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Review

Clostridium difficile infection and inflammatory bowel disease

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ABSTRACT

Over the past 15 years, *Clostridium difficile* infection (CDI) in patients with inflammatory bowel disease (IBD) has increased both in incidence and severity. Traditional risk factors for CDI are similar in IBD and non-IBD populations, but there is a significant proportion of IBD patients which have distinctive characteristics. Patients with ulcerative colitis (UC) are more susceptible to CDI and have more severe outcomes than those with Crohn's disease (CD). CDI may be difficult to distinguish from an IBD flare due to similar clinical presentation, and therefore screening for CDI is recommended at every flare in such patients. 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. Vancomycin and metronidazole appear to have similar efficacy in patients with moderate disease, but vancomycin is preferred in severe disease. Measures must be taken to prevent the spread of infection. Clinicians should have a high index of suspicion for CDI when evaluating a patient with IBD flare, as rapid detection and prompt treatment of infection improve outcomes. This review summarizes the available literature on epidemiology, risk factors, clinical aspects, diagnostic methods, treatment, outcome, and prevention of CDI in IBD patients.

Keywords: *Clostridium difficile* infection, inflammatory bowel disease, ulcerative colitis, Crohn's disease, epidemiology, risk factors

INTRODUCTION

Over the past two decades there has been a dramatic worldwide increase in both incidence and severity of *Clostridium difficile* infection (CDI) (1). Illustratively, in USA alone, hospital discharges with CDI as the main diagnosis registered a 237% increase from 2000 to 2009, and accounted for hospital mortality rate similar to that of gastrointestinal bleeding (2), with healthcare costs estimated between 1.2 and 3 billion US dollars each year (3). In addition to broad-spectrum antimicrobial therapy, which is the most widely recognized causative factor for CDI (4), other potential risk factors, such as advanced age, prolonged hospitalization, chemotherapy, immunosuppression, multiple co-morbidities, hypoalbuminemia, renal insufficiency, use of proton pump inhibitors, and the emergence of a hypervirulent strain of the bacterium known as NAP1 (North American pulsed field type1) in some North-American and European areas, have been identified to explain the increased incidence of CDI (5-7).

Paralleling the increasing incidence of CDI in the general population, there has been an even higher increase in incidence of CDI among patients with inflammatory bowel disease (IBD) (8-12). CDI was first associated with IBD in the early 1980s (13), but was somehow neglected until ten years ago, when several studies and reviews clearly demonstrated that patients with one of the two major forms of IBD (ulcerative colitis-UC; Crohn's disease-CD) are at high-risk for CDI (8-12,14-21). Besides the well-known risk factors for CDI in non-IBD population, there are some typical IBD-related risk fac-

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tors, such as the extent and severity of the underlying disease, long-term immunosuppression, lack of antibiotic exposure or recent hospitalization, younger age, steroid use, and predominantly community-acquired infection (8,22). Patients with UC are more susceptible to CDI than those with CD (8,11,12,20,22). CDI may resemble a flare of IBD as symptoms are often similar, and consequently screening for CDI is recommended at every flare in such patients (14-16,18-21). Despite its low sensitivity, enzyme immunoassay for detecting *Clostridium difficile* (*C. difficile*) toxins in stool remains the most widely used test for the diagnosis of CDI in many countries (23). Metronidazole and vancomycin appear to have similar efficacy as first-line treatment for mild or moderate CDI, but oral vancomycin is the preferred agent in patients with severe disease (24). Current therapeutic strategies may be replaced by newer antibiotics, monoclonal antibody targeted toxins, and fecal microbiota transplantation (25). Patients with IBD and superimposed CDI have worse outcomes than those with IBD alone (8,10,12,26,27). Infection-control measures, such as isolation of infected patients, hand hygiene and protective equipment for healthcare workers, and environmental cleaning must be taken to prevent the spread of infection (28).

This review aims to summarize the latest available data on epidemiology, pathogenesis, diagnosis, treatment, outcome, and prevention of superimposed CDI in IBD patients.

REVIEW METHOD

We performed a systematic search of electronic databases Medline/PubMed, EMBASE, Scopus, Science Direct, CINAHL, and Web of Science (ISI Web of Knowledge) from June 1990 to October 2013, using various combinations of the following key words: "inflammatory bowel disease", "ulcerative colitis", "Crohn's disease", and "*Clostridium difficile* infection", "*Clostridium difficile*-associated diarrhea", "pseudomembranous colitis". Only articles published in English on adults from all geographic regions were included in this study. Relevant full-text articles were studied in detail, while reference lists were searched manually to identify any additional studies that may have been overlooked during the computer-assisted literature search. From each included study, the following data were extracted: author, country, journal and year of publication, epidemiology, risk factors, pathogenesis, diagnosis, treatments, outcomes, and preventive measures for CDI.

EPIDEMIOLOGY

Both single-center studies (8,9,22,27,29-31) and large nationwide data analyses (9,11,12,26) have independently reported an increased CDI incidence among IBD patients.

Rodemann et al. (22) in a retrospective study at the Barnes-Jewish Hospital in St. Louis, Missouri, USA, found that in the interval 1998-2004 CDI rates tripled in UC patients (from 18.4 to 57.6/1000 admissions) and doubled in CD patients (from 9.5 to 22.3/1000 admissions). A similar increase in CDI rate in IBD patients (1.8% in 2004 and 4.6% in 2005, $p<0.01$) was reported by Issa et al. (8) from a tertiary care center in Wisconsin. Studies from two other academic USA centers, one in Mount Sinai Hospital, New York (27) and the second in Mayo Clinic, Scottsdale, Arizona, reported that of their IBD patients admitted with flares 47% and 20%, respectively had CDI (29). The increasing rates of CDI among IBD patients reported from single tertiary care centers in USA has also been noted in Europe and other geographic regions (10,30). Thus, Bossuyt et al. (10), from Leuven, Belgium, reported a 3.75-fold increase in CDI in both IBD and non-IBD patients, between 2000 and 2008, while Kaneko et al. (30) from Yokohama City University Medical Center, Yokohama, Japan, found that 40% of their 137 patients with UC flares were diagnosed with CDI. From India, Kochhar et al. (31) reported that 32% of patients with UC flares had a superimposed CDI.

Similarly to the above mentioned single-center studies, several studies using nationwide data also reported increased CDI incidence in IBD patients (9,11,12,26). Nguyen et al. (12) analyzed data from the National Inpatient Sample (NIS), a component of the Healthcare Cost and Utilization Project (HCUP) containing information on more than 90% of USA community hospital discharges, and found that over a 7-year period (1998-2004) CDI incidence among hospitalized IBD patients nearly doubled in those with UC (26.6/1,000 to 51.2/1,000) (2.7% to 5.1%). Using data from NIS 200, Ananthakrishnan et al. (26) found a continuing and significant increase in the frequency of CDI among all IBD hospitalizations nationwide (from 2.5% in 1998 to 5.3% in 2007 for UC, and from 0.8% in 1998 to 1.5% in 2007 for CD; $p<0.01$). Ricciardi et al. (11) in a retrospective analysis of all IBD patients in the NIS from 1993-2003 found a significantly increased prevalence of CDI in patients with UC and colonic CD, but not in those with CD limited to the small bowel. In Europe, Jen et al. (9) using Hospital Episodes Statistics (HES) dataset, which covers all in-patient activity delivered by NHS hospitals in England, found that the incidence of co-existent CDI in IBD patients admitted to hospital was nearly twice higher in 2008 than in 2002.

In contrast with all the above mentioned studies, there are others which report low incidence of CDI in IBD patients. Thus, Ott et al. (32) in a retrospective study from a tertiary referral center in Germany found only 10 patients with concomitant CDI among 242 with UC and 279 with CD admitted with an acute flare between 2001 and 2008. Recently, Masclee et al. (33) in a retrospective as well as prospective cohort study in the Netherlands found a low prevalence of CDI in IBD patients. However, overwhelming data suggest an increased incidence rate of CDI in IBD patients as compared to non-IBD population.

Almost all studies on CDI in IBD were conducted in hospitalized patients. Recent reports suggest a high prevalence of CDI in asymptomatic IBD patients. Clayton et al. (34) in a retrospective study including 64 patients with UC and 58 with CD, all in clinical remission and without recent exposure to antibiotics,

corticosteroids, immunomodulatory drugs or recent hospitalization, found that that the frequency of toxigenic *C. difficile* was higher in IBD patients than in healthy volunteers (8.2 *vs.* 1.0%; p=0.02), which is consistent with community-acquired infection.

RISK FACTORS

In addition to the traditional risk factors for CDI similar to those in the general population, there are some IBD-specific risk factors for CDI.

Traditional risk factors, of which prior antibiotics use remains the most important, include advanced age, multiple comorbidities, prolonged hospitalization, and immunosuppression. Clindamycin was initially associated with CDI, but more recently, fluoroquinolones, widely used in IBD patients, have become the most common risk factor for CDI (4). The mechanism through which the use of antibiotics leads to increased risk for CDI development is the disruption of normal intestinal flora and the subsequent proliferation of *C. difficile*. However, in IBD patients, antibiotics do not play such an important role in CDI development as they do in the general population (8,10). One study (10) reported that antibiotic use before the development of CDI was found in only 40% of IBD patients as compared to 69% in non-IBD patients, while another study identified no recent antibiotic use in 39% of IBD patients with CDI (8).

As in the general population, advanced age and comorbidities increase the risk for CDI in IBD patients (22,26). Although the proportion of older IBD patients has increased in recent years, a nationwide retrospective study found an average age of CDI in IBD cohorts significantly lower than in general population controls (9). Nguyen et al. (12) reported a 13% increase in the risk for CDI with each 1-point increase in the Charlson's comorbidity burden index. Prolonged and frequent hospitalizations are a risk factor for CDI in both IBD and non-IBD patients, although several studies have reported that CDI in IBD patients is often acquired outside the hospital (8,22).

Inflammatory bowel disease patients often require long-term immunosuppressive therapy, which is another risk factor for CDI both in IBD and non-IBD patients (e.g., organ transplant recipients). Issa et al. (8) found maintenance immunosuppressive therapy to be associated with a double risk of CDI (OR 2.58; CI: 1.28-5.12). However, other studies found no such association (35). Studies on imumunosuppression with corticosteroids have also reported conflicting results, some finding no association with the risk of CDI in IBD patients, others reporting an increased risk of CDI (36). Schneeweiss et al. (36) found that corticosteroid initiation tripled the risk of CDI among the IBD patients (relative risk 3.4, 95% CI 1.9-6.1), while no such association with the initiation of immunomodulators or biologics (infliximab) was found. Biological agents (e.g., infliximab, adalimumab) are not associated with increased risk of CDI in IBD patients (36), nor is the use of aminosalicylates (34). PPI use in non-IBD patients has been suggested to increase the risk for CDI (6), but other studies did not find any association between PPI use and CDI in IBD patients (10).

IBD-specific risk factors. Firstly, IBD itself is an independent risk factor for CDI, with a three-fold increased risk as compared with non-IBD population (22). Patients with UC are at higher risk for CDI than those with CD (8,11,12,22), and colonic CD patients are at higher risk for CDI than those with small bowel CD (8,12). IBD patients with extensive disease and greater disease activity are at higher risk for CDI (8).

PATHOGENESIS

Clostridium difficile is an anaerobic, gram-positive, spore-forming bacterium transmitted via the fecal-oral route. The association between *C. difficile* and IBD is mediated by several factors such as the use of therapeutic drugs (including antibiotics), which alter the colonic flora, together with decreased immune status, and genetic predisposition (37), all favoring CDI. *C. difficile* affects the tissue through toxin production. Pathogenic strains of *C. difficile* produce two exotoxins: toxin A (enterotoxin) and toxin B (cytotoxin). After binding to receptors on the enterocyte, the toxin penetrates the cell through receptor-mediated endocytosis followed by glycosylation of Rho and Ras proteins, leading to disruption of the epithelial cytoskeleton, and subsequently to inflammatory diarrhea (38). There are other toxins produced by *C. difficile*, among which the binary toxin (39) which is associated with a more severe stage of the disease.

The hipervirulent strain of *C. difficile* responsible for CDI outbreaks in the province of Quebec, Canada between 2002 and 2005 was named BI/NAP1/027 (group BI, North American pulse-type 1, ribotype 027). NAP1 not only carries the binary toxin, but also produces 16 times more toxin A and 23 times more toxin B than typical strains (7). Except for one study (10), no other researches have managed to determine the effect of this hypervirulent strain on patients with IBD.

CLINICAL FEATURES

The clinical spectrum of CDI ranges from an asymptomatic carriage to fulminant colitis with toxic megacolon. Watery diarrhea is the cardinal clinical symptom of CDI. However, CDI in IBD patients may show atypical features including bloody or mucous diarrhea (40), which are difficult to distinguish from an IBD flare (8,22). In many patients there are associated systemic symptoms, such as low-grade fever or anorexia. Laboratory findings in CDI and IBD flares are also similar (leukocytosis, anemia, hypoalbuminemia). Moreover, at colonoscopy pseudomembranes are often absent in IBD patients with CDI (41).

DIAGNOSIS

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

Table 1. Diagnostic tests for *Clostridium difficile*

Method	Sensitivity	Specificity	Comments
EIA for toxins A/B	Low	High	Inexpensive, rapid results (within 2 hours), available for all laboratories; high false-negative rate
EIA for GDH	High	Low	Rapid results (<1 hour), cannot distinguish toxin-positive from toxin-negative strains, useful as screening test
Cell culture cytotoxicity	High	High	Diagnostic gold standard for toxin B, time-consuming, used only in research laboratories
PCR	High	High	Rapid results (within 1 hour), expensive, widely available, false-positive results
Selective anaerobic culture	High	Low	Slow turnaround time, cannot distinguish toxin-positive from toxin-negative strains, low cost, it may be used for epidemiologic studies

EIA: enzyme immunoassay; GDH: glutamate dehydrogenase; PCR: polymerase chain reaction

encoding *C. difficile* toxin B (*tcd*B) or the toxin regulatory gene (*tcd*C), cell culture cytotoxicity assay (CTA), and selective anaerobic culture (Table 1). The choice of test depends on its availability, cost, turnaround, sensitivity and specificity. As a general rule, testing should be done only in symptomatic IBD patients with loose, watery, or semi-formed stools (unless an ileus is present) (42).

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 (21). 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 non-IBD patients is limited. Thus, in patients with multiple stool samples tested by EIA, approximately 90% were accurately diagnosed on the initial test, subsequent testing yielding a positive result in less than 10% of patient. Therefore, repeated EIA testing during one episode is not recommended, but if clinical suspicion of CDI remains high a more sensitive assay is recommended. Still, in IBD patients, EIA sensitivity is even lower (54%) than in non-IBD population (8), and repeating the test in a previously negative patient with suspected CDI may be useful as proven by some studies which found that multiple consecutive samples increased detection of CDI, but also the costs (8). In one study, Issa et al. (8) found that repeated EIA-stool testing for toxins in symptomatic IBD patients increased the CDI diagnosis rate from 54% with cases identified by the first stool testing to 92% when four successive stools were tested. More recently, in another study (43), approximately one in five IBD patients with CDI required repeated testing to yield a positive result with EIA.

EIA for GDH antigen detection has a high negative predictive value and is, therefore, useful as a screening test, with results available in less than one hour. However, as GDH antigen detection is unable to distinguish between toxogenic and non-toxogenic *C. difficile* strains, a second more specific test such as PCR for *C. difficile* DNA extraction or EIA for toxin A and B is needed on specimens that are GDH positive (42).

PCR-based assays are highly sensitive and specific (44), commercially available, with results available within the 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. Recently, Wang et al. (45), in a study comparing the frequency and clinical outcome in hospitalized IBD patients with CDI, found a greater percentage of patients tested positive by PCR as compared to EIA, but CDI outcomes diagnosed by PCR were comparable to those detected by EIA.

Cell culture cytotoxicity assay, which detects the cytopathic effect of toxin B, is still considered the gold standardfor the diagnosis of *C. difficile infection*. It has a higher sensitivity than enzyme immunoassays, but it is more expensive and time-consuming (results are available in 24-48 hours), this test being therefore used only in research laboratories.

Selective anaerobic culture (C. difficile culture) testing *C. difficile* isolates for toxin production is a highly sensitive diagnostic test, but unable to distinguish toxin-producing from non-toxin producing *C. difficile* strains. It may be used in epidemiologic studies, but not in clinical practice, given its long turnaround time (24-48 hours).

Which IBD-patients should be tested for *C. difficile?* Due to the high prevalence of CDI in IBD patients and clinical/laboratory similarity between CDI and IBD exacerbation, it is recommended that all IBD patients with a disease flare should be tested for *C. difficile* (14-16,18-21). There is no indication for post-treatment testing to confirm cure. Asymptomatic carriage in IBD patients (remission/inactive disease) is more frequent than in general population. Screening for asymptomatic carriers in the general population is not recommended (34), but screening and treatment of asymptomatic IBD patients under immunosuppressant therapy may be important (8).

In many countries, the most commonly used and widely available test for *C. difficile* in routine clinical practice is stool EIA for toxin A and B. Considering that this test has low sen-

Table 2. Treatment of *Clostridium difficile* infection

1. Stop inciting broad-spectrum antimicrobial therapy
2. Antiperistaltic agents should be avoided
3. Initial episode of CDI:
   - Mild/moderate infection: oral metronidazole 500 mg tid or 250 mg qid for 10-14 days
   - Severe infection: vancomycin 125 mg qid for 10-14 days
4. Recurrent CDI:
   - First recurrence: the same regimen used to treat the initial episode
   - Second or multiple recurrences: oral vancomycin, using a tapered and/or pulsed regimen.

   Vancomycin, tapered dose: week 1: 125 mg qid; week 2: 125 mg bid; week 3: 125 mg once daily; week 4: 125 mg every other day; week 5 and 6: 125 mg every 3 days.

   Vancomycin, pulse therapy: 125 mg every 2 days or 500 mg every 3 days for 3 weeks
5. Complicated CDI (megacolon, ileus, organ failure): oral vancomycin 500 mg qid with or without iv metronidazole 500 mg tid; if ileus, vancomycin 500 mg in 100 mL NS per rectum qid.

CDI: clostridium difficile infection; NS: normal saline; bid: twice daily; qid: four times daily; tid: three times daily

sitivity when a single stool sample is examined, a two-step method has been suggested, consisting in screening with EIA for GDH, followed by EIA for toxin A and B or molecular assay (42).

TREATMENT

General measures

In IBD patients, rapid diagnosis and prompt treatment of CDI are of paramount importance in order to prevent complications and improve outcome. General measures should be taken, such as cessation of the antibiotic that led to development of CDI, supportive care with the correction of fluid losses and electrolyte imbalances, avoidance of antimotility agents, isolation of patients in single rooms or dedicated wards, hand hygiene in healthcare settings and environmental cleaning. It should be underlined that in patients who developed CDI after antibiotic use, simple discontinuation of the offending antibiotic leads to resolution of symptoms in 10%-20% of cases (10). However, this paradoxical infection (caused by antibiotics and treated with antibiotics!) requires specific antimicrobial therapy in most patients.

Medical treatment (Table 2)

Antibiotics

Two antibiotics, metronidazole and vancomycin, given orally, have traditionally been favored in the treatment of CDI and proved to be effective. More recently, other antibiotics including fidaxomicin, nitazoxanide, and rifaximin have been used, with no significant difference in efficacy compared to vancomycin. Given the absence of guidelines and randomized control studies, in IBD patients with CDI the choice of antibiotic therapy should be based on the severity of the disease and on whether it is an initial episode of infection or a recurrence, in which case a treatment similar to that applied in non-IBD patients with CDI is required.

Metronidazole (500 mg orally 3 times a day or 250 mg orally 4 times daily for 10-14 days) is the drug of choice for an initial episode of mild to moderate CDI because it is effective, cheap, and has low drug resistance. Metronidazole is the only antibiotic that can be administrated intravenously for the treatment of CDI in patients unable to take it orally. Metronidazole had been the first-line drug in the treatment of mild/moderate CDI for over 3 decades, and several initial studies reported success rates of 75%-90%. However, metronidazole (unlicensed for CDI treatment in USA) has such side-effects as metallic taste, nausea, and risk of peripheral neuropathy; in addition, there is an increased recurrence rate of CDI after therapy with metronidazole (10). Following reports (8) on failure of metronidazole therapy in hospitalized IBD patients with CDI, many centers have now adopted vancomycin as first-line therapy in these patients.

Vancomycin (125 mg orally 4 times a day for 10-14 days) is the agent of choice for the first episode of severe CDI. Vancomycin has proved superior to metronidazole in achieving bacteriologic cure in the treatment of severe CDI (24). In patients with complicated CDI, vancomycin (500 mg orally 4 times a day) combined with metronidazole (500 mg intravenously 3 times a day) is recommended. If ileus is present, vancomycin 500 mg in 100 ml normal saline as a retention enema 4 times a day is advised. Unlike metronidazole, vancomycin can be used during pregnancy and in children, but it is more expensive and there is significant concern about the emergence of vancomycin-resistant enterococci.

Fidaxomicin, approved by FDA (US Food and Drug Administration) and EMA (European Medicines Agency) for the treatment of CDI in non-IBD patients, has 90%, cure rates, but there are no data regarding its use in IBD patients with CDI. Other antibiotics, such as rifaximin, nitazoxanide, fusidic acid and tigecycline,

which have been used in the treatment of CDI did not show superior efficacy as compared to metronidazole or vancomycin.

There remains an unresolved issue: whether immunomodulatory drugs could be maintained or added to therapy in the setting of IBD complicated with CDI. A retrospective multicenter study has demonstrated that IBD patients with CDI treated with a combination of antibiotics and maintenance or newly added immunomodulatory drugs were more likely to have severe outcomes (colectomy, mortality) than those treated only with antibiotic (41). However, there is a significant disagreement among gastroenterologists on whether antibiotics alone or combined antibiotics/immunomodulators should be administered in IBD patients presenting with flares and CDI.

Probiotics may be effective in preventing recurrent CDI but there is no data on their use either with antibiotics or alone for the treatment of CDI in IBD patients.

Fecal microbiota transplantation (fecal bacteriotherapy) was found to be effective for refractory or recurrent CDI (25), but data concerning its use in IBD patients are scarce.

Recurrent CDI

In the absence of evidenced-based studies, recurrent CDI, occurring in 10%-30% of IBD patients either as a relapse with the same strain or a re-infection with another strain, is treated similarly as in the non-IBD population (8,22). The first recurrence of CDI should be treated with the same regimen used for the initial episode; however, if severe, vancomycin should be used in those treated initially with metronidazole. The second recurrence should be treated with vancomycin, using a tapered (a stepwise decrease in dose over a period of time) or pulsed (high dose given fewer times over a prolonged period of time) regimen (42). For the third or multiple recurrences after tapered and/or pulsed vancomycin, several alternative therapeutic approaches have been tried: fecal microbiota transplant, probiotics, and newer antibiotics. However, there are few studies centered on such treatments in IBD patients.

Surgical treatment

Indications for surgical treatment include severe complications (perforation, toxic megacolon) and failure of medical therapy. Patients with colonic perforation or toxic megacolon require an emergency colectomy, but timing of surgery in those with drug therapy failure differs between centers. The operation of choice is total colectomy with ileostomy or proctocolectomy with ileoanal pouch anastomosis if a restorative option is preferred.

OUTCOMES

More than 90% of the published studies found by searching Medline and other databases aim to assess CDI incidence in IBD patients, while less than 10% report on infection outcomes. Though scarce, most of these studies show that CDI has a negative impact both on short-term (within 30-90 days of index admission) and long-term (at least 1 year following index admission) IBD outcomes, increasing the need for surgery, as well as mortality rate and healthcare costs.

Short-term outcomes include length of hospital stay, colectomy, and mortality rate. Studies report variable results regarding length of hospital stay in IBD patients with concomitant CDI: some found similar stays (22,27), some shorter (10), while others reported longer stays than in IBD patients without CDI (8,9,12). Contrasting results have also been reported regarding colectomy and mortality rate in IBD patients with superimposed CDI (8,9,12,26). Ananthakrishnan et al. (46) in an analysis of NIS database found that IBD patients with CDI had a six-fold higher risk of colectomy than those with IBD alone. Increased colectomy rates in IBD patients with CDI have also been reported by other studies (9,12,26). However, other studies found no significant differences in colectomy risk between IBD patients with CDI and those without CDI (10,30,35,41). A four-fold higher mortality rate in hospitalized patients with concurrent IBD and CDI as compared to those with IBD alone was reported by two USA studies using NIS data (12,46), while another study from United Kingdom (9), analyzing nationwide data, found that IBD patients with CDI were approximately six times more likely to die in hospital than those admitted for IBD alone, contrasting reports from single-center studies which found a similar or a non-significant increase in the relative mortality risk in IBD patients co-infected with *C. difficile* compared with uninfected IBD patients (10,26).

Long-term outcomes have been reported by few studies (27,47-49). Two studies (27,47) showed an increased number of visits to the emergency room, more UC-related hospitalizations, and higher colectomy rates than in those with UC alone in the year following initial infection. In addition, over half of UC patients had an escalation in medical therapy one year following CDI (47,49). Recently, a retrospective study on UC hospitalized patients with and without CDI found that those with CDI had a higher adjusted 5-year risk of mortality (48).

PREVENTION

Limiting the frequency and duration of antibiotic therapy seems a favorable solution for reducing CDI rates, and, therefore, the empirical use of broad-spectrum antibiotics, particularly fluoroquinolones, should be avoided in IBD patients. Once a patient with IBD is diagnosed with CDI, the following measures should be taken: single room isolation of the infected patient or cohorting with patients with similar infection, hand hygiene and use of protective equipment by healthcare workers and visitors, as well as environmental decontamination. Isolation in a single room with en suite toilet facility or dedicated isolation wards is an important step to prevent infection from spreading. As *C. difficile* is carried on and transmitted via the hands of healthcare workers, hand decontamination of is one of the most important measures for preventing the nosocomial

transmission of this infection (28). It should be underlined that the best method for decontamination is hand washing with soap and water before and after contact with infected patients (28). Alcohol gels, commonly used, are not effective against *C. difficile* spores. In conjunction with hand hygiene, healthcare workers should wear disposable gloves and gowns at each contact with patients. Environmental disinfection should be done with such sporicidal agents as hypochlorite solutions (unbuffered or phosphate-buffered) as *C difficile* spores are resistant to conventional cleaning agents (50).

CONCLUSIONS

Although the association of CDI and IBD was first described more than three decades ago, it became a subject of much interest when recently several studies showed a dramatic increase in the incidence and severity of CDI in IBD patients, particularly in those with UC. CDI may be difficult to distinguish from an IBD flare due to similar clinical presentation; therefore, screening for *C. difficile* is recommended at every flare in such patients. Traditional risk factors for CDI are similar in IBD and non-IBD population though many IBD patients have distinctive characteristics such as younger age, lack of antibiotic exposure or recent hospitalization, and extensive underlying disease. EIA for *C. difficile* toxins A and B remains the most widely used diagnostic test, although, recently, many laboratories have replaced it by more sensitive tests such as PCR. Vancomycin and metronidazole are currently the two main antibiotic treatments, but newer therapies aiming to improve outcomes in IBD patients are on the horizon.

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