though seems to be effective

IBD: Inflammatory bowel disease; CDI: *Clostridium difficile* infection.

matory cytokines and leukotrienes such as tumor necrosis factor (TNF), interleukin (IL)-6, IL-8, IL-1β, leukotrienes B4, and interferon-γ leading to apoptosis of gut epithelial cells and increased permeability of the intestinal mucosa, which in turn can play a role in the pathogenesis of IBD[49,50].

So, as elaborated above, there is a possible association between IBD and *C. difficile*, though there are many issues to be resolved, such as: whether CDI is a risk factor for the development of IBD, or the active inflammatory process in patients with IBD predisposes them to CDI, and what are the exact mechanisms that are responsible for this association.

CDI IN PATIENTS WITH IBD

The unique features and clinical implications of CDI in patients with IBD are summarized in table 1.

Risk factors

As noted above, patients with IBD are at increased risk for CDI, but this risk varies among different subsets of these patients. One of the major risk factors for CDI in patients with IBD is colonic IBD, either UC or CD with colitis-with 91% of patients with IBD suffering from CDI, reported to have colonic IBD, and a higher incidence of CDI was found in patients with left sided and extensive disease as compared to distal disease[29]. Other risk factors for CDI in patients with IBD are similar to those in the general population, such as- older age, medications (antibiotic/immunosuppressive agents), hospitalization, residence at a long term facility and comorbidities[21,51,52]. However, there are a few differences in risk factors for CDI in patients with IBD. IBD patients with CDI tend be younger, and 76% of *C. difficile* infections in these patients represent outpatient acquired infections, as opposed to patients without IBD were the most part of *C. difficile* infections are hospital acquired[29,53]. IBD has been found to be a risk factor for outpatient acquired CDI. In a study done in our medical center, on 115 patients with CDI, we found a trend towards a higher rate of IBD in community acquired CDI versus hospital acquired CDI (20.2% *vs* 9.7% , unpublished data).

Also, up to 40% of IBD patients do not have documented antibiotic exposure prior to presentation with CDI[54]. Patients with IBD receive various types of immunosuppressive drugs that might predispose to CDI, and steroid treatment has been found to increase the risk of CDI 3 fold in these patients, though other immunomodulatory drugs such as purine analogs, methotrexate and biological agents, have not been consistently found to increase the risk of CDI[29,41,55,56]. Combination treatment with different immunomodulatory agents can increase the risk of CDI as was found in pediatric patients receiving concomitant therapy of methotrexate and anti-TNF-α, where 28% of patients developed CDI[57].

Clinical characteristics

Patients with IBD can have different and unique clinical presentations of CDI. To begin with, the similarity in symptoms between CDI and a flare of IBD (diarrhea, abdominal pain, fever and leukocytosis) make it extremely difficult to distinguish between the two[29,41]. *C. difficile* in IBD may also show atypical features such as frequent bloody stools, as opposed to watery stools in patients without IBD. Diarrhea may even be absent in postoperative patients who receive narcotics for pain control and develop paralytic ileus. In IBD patients with ileostomies, *C. difficile* can cause acute enteritis, which can manifest as an increase in ileostomy output, nausea, fever and leukocytosis[53]. In patients who have undergone ileal pouch anal anastomosis as treatment for IBD, *C. difficile* infection might be a triggering factor for pouchitis, which presents as an increase of the number of stools per day, with or without constitutional symptoms such as weight loss[58,59]. In one study 10.7% of patients with ileal pouch anal anastomosis, presenting with pouchitis, were found to have CDI[60]. Another study demonstrated that 18.3% of cases of pouchitis were positive for *C. difficile* toxin, with men 3.5 times more likely than women to develop *C. difficile* pouchitis[61].

Typical findings of CDI on colonoscopy (such as pseudomembranous exudates, which are found in up to 60% of patients with CDI) are often absent in patients with IBD (0%-13% of cases)[62]. This might be due to a weakened inflammatory response in the colonic epithelial

environment in patients with chronic active IBD or due to immunosuppressive drugs that hamper the development of pseudomembranes, which are caused by disruption of cellular cytoskeleton by toxins, ulcer formation and leakage of serum proteins, inflammatory cells and mucus.

Outcomes

C. difficile infections have a different and often more severe clinical course in patients with IBD. These patients have higher rates of endoscopies, higher rates of complications such as toxic megacolon and colonic perforation, higher rates of colectomies, longer length of hospital stay, and increased mortality[29,30]. Different studies found high rates of colectomies in these patients, ranging from 20% to 45%[28,29], with one study finding a 6 fold increase in bowel surgery in patients with CDI with and without IBD[30]. Patients with IBD also experience more recurrences of CDI, than patients without IBD[29]. Mortality is also increased in these patients with one study demonstrating a 6%-18% case fatality rate in patients with IBD and CDI *vs* 1.4%-2.1% fatality rate in patients with CDI alone[40]. A large study of the inpatient care database in the United States found that hospitalized patients with concurrent CDI and IBD had a 4 times higher mortality rate than those admitted for IBD or CDI alone[63].

All of these special aspects of CDI in patients with IBD should cause physicians to be alert to the possibility of CDI in a patient with an IBD exacerbation and prompt rapid diagnosis and treatment.

Diagnosis

CDI is a clinical diagnosis supported by laboratory findings. As mentioned before, it is often difficult to distinguish between CDI and an exacerbation of IBD, because of the similarity in symptoms, and moreover, IBD patients may have a different clinical presentation of CDI. Laboratory findings in both CDI and IBD are also similar, including: leukocytosis, hypoalbuminemia, and fecal leukocytosis[53]. Endoscopic findings that are typical for CDI, such as colonic pseudomembranes, are also lacking in most patients with IBD that present with CDI[28]. As noted above, patients with IBD and CDI often acquire the infection in the outpatient setting and in many there is no previous documented antibiotic exposure[29,53].

Due to the high prevalence of CDI in patients hospitalized with an IBD exacerbation, the suspected causal association between CDI and flare of IBD, and the prognostic implications of CDI in these patients, it is recommended by the American college of gastroenterology CDI Guidelines Task Force, to test all IBD patients hospitalized with a disease flare for *C. difficile*[64]. Also, the European Crohn's and Colitis Organization guidelines recommend testing for Clostridium difficile infection in patients with severe or refractory UC[65]. Patients should be tested even in the absence of traditional risk factors such as antibiotic exposure.

There are various laboratory tests used in the diagnosis of CDI. Only loose, watery, or semi-formed stool should be tested for *C. difficile* and specimens should be kept at 4 ℃ if delay in testing is anticipated due to degradation of *C. difficile* toxin at room temperature[66,67]. The different tests that have been used to date are[68-70]: (1) Selective anaerobic culture: the most sensitive diagnostic method, cannot distinguish toxin-producing strains from non-toxin producing strains, time and labor consuming and thus reserved for epidemiologic studies[71]; (2) Cell culture cytotoxicity neutralization assay: detects the presence of toxin B in stool by its cytopathic effects in a cell or tissue culture, is time consuming, with a sensitivity of 65%-90%, and is rarely performed today[71]; (3) enzyme immunoassay (EIA) for *C. difficile* toxins A and B: sensitivity for toxins A and B is 60%-75% and specificity is higher (up to 99%)[72,73]. Was the routine diagnostic assay for CDI in most microbiology laboratories in recent years, but due to its low sensitivity, is not recommended today as the initial diagnostic assay[70]; (4) EIA for *C. difficile* glutamate dehydrogenase (GDH), an enzyme produced in all *C. difficile* strains: sensitivity of 75% > 90%, but cannot differentiate between toxin positive and toxin negative strains[74]; and (5) Polymerase chain reaction (PCR): detect toxin A and B genes, are highly sensitive and specific[75,76], and provide rapid results (within as little as 1 h).

Current recommendation for CDI diagnosis implement either one step molecular assays or two step algorithms with screening with EIA for GDH, followed by EIA for toxins and/or a molecular assay[67,68]. In patients with IBD, there is no evidence to date, that testing for CDI should be done differently. A recent retrospective study that compared the frequency and clinical outcomes of IBD inpatients with CDI, found that a greater percentage of patients tested positive by PCR for toxin B as compared with ELISA for toxins A + B, but the clinical outcomes were the same, regardless of method of testing[77]. More research is needed to determine the optimal diagnostic test for CDI in patients with IBD. Due to high rates of asymptomatic colonization of *C. difficile* in patients with IBD, only patients with significant diarrhea should be tested for CDI.

Treatment

Treatment of CDI includes general measures such as supportive care with attention to correction of fluid losses and electrolyte imbalances, cessation of the inciting antibiotic as soon as possible (if possible), implementation of infection control policies-including hand hygiene with soap and water which is more effective than alcohol-based hand sanitizers in eradication of *C. difficile* spores[67,78]. Antimotility agents such as loperamide and opiates have traditionally been avoided in CDI for fear of decreasing toxin clearance and increasing the risk of ileus and/or megacolon, but the evidence that they cause harm is equivocal[79].

Specific antibiotic therapy should be started as soon as possible, and empiric therapy is indicated pending results of diagnostic testing if the clinical suspicion is high and

when severe or complicated CDI is suspected. Currently, there are several drugs in use for treatment of CDI including: metronidazole (oral or intravenous), vancomycin (oral or per rectum), oral rifamixin, and a newer drug- oral fidaxomicin. A Cochrane systematic review from 2011 found no statistically significant difference in efficacy between vancomycin and other antibiotics including metronidazole, fusidic acid, nitazoxanide or rifaximin[80]. The updated guidelines for the treatment of CDI released by the Infectious Diseases Society of America and the Society for Healthcare epidemiology of America suggest that the initial choice of treatment should be determined based on the severity of illness and depending if it is a first episode of CDI or a recurrence[69]. There are different scoring systems to assess the severity of illness, including the severity score index that consists of 9 criteria, each accounting for one point: altered mental status, white blood cell count > 20000 or < 1500, albumin < 2.5 mg/dL, ascites or colitis by imaging, mean arterial pressure < 65 mmHg, fever > 38.3 ℃, tachycardia > 110 bpm and admission to intensive care unit. 1-3 points indicates mild disease, 4-6 points moderate disease, and ≥ 7 points severe disease[81]. For an initial episode of mild to moderate CDI-metronidazole, at a dose of 500 mg orally 3 times per day for 10-14 d, is considered the drug of choice. Vancomycin at a dose of 125 mg orally 4 times per day for 10-14 d is the drug of choice for an initial episode of severe CDI. Vancomycin, administered 500 mg orally 4 times per day (and 500 mg in approximately 100 mL normal saline per rectum every 6 h as a retention enema, if ileus is present) with or without intravenously administered metronidazole 500 mg intravenously every 8 h, is the regimen of choice for the treatment of severe, complicated CDI. Treatment of the first recurrence of CDI is usually with the same regimen as for the initial episode but should be stratified by disease severity, Treatment of the second or later recurrence of CDI is with vancomycin therapy using a tapered and/or pulse regimen[67].

Recent studies of fidaxomicin, 200 mg orally twice daily, compared with oral vancomycin, demonstrated non inferiority of clinical response after 10 d of treatment and superior sustained responses with a decrease in recurrences (13% *vs* 24% with vancomycin treatment)[82]. Among patients who received concomitant antibiotics, treatment with fidaxomicin resulted in higher cure rates (90% *vs* 79.4%) and lower recurrence rates (16.9% *vs* 29.2% with vancomycin)[83]. Due to these and other findings, fidaxomicin might be a promising treatment for patients with risk factors known to portend relapse and severe infection[84], though two different economical analyses reported conflicting results of the cost effectiveness of using fidaxomicin as first-line treatment for CDI[85,86].

In patients with IBD and CDI, there are no guidelines or evidence from prospective studies to suggest that one antibiotic regimen is better than another. Failure rates of up to 50% have been reported in IBD patients treated with metronidazole[87]. Considering the worse outcomes of patients with IBD and CDI, some institutions use vancomycin as first line therapy in these patients. In a single center study, where vancomycin was adopted as first line therapy in IBD patients with CDI, colectomy rates decreased from 45.5% to 25% within 1 year after the change of policy[88]. There are no data as of yet regarding the use of fidaxomicin in the IBD patient population, though in another group of immune suppressed patients-recipients of solid organ and hematopoietic stem cell transplantation, fidaxomicin achieved over all cure rates in 86% of episodes and recurrence rate was 7%[89].

Concomitant use of immunomodulators is another unresolved issue in patients with IBD and CDI. A retrospective multicenter European study comparing hospitalized IBD patients with CDI treated with antibiotics and immunomodulators or antibiotics alone, found that the primary outcome of complications including colectomy or death within 3 mo occurred in 12% of patients treated with both, as compared to none of the patients treated with antibiotics alone[90]. The use of 2 or more immunomodulators further increased the risk of complications. In a survey of North American gastroenterologists, there was significant disagreement on whether combination antibiotics and immunomodulators or antibiotics alone should be given in patients with an IBD flare and CDI[91]. The American College of Gastroenterology CDI task force, has given a conditional recommendation, with low quality supporting evidence, that ongoing immunosuppression can be maintained in patients with CDI, although escalation of immunosuppression should be avoided[64].

Fecal macrobiota transplantation (FMT) through retention enemas, rectal tube, colonoscopy, nasogastric and nasoduodenal tubes, or upper endoscopy is another option for treating recurrent CDI through restoration of a healthy microbiome in the lower gastrointestinal tract. Different studies have reported success rates of FMT approaching 90% in patients with recurrent CDI[92,93]. A randomized prospective trial, found that duodenal infusion of donor feces following vancomycin treatment was significantly more effective for the treatment of recurrent CDI than the use of vancomycin alone[94]. Data on the use of FMT among IBD patients is limited, though a recent systematic review found that out of 12 patients with IBD and CDI treated with FMT, all became toxin negative, with symptomatic resolution in 11 out of 12 patients[95]. A recent review of FMT[96] notes that though there are no guidelines concerning FMT for treatment of CDI in patients with IBD, after FMT and eradication of *c.difficile*, the severity of IBD is gradually reduced with improved responses to medications for IBD. FMT is considered a safe treatment, though a recent paper reported a case of a flare of UC in a patient who received FMT for CDI[97].

In patients after restorative proctocolectomy and ileal pouch anal anastomosis that present with *C. difficile* pouchitis, treatment is empirical because there are no published prospective trials. Studies suggest that metronidazole is not completely protective against CDI of

the pouch, as this infection has developed in patients on metronidazole therapy, thus in these patients vancomycin might be considered as first line therapy[59].

CONCLUSION

Patients with IBD are at increased risk of developing CDI and having worse outcomes, including higher rates of colectomy and death. There has also been a rise in the percentage of patients with IBD that suffer from CDI during recent years, even in those lacking classic risk factors for CDI. Patients with IBD often present with unique and more severe symptoms of CDI. Diagnosis of CDI in patients with IBD warrants a high index of suspicion and physicians should be alert to the possibility of CDI in any patient with an IBD exacerbation. All hospitalized patients with a flare of IBD should be tested for CDI and antibiotic treatment should be initiated rapidly, especially in severe cases, where vancomycin is the treatment of choice. More studies are needed to better understand the pathogenetic role of CDI in IBD exacerbations, to define what are the best diagnostic methods for CDI in these patients, to assess the efficacy of newer treatments such as fidaxomicin in patients with CDI and IBD, and to better address the question of concurrent treatment with immunomodulatory agents.

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