World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i33.11736

World J Gastroenterol 2014 September 7; 20(33): 11736-11742
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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Impact of *Clostridium difficile* infection on inflammatory bowel disease outcome: A review

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Received: February 11, 2014 Revised: April 23, 2014
Accepted: June 12, 2014
Published online: September 7, 2014

Abstract

Although a considerable number of studies support a substantial increase in incidence, severity, and healthcare costs for *Clostridium difficile* infection (CDI) in inflammatory bowel disease (IBD), only few evaluate its impact on IBD outcome. Medline and several other electronic databases from January 1993 to October 2013 were searched in order to identify potentially relevant literature. Most of the studies showed that IBD patients with CDI present a greater proportion of worse outcomes than those without CDI. These patients have longer length of hospital stay, higher rates of colectomies, and increased mortality. Patients with ulcerative colitis are more susceptible to CDI and have more severe outcomes than those with Crohn's disease. However, studies reported variable results in both short- and long-term outcomes. Contrasting results were also found between studies using nationwide data and those reporting from single-center, or between some North-American and European studies. An important limitation of all studies analyzed was their retrospective design. Due to contrasting data often provided by retrospective studies, further prospective multi-center studies are necessary to evaluate CDI impact on IBD outcome. Until then, a rapid diagnosis and adequate therapy of infection are of paramount importance to improve IBD patients' outcome. The aim of this article is to provide up to date information regarding CDI impact on outcome in IBD patients.

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Key words: *Clostridium difficile* infection; Ulcerative colitis; Crohn's disease; Outcome

Core tip: This review summarizes the impact of *Clostridium difficile* infection (CDI) on inflammatory bowel disease (IBD) outcome. Most of the studies showed that IBD patients with CDI have more of the whole range of short- and long-term worst outcomes than those without CDI. Patients with ulcerative colitis have more severe outcomes than those with Crohn's disease. A prompt diagnosis and adequate treatment of CDI are of paramount importance to improve IBD patients' outcome.

Trifan A, Stanciu C, Stoica O, Girleanu I, Cojocariu C. Impact of *Clostridium difficile* infection on inflammatory bowel disease outcome: A review. *World J Gastroenterol* 2014; 20(33): 11736-11742 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i33/11736.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i33.11736

INTRODUCTION

Over the past 15 years, both incidence and severity of

Clostridium difficile (*C. difficile*) infection (CDI) have increased dramatically worldwide[1,2]. In addition to broad-spectrum antibiotic therapy[3,4], other potential risk factors such as advanced age, prolonged hospitalization, immunosuppression, multiple co-morbidities, the use of proton pomp inhibitors, and the occurrence of a hypervirulent strain of *C. difficile* known as NAP1 (North American pulso-type 1) in some North-American and European areas, have been identified[5-10].

Referring to the same period, several studies clearly demonstrated a significant increase in CDI incidence in patients with inflammatory bowel diseases (IBD)[11-17]. Both ulcerative colitis (UC) and Crohn's disease (CD) present high-risk for CDI, although patients with UC are more susceptible than those with CD[11,12,15,16]. Overall, IBD patients with CDI show more of the whole range of short- and long-term worst outcomes than those without CDI or with CDI alone[11-13,16-19]. However, studies report variable results concerning mortality and colectomy rates, length of hospital stay, and healthcare costs for IBD patients with CDI[11,13,14,16,18-21].

This review aims to summarize available literature regarding CDI impact on both short- and long-term outcome in adult IBD patients.

RESEARCH

A systematic literature search was performed on Medline/PubMed, EMBASE, Scopus, Science Direct, CINAHL, and Web of Science (ISI Web of Knowledge) databases from January 1993 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". We included only English written studies carried out on adults, from all geographic regions. A manual search of references from the identified studies was also undertaken to identify any additional studies that may have been missed in the computed-assisted literature search. As our objective was to assess the impact of CDI on IBD patients' outcome, only studies reporting outcome of IBD patients co-infected with CDI were taken into analysis. The following data were extracted from each study included: length of hospital stay, colectomy rate, mortality, and healthcare costs. In addition, given the increased need for surgical intervention in UC patients with CDI, a short review of *Clostridium difficile* enteritis and pouchitis has also been made.

SHORT-TERM OUTCOMES

Length of hospital stay

Studies report different results concerning the length of hospital stay in IBD patients with CDI: some report similar stays[12,19], some shorter ones[14], while others (Table 1)[11,13,16,17,21] refer to longer stays than in patients without CDI or with CDI alone. Jodorkovsky *et al*[19] reported a similar mean length of hospital stay in days for IBD (UC) patients with superimposed CDI and those without CDI (11.7 *vs* 11.0, $P = 0.70$), while Bossuyt *et al*[14] found significantly shorter stays in IBD patients with CDI (mean 15.2 d) as compared to non-IBD patients co-infected with *C. difficile* (mean 27.7 d) ($P < 0.001$). By contrast, other studies reported longer length of hospitalization in IBD patients with CDI than in those with IBD alone[11,13,16,17,21]. Thus, Issa *et al*[11], in a retrospective, observational study evaluating IBD patients followed in the Inflammatory Bowel Disease Center, Medical College of Wisconsin, Milwaukee, United States, found a mean length of hospital stay of 13.5 d for their UC patients admitted with CDI as compared to 6 d for those without CDI. From the same center, in a study using nationwide data (including over 2000 IBD patients with CDI, over 44000 with CDI alone, and more than 77000 with IBD alone) was found a 3-d longer hospital stay in IBD patients with CDI. Nguyen *et al*[16] using the Nationwide Inpatient Sample (NIS) reported a 65% increase in the number of days for CD and 46% for UC patients with CDI as compared to non-IBD patients. A recent study using Hospital Episodes Statistics (HES) which covers all in-patient activity delivered by NHS hospitals in England, reported a 27.9 d longer hospital stay in patients with IBD complicated by hospital-acquired CDI than in those with IBD alone[17], much higher than in the above two mentioned North-American studies using similar national datasets[13,16], the difference being partially accounted for by data collection methods. From Canada, a retrospective population-based cohort study of 181 UC patients with CDI and 1835 without CDI hospitalized in Ontario, between 2002-2008, reported a significantly increased mean length of hospital stay in UC patients co-infected with *C. difficile* (11 d *vs* 6 d, $P = 0.0001$)[21].

Colectomy rate

Contrasting results have also been reported regarding colectomy rate in IBD patients with superimposed CDI. Analysis of the NIS HCUP (Healthcare Cost and Utilization Project) data containing more than 90% of United States community hospital discharges[22], showed a six fold (OR = 6.6; 95%CI: 4.7-9.3) increase in colectomy rate in IBD patients with concomitant CDI in comparison with CDI patients without underlying IBD[13]. It should be underlined that this analysis also includes IBD patients admitted for elective surgery, a fact which contributed to such a high colectomy rate[23]. However, other studies too reported higher colectomy rates in IBD patients with CDI than in CDI-free IBD population or in patients with CDI alone[11,17-19]. One case-control study reported a 23.4% emergent colectomy rate in patients with both CDI and IBD (UC) as compared to 13.5% (OR = 2.09, 95%CI: 0.72-6.1; $P = 0.17$) in those with IBD alone[19]. Another study reported a rate of urgent colectomy as high as 45% in hospitalized patients with IBD colitis and co-existing CDI in 2004, which decreased to 25% in 2005, probably due to changes in the treatment

Table 1 Main short-term outcomes in inflammatory bowel disease patients with *Clostridium difficile* infection as compared to those with inflammatory bowel disease alone or *Clostridium difficile* infection alone

Ref.	Journal and year of publication	Study design and time frame	Outcome
Murthy *et al*[21] Canada	Aliment Pharmacol Ther 2012	In-patients, Ontario, Canada, 2002-2008	Increased LOS (11 d *vs* 6 d, $P = 0.0001$), similar rate of colectomy (12% *vs* 9.8%; $P = 0.30$), and higher mortality rate (3.3% *vs* 0.38%, $P < 0.0001$) as compared with UC patients without CDI
Navaneethan *et al*[24] United States	J Crohns Colitis 2012	Out-/in-patients; 2002-2007	No significant difference in the colectomy risk within 3 months of index admission between UC patients with CDI and those with UC alone
Ananthakrishnan *et al*[28] United States	Aliment Pharmacol Ther 2012	In-patients; 1998-2010	4.4% colectomy and 15.2% mortality rates
Jen *et al*[17] United Kingdom	Aliment Pharmacol Ther 2011	Case-control analysis of United Kingdom Hospital Episodes Statistics, out-/in-patients; 2002-2007	Increased mortality (OR = 6.32), higher risk for surgery (OR = 1.87), and 27.9 d longer LOS than patients with IBD alone
Ananthakrishnan *et al*[18] United States	Inflamm Bowel Dis 2011	Case-control analysis of NIS database, out-/in-patients; 1998, 2004, 2007	Increase in colectomy rate from 1998 (OR = 1.39, 95%CI: 0.81-2.37) to 2007 (OR = 2.51, 95%CI: 1.90-3.34) ($P = 0.03$), and in mortality risk (1998: OR = 2.38, 95%CI: 1.52-3.72) (2007, OR = 3.38, 95%CI: 2.66-4.29) ($P = 0.15$)
Kaneko *et al*[25] Japan	Clin Res Hepatol Gastroenterol 2011	Out-/in-patients; 2006-2009	No association between CDI and colectomy rate in UC patients
Kariv *et al*[20] United States	J Crohns Colitis 2011	Out-/in- patients with UC; 2000-2006	No difference in colectomy rates (48% *vs* 50.9%, $P = 0.81$) between infected and non-infected UC patients, no mortality in UC patients with or without CDI
Jodorkovsky *et al*[19] United States	Dig Dis Sci 2010	In-patients; 2004/06-2005/06	Similar mean LOS for IBD patients with CDI and those without CDI (11.7 d *vs* 11.0 d; $P = 0.70$); similar use of cyclosporine therapy (48% *vs* 47%); higher emergent colectomy rate (23% *vs* 13.4%, $P = 0.17$)
Bossuyt *et al*[14] Belgium	J Crohns Colitis 2009	In-patients; 2000-2008	LOS shorter as compared to non-IBD patients (15.2 d *vs* 27.7 d, $P = 0.001$); one patient with UC+ CDI had a semi-urgent colectomy; no mortality in IBD patients, 2 deaths in non-IBD patients
Ricciardi *et al*[15] United States	Dis Colon Rectum 2009	Case-control analysis of NIS database, out-/in-patients; 1993-2003	Increased case fatality in UC+CDI patients but not in those with CD+CDI; operative mortality for UC+CDI patients reached 25.7%
Ben-Horin *et al*[26] Israel and some European countries	Clin Gastroenterol Hepatol 2009	Multi-center, in-patients; 2000-2008	Low colectomy rate (6%) in IBD patients with CDI
Ananthakrishnan *et al*[13] United States	Gut 2008	Case-control analysis of NIS database, out-/in-patients; 2003	Four-fold higher mortality rate (OR = 4.7, 95%CI: 2.9-7.9) compared with IBD alone and twice higher than in those with CDI alone (OR = 2.21, 95%CI: 1.4-3.4); 3-d longer compared with IBD alone; six-fold greater risk of bowel surgery than those with CDI alone (OR = 6.6, 95%CI: 4.7-9.3); 11406 higher hospital adjusted charges
Nguyen *et al*[16] United States	Am J Gastroenterol 2008	Case-control analysis of NIS database, out-/in-patients; 1998-2004	Increased mortality in UC (OR = 3.79, 95%CI: 2.84-5.06) but not in CD patients (OR = 1.66, 95%CI: 0.75-3.66); increased LOS with 65% for CD and 46% for UC, and increased hospital charges compared with non-IBD patients
Rodemann *et al*[12] United States	Clin Gastroenterol Hepatol 2007	In-patients, 1998-2004	LOS similar to non-IBD patients
Issa *et al*[11] United States	Clin Gastroenterol Hepatol 2007	Observational study, out-/in-patients; 2004-2005	Increased LOS (13 d *vs* 6 d); the colectomy rate in UC+CDI decreased from 45% in 2004 to 25% in 2005

C. difficile: *Clostridium difficile*; CDI: *Clostridium difficile* infection; CD: Crohn's disease; IBD: Inflammatory bowel disease; LOS: Length of hospital stay; NIS: National Inpatient Sample; OR: Odds ratio; UC: Ulcerative colitis.

regimen (use the vancomycin as a primary antibiotic, and a rapid decrease in steroid dosing)[11]. Using data from NIS, Ananthakrishnan *et al*[18] reported a significant increase in total colectomy odds from 1998 (OR 1.39, 95% CI: 0.81-2.37) to 2007 (OR = 2.51, 95%CI: 1.90-3.34) ($P = 0.03$) in IBD patients with CDI compared to IBD patients without CDI. Jen *et al*[17] using HES data for 2002/03 to 2007/08 found that IBD patients with CDI were exposed to a risk of undergoing gastrointestinal surgery or emergency colectomy 1.2 to 3 times higher than those with IBD alone.

In contradiction with previously mentioned studies, others communicated low rates of urgent colectomy in IBD patients with CDI. Thus, according to two recent studies from Cleveland Clinic's Digestive Disease Institute, United States, CDI in UC patients had no negative impact on colectomy risk within 3 mo of CDI diagnosis. In one study[20] including 78 patients (39 patients with UC and CDI, 39 with UC alone), 25 underwent colectomy, 12 of whom (48%) were among those with UC and CDI, and 13 (50.9%) with UC alone ($P = 0.81$). Also, in the second study[24], including 146 patients (45 with UC and CDI, 101 with UC without CDI), within 3 mo of index admission there was no significant difference concerning colectomy risk between UC patients with CDI and those without CDI; however, on long-term follow-up (one

Table 2 Long-term outcomes in inflammatory bowel disease patients with *Clostridium difficile* infection compared to those with inflammatory bowel disease alone

Ref.	Journal and year of publication	Study design and time frame	Outcome
Murthy *et al*[21] Canada	Aliment Pharmacol Ther 2012	In-patients; 2002-2008	UC patients with CDI was associated with increased adjusted 5-yr risk of mortality, but not of colectomy, as compared with UC without CDI
Navaneethan *et al*[24] United States	J Crohns Colitis 2012	Out-/in-patients; 2002-2007	One year following CDI: increased rates of ERV (37.8% *vs* 4%, $P = 0.001$) and colectomy (35.6% *vs* 9.9%, $P = 0.001$); escalation in medical therapy in 58.8% as compared to the prior year (12.9%) ($P = 0.0001$)
Jodorkovsky *et al*[19] United States	Dig Dis Sci 2010	In-patients; 2004-2005	One year following CDI: UC patients with CDI had increased rate of ERV (8 *vs* 1, $P = 0.012$), higher number of UC– related hospitalizations (58 *vs* 27, $P = 0.001$), and two-fold higher rates of colectomy (44.6% *vs* 25%, $P = 0.04$) compared to UC alone
Chiplunker *et al*[27] United States	Gastroenterology 2009	Case-control, in-patients; 2005-2006	One year following CDI: over half required an escalation in their IBD medical therapy, 46% had more hospitalisations, colectomy occured in 10.3% , and no mortality

CDI: *Clostridium difficile* infection; ERV: Emergency room visits; IBD: Inflammatory bowel disease; OR: Odds ratio; UC: Ulcerative colitis.

year), UC patients with CDI showed a significantly higher rate of colectomy than those without CDI. Kaneko *et al*[25] in a retrospective study from Yokohama City University Medical Center, Japan, reported that CDI did not have an impact on colectomy rate in their hospitalized UC patients with active disease, the difference in colectomy rate between UC+CDI patients (33.6%) and those without CDI (23.1%) being statistically insignificant (OR = 1.03, 95%CI: 0.41-2.63; $P = 0.94$). Two European studies[14,26] also reported low rates of colectomy (5% and 6%, respectively) in IBD patients co-infected with *C. difficile*. Recently, Murthy *et al*[21] found a similar rate of colectomy between UC patients with and without CDI (12% *vs* 9.8%, $P = 0.30$).

The different colectomy rates between single-center studies and those using nationwide data could be partially accounted for by differences in healthcare practice and threshold for surgery, response to CDI medical therapy, and data collection methods used[23].

Mortality rates are higher in IBD patients with CDI than in those without CDI or with CDI alone[13,16,17,21]. Among IBD patients, mortality is higher in UC than in CD[16]. All studies analysing nationwide databases reported high rates of mortality in IBD patients with CDI[13,16,17,21]. Nguyen *et al*[16] analyzed NIS discharge records from 1998 to 2004 and found that CDI was associated with a nearly four fold increase in mortality among hospitalized patients with UC (OR 3.79, 95% CI: 2.84-5.06) unlike those with CD (OR = 1.66, 95%CI: 0.75-3.66) as compared to non-IBD patients. Similarly, Ananthakrishnan *et al*[13], using also data from NIS, found that IBD patients with superimposed CDI had a four fold increase in mortality compared to patients hospitalized with IBD alone (OR = 4.7; 95%CI: 2.9-7.9) and twice higher than those with CDI alone (OR = 2.2, 95%CI: 1.4-3.4). In contrast to Nguyen *et al*[16] study, where mortality was higher only in UC, this study reported an increased mortality rate in both UC and CD patients. Jen *et al*[17] using HES data, reported that for the studied period (2002-2008), IBD patients with CDI were approximately six times more likely to die in hospital than those admitted for IBD alone (adjusted OR = 6.32, 95%CI: 5.67-7.04), and suggested that such high mortality rate may be partially due to increased number of all emergency gastrointestinal surgery and colectomy rates during admissions. Murthy *et al*[21] also reported a higher mortality rate in hospitalized UC patients co-infected with *C. difficile* than in uninfected UC patients (3.3% *vs* 0.38%, $P = 0.0001$).

Nevertheless, other studies showed a mortality rate for IBD patients with CDI similar to or not statistically higher than what was reported for non-infected IBD patients[14,18]. Thus, Bossuyt *et al*[14] registered no deaths among their patients with UC and CDI, while Ananthakrishnan *et al*[18] found a non-significant increase in the relative mortality risk in IBD patients with superimposed CDI from 1998 (OR = 2.38, 95%CI: 1.52-3.72) to 2007 (OR = 3.38, 95%CI: 2.66-4.29; $P = 0.15$).

LONG-TERM OUTCOMES

Few studies reported on long-term outcomes after an initial episode of CDI in IBD patients (Table 2)[19,21,24,27]. In a retrospective study including 47 patients with UC and CDI and 52 with UC without CDI, Jodorkovsky *et al*[19] reported that, over the year following the initial infection episode, a significant increase in the number of visits to the emergency room (8 *vs* 1, $P = 0.012$) was registered, as well as a higher number of UC-related hospitalizations (58 *vs* 27, $P = 0.001$) and a two-fold increase in colectomy rate (44% *vs* 25%, OR = 2.38, 95%CI: 1.01-5.6; $P = 0.04$) as compared to UC patients without CDI. Murthy *et al*[21], in a retrospective cohort study of UC patients with and without CDI, found that CDI was associated with higher adjusted 5-year risk of mortality [adjusted hazard ratio (aHR) = 2.40, 95%CI: 1.37-4.20], but not of colectomy (aHR = 1.18, 95%CI: 0.90-1.54). In another retrospective study[24], UC patients with CDI had significantly more UC-related emergency room visits (37 *vs* 4, $P < 0.001$) and a higher rate of colectomy (35.6% *vs* 9%, $P < 0.001$)

than those with UC alone in the year following initial infection. In addition, 55.8% of patients with UC and CDI had an escalation in medical therapy in the year after index infection admission as compared to 12.9% in the previous year ($P < 0.0001$). In a multivariate analysis for risk factors of colectomy, severe disease on endoscopy (OR = 16.7, 95%CI: 4.1-67.9; $P < 0.001$) and CDI (OR = 10.0, 95%CI: 2.7-36.3; $P < 0.001$) were found to be independently associated with colectomy within 1 year. Chiplunker *et al*[27] in a retrospective, case-control study on 81 patients with IBD comparing disease progression 1 year before and 1 year after the initial infection with *C. difficile*, found that 46% of patients had more hospitalizations and over a half of them (53%) required an escalation in medical therapy during the year following CDI. No deaths occurred during the 1 year follow-up.

Healthcare costs are higher in IBD patients with CDI than in those with IBD alone due to longer hospital stay, higher number of IBD-related hospitalizations, increased need for surgery, and hospital care charges[13,16]. Nguyen *et al*[16] found a mean cost increased by 46% and 63% for UC and CD patients, respectively, while Ananthakrishnan *et al*[13] reported higher increased hospital adjusted expenses of US$ 11406.

DISCUSSION

The majority of published studies (90%) found by searching Medline and other databases aim to assess CDI incidence in IBD patients, while only 10% of them report on outcome following infection. All studies reporting on outcome in IBD patients with concomitant CDI were retrospective, small single-center cohort studies or large nationwide database studies mostly conducted in North America and Europe. Apart from being retrospective, available studies on outcome have several other limitations such as incomplete information on disease severity, absence of reference to *C. difficile* diagnosis, antibiotic and immunomodulatory therapy. It should be underlined that most of analyzed studies relate to hospitalized IBD patients in the early 2000s, when enzyme immunoassay of stool for *C. difficile* toxins A and B has dominated the laboratory diagnosis of CDI, despite its low sensitivity.

Though few in number, studies reporting outcomes associated with CDI in IBD patients most often show that CDI has a negative impact both on short- and long-term IBD outcomes, increasing the need for surgery, morbidity and mortality rates, as well as healthcare costs[11,13,16-18,21,24,27]. Both major forms of IBD are under increasing risk for CDI, although patients with UC are most susceptible to infection and have more severe outcomes[15,16,19]. Short-term outcomes, defined as those measured within 30-90 d of index admission, include length of hospital stay, colectomy and mortality rates. Long-term outcomes, measured at least 1 year following index admission, include emergency room visits, UC-related hospitalizations, escalation in medical therapy, colectomy and mortality rates.

Studies report conflicting results on the length of hospital stay in IBD patients with concomitant CDI: some found similar stays[12,19], others shorter ones[14], while most of them reported longer hospitalization periods than in IBD patients without CDI or with CDI alone[11,13,16,17,21]. Similar or shorter hospitalization periods were reported by single-center studies[12,14,19], while longer stays were found in studies using nationwide databases[13,16,17,21]. Discrepancies between studies may be explained by disease severity and response to medical therapy in IBD patients included in the analyses.

Contrasting results have also been reported with regard to colectomy rates in IBD patients with CDI[11,13,14,17-21,24-26]. Thus, some studies analyzing nationwide data (US NIS HCUP, UK HES) reported high colectomy rates[13,18], while other single-center ones[20,24,25] found CDI to have no negative impact on colectomy rate in UC patients. There are discrepancies in what concerns colectomy rates even between studies using nationwide data in North America[13,18] and Europe[17], probably due to differences in data collection methods and threshold for surgery[23]. In addition, studies analyzing nationwide data for colectomy also include IBD patients admitted for elective surgery, a fact which can contribute to high colectomy rates[23]. Lower risks for colectomy, as reported by single-center North-American[20] and European[14,26] studies, may be partially explained by CDI prompt response to medical therapy, followed by clinical remission of IBD flare, thus preventing surgery[20].

Variable results regarding mortality rate in IBD patients with concomitant CDI are also to be noted[13,14,16-18,21]. High mortality rates reported by some studies using nationwide data[13,16,17] may be accounting for by to the increased use of colectomy in IBD patients with CDI[20], and also by the inclusion of all hospitalized patients who presumably have more severe disease than those from cohort studies[17,23].

Few studies reported long-term outcomes after an initial CDI episode in IBD (UC) patients. Two[19,24] reported an increased number of visits to the emergency room and in UC-related hospitalizations, and higher colectomy rate than in patients with UC alone in the year following initial infection. UC patients with CDI had an escalation in medical therapy 1 year after index admission as compared to the previous year[24,27]. Another study including UC hospitalized patients with and without CDI, found that those with associated CDI had a higher adjusted 5-year risk of mortality, but not of colectomy[21].

We may add that only one study aimed to identify predictive factors for severe outcomes (colectomy, death) associated with CDI in IBD patients[28]. Ananthakrishnan *et al*[28] in a retrospective study using multi-institutional electronic medical record database from two large referral hospitals over the period 1998-2010, reported a 4.4% colectomy and 15.2% mortality rates during 180-d follow-up of 294 IBD patients with CDI (mostly with UC), and found that among several demographic variables and laboratory parameters, only serum albumin below 3

g/dL, hemoglobin below 9 g/dL, and serum creatinine above 1.5 mg/dL were independent predictors of severe outcomes[28].

CDI IN IBD PATIENTS FOLLOWING SURGICAL INTERVENTION

Clostridium difficile enteritis usually occurs in IBD patients who have undergone colonic surgery, mainly proctocolectomy[29-31]. *C. difficile* enteritis is generally rare, although the number of cases reported in literature has recently increased[32]. The predisposition of IBD patients with previous colonic surgery to *C. difficile* enteritis may be accounted for by the colonization of the neo-terminal ileum with colonic-type bacterial flora[33], and phenotypic changes in the epithelium of pelvic ileoanal pouches[34]. *C. difficile* enteritis diagnosis and treatment are similar to that for colonic CDI. If some studies reported increased mortality among patients with *C. difficile* enteritis[35], other ones found low or even no mortality[29].

Clostridium difficile pouchitis has been reported in IBD patients with ileal pouch anal anastomosis (IPAA)[36-38]. Shen *et al*[36] found that 18.3% of their 115 patients with IPAA had CDI. Morphologic changes in the pouch epithelium secondary to prolonged exposures to fecal stream may favor CDI[34]. In addition, frequent antibiotic treatment for acute or chronic pouchitis is another risk factor for CDI in such patients[36]. Recently, Tyler *et al*[39] reported that genetic polymorphisms, particularly the NOD2insC risk allele, are associated with increased risk of developing pouch inflammation among patients with UC and IPAA. Treatment with vancomycin, tinidazole, or rifaximin has been used with benefit in many patients[37,38].

CONCLUSION

IBD patients with CDI are under a higher risk of worse outcomes than those without CDI. Because the available data are often conflicting and obtained from retrospective studies, further prospective multi-center studies are required to evaluate the impact of CDI on IBD outcomes. Until then, to improve patient outcome, clinicians should have a high index of suspicion for CDI in all IBD patients presenting with a disease flare in order to rapidly establish diagnosis and prompt treatment of infection.

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P- Reviewer: Barkin JA, Ozen H, van Langenberg DR
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
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ISSN 1007-9327

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