

# World Journal of *Gastroenterology*

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Editorial board member of *World Journal of Gastroenterology*, Takeshi Ogura, MD, PhD, Associate Professor, 2<sup>nd</sup> Department of Internal Medicine, Osaka Medical College, Takatsukishi 464-8681, Japan

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E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
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# Management of inflammatory bowel disease with *Clostridium difficile* infection

Julie D'Aoust, Robert Battat, Talat Bessissow

Julie D'Aoust, Division of Internal Medicine, Jewish General Hospital, Montreal QC H3G 1A4, Canada

Robert Battat, Division of Gastroenterology, Jewish General Hospital, Montreal QC H3G 1A4, Canada

Robert Battat, Talat Bessissow, Division of Gastroenterology, McGill University Health Centre, Montreal QC H3G 1A4, Canada

**Author contributions:** D'Aoust J and Battat R should be as co-first authors and contributed equally to the study; D'Aoust J, Battat R and Bessissow T planning and conducting the study; D'Aoust J, Battat R and Bessissow T collected data, drafting the manuscript.

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**Correspondence to:** Talat Bessissow, MD, FRCPC, Division of Gastroenterology, McGill University Health Centre, 1650 Avenue Cedar C7-200, Montreal QC H3G 1A4, Canada. [talat.bessissow@mcgill.ca](mailto:talat.bessissow@mcgill.ca)  
Telephone: +1-514-9341934  
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## Abstract

### AIM

To address the management of *Clostridium difficile* (*C. difficile*) infection (CDI) in the setting of suspected inflammatory bowel disease (IBD)-flare.

### METHODS

A systematic search of the Ovid MEDLINE and EMBASE databases by independent reviewers identified 70 articles including a total of 932141 IBD patients or IBD-related hospitalizations.

### RESULTS

In those with IBD, CDI is associated with increased morbidity, including subsequent escalation in IBD medical therapy, urgent colectomy and increased hospitalization, as well as excess mortality. Vancomycin-containing regimens are effective first-line therapies for CDI in IBD inpatients. No prospective data exists with regards to the safety or efficacy of initiating or maintaining corticosteroid, immunomodulator, or biologic therapy to treat IBD in the setting of CDI. Corticosteroid use is a risk factor for the development of CDI, while immunomodulators and biologics are not.

### CONCLUSION

Strong recommendations regarding when to initiate IBD specific therapy in those with CDI are precluded by a lack of evidence. However, based on expert opinion and observational data, initiation or resumption of immunosuppressive therapy after 48-72 h of targeted antibiotic treatment for CDI may be considered.

**Key words:** Biologic therapy; *Clostridium difficile*;

Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Corticosteroids

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**Core tip:** *Clostridium difficile* infection (CDI), common and increasing in inflammatory bowel disease (IBD), is associated with worse outcomes in IBD. Vancomycin-containing regimens are effective first-line therapies for CDI in IBD. Ambiguity exists on the treatment of IBD flare in patients with CDI; however, case reports suggest corticosteroid initiation after appropriate antibiotic therapy may be effective.

D'Aoust J, Battat R, Bessissow T. Management of inflammatory bowel disease with *Clostridium difficile* infection. *World J Gastroenterol* 2017; 23(27): 4986-5003 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i27/4986.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i27.4986>

## INTRODUCTION

Inflammatory bowel disease (IBD), comprised of Crohn's disease (CD) and ulcerative colitis (UC), are chronic, idiopathic inflammatory gastrointestinal disorders. The pathogenesis of IBD, although incompletely understood, is thought to arise from interactions between environmental and host factors. CD and UC are characterized by recurrent episodes of relapsing inflammation of the gastrointestinal tract with variable clinical manifestations and potentially serious complications including bleeding, perforation and abscess formation<sup>[1,2]</sup>.

*Clostridium difficile* (*C. difficile*), a gram-positive spore-forming anaerobe, is highly transmissible through the fecal-oral route and its exotoxins cause a spectrum of disease ranging from mild or moderate diarrhea to fulminant infectious colitis occasionally complicated by toxic megacolon, colonic perforation, sepsis, and death<sup>[3]</sup>.

Several diagnostic assays exist to assess for *Clostridium difficile* infection (CDI). DNA-based tests or nucleic acid amplification tests *via* polymerase chain reaction (PCR) for *C. difficile* toxin genes (*tcdA* and *tcdB*) have been found to be more sensitive than toxin A and B enzyme immunoassays (EIA) and are currently recommended as the preferred diagnostic test for CDI<sup>[4]</sup>. Other, less commonly used diagnostic assays for CDI include EIA for glutamate dehydrogenase (GDH, a protein produced by both toxigenic and non-toxigenic strains) with confirmatory testing *via* EIA for toxin genes. This has fallen out of favor in view of the more sensitive and rapid PCR assay. The advent of DNA-based testing may partially contribute to the observed increased incidence of CDI. Toxigenic culture is considered to be the gold standard

diagnostic assay, albeit the slowest, requiring several days to result and therefore possibly delaying initiation of therapy.

While *C. difficile* is often pathogenic and accounts for significant morbidity and mortality in the health-care and community setting, it has also been found to colonize the stool of healthy children and adults<sup>[5-7]</sup>. CDI is most commonly defined as the presence of *C. difficile* toxin in the context of characteristic clinical manifestations including diarrhea and abdominal pain<sup>[4]</sup>. CDI rates are increasing in the general population. Health care institutions have seen large outbreaks of CDI as well as the emergence of hypervirulent strains<sup>[8-10]</sup>. Surveillance of CDI in the United States has demonstrated a shift in the epidemiology to more community-acquired infections. A nationwide study of CDI in the United States using Emerging Infections Program data from the Centers for Disease Control estimated 453000 incident infections in 2011, of which only 24% were identified during hospitalization, as opposed to the outpatient setting<sup>[11]</sup>.

Decreased intestinal microbial diversity along with an inadequate immune response is thought to play a causative role in the development CDI<sup>[12-14]</sup>. Antibiotic exposure, leading to alterations in the gut microbiota, has been identified as a traditional risk factor for CDI. IBD also predisposes to CDI and accounts for considerable excess morbidity and mortality along with increased systemic costs in IBD patients. Reductions in gut microbial diversity as well as an increase in pro-inflammatory species have been identified in IBD patients<sup>[15]</sup>. Although a causative role for this dysbiosis in the development of IBD has not been well established, it is plausible that dysbiosis may play a role in increasing CDI risk in IBD patients. Due to an overlap in symptomatology, CDI also gives rise to a series of diagnostic and therapeutic challenges in the IBD population.

This systematic review aims to summarize the management of patients with CDI and concurrent, suspected IBD flares. The epidemiology, risk factors, and methods of diagnosis for CDI in IBD patients are also summarized.

## MATERIALS AND METHODS

### Data sources and searches

We performed a systematic search of MEDLINE and Ovid EMBASE databases (Figure 1). Eligibility criteria for included studies were decided a priori. Two authors (D'Aoust J and Battat R) independently judged study eligibility. "Clostridium difficile", "pseudomembranous colitis", "inflammatory bowel disease", "Crohn's disease", and "ulcerative colitis" were used as search terms. MESH subheadings were combined using the Boolean operators "AND" and "OR" for full articles published in the English language between 1946 and the third week of January 2017. Additional publications

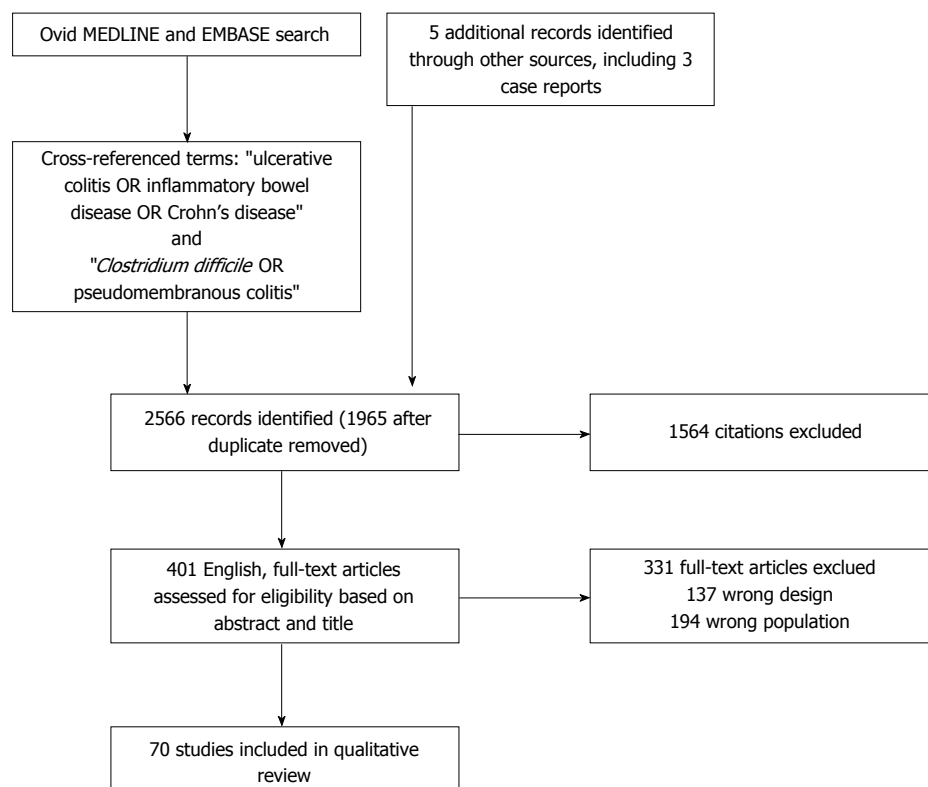


Figure 1 Search strategy for the selection of articles on *Clostridium difficile* infection in inflammatory bowel disease.

were retrieved from included studies and relevant review articles. Publications identified as duplicates were excluded. Cases of disagreement were resolved by discussion and joint analysis of articles by two reviewers (D'Aoust J and Battat R).

### Study selection

Study titles and abstracts obtained from database searches were reviewed to identify those addressing CDI in IBD. Studies analyzing adult and pediatric patients were included. Case reports and case series were included if the management of IBD and CDI was discussed, due to limited data on this topic. Articles not pertaining to this topic in the title or abstract were excluded. Letters, editorials, and review articles were excluded. Data referring to the incidence, risk factors, diagnosis, management, and outcomes of *C. difficile* infection in patients with IBD were extracted from the articles. Data extraction was performed and agreed on by two authors (D'Aoust J and Battat R).

## RESULTS

The search strategy, summarized in Figure 1, revealed 396 full-texts, English-language articles. Sixty-five articles were retained from the database search after applying the exclusion criteria. Two additional articles were retrieved from references. Two case reports discussing the management of CDI with corticosteroids were included. One additional case series on this topic

was retrieved from relevant references for inclusion. Articles retained included a total of 932141 IBD patients or IBD-related hospitalizations (526765 UC; 312240 CD; 161 IC; 92 975 not-reported).

## DISCUSSION

### Epidemiology of CDI in IBD

Both an increasing burden of disease, as well as preponderance for community-acquired infection is reflected in the IBD population. Several studies have documented the changes in CDI epidemiology over time in IBD patients (Table 1). In adult inpatients with IBD, CDI incidence increased two to threefold in the early 2000s and more so in pediatric populations, with the largest rise in incidence among UC patients<sup>[16-19]</sup>. Several studies demonstrate a disproportionate rise in CDI in the IBD population as compared to the general population<sup>[16,17]</sup>, while others do not<sup>[20]</sup>.

The epidemiological studies of CDI in IBD are heterogeneous with regards to patient population, disease activity, sampling time frame, and diagnostic assay sensitivity. Reported incidences of CDI in pediatric and adult populations reflect this heterogeneity (Table 1). In mixed inpatient and outpatient adult IBD populations, the incidence of CDI ranges between 5.1%-16.7%<sup>[21-25]</sup>.

Studies report the incidence of CDI in CD adult inpatients between 1.0 and 7.7%<sup>[26-30]</sup>. In adult UC inpatients, the incidence of CDI ranges from 2.8%

**Table 1** Epidemiology of *Clostridium difficile* infection in inflammatory bowel disease

Ref.	Patient population	Sampling time frame	Diagnosis method	Disease activity	Conclusions
Keighley <sup>[92]</sup> (1983)	IBD adult inpatients	1978-1980	Stool culture on selective medium + cytotoxicity assay	Active	CDI incidence (%) IBD: 5.7; UC 4.7; CD 6.3
Gurian <i>et al</i> <sup>[93]</sup> (1983)	IBD adult inpatients and outpatients	1980-1981	Stool culture on selective medium + cytotoxicity assay	Active	CDI incidence (%) IBD: 0
Rolny <i>et al</i> <sup>[26]</sup> (1983)	IBD adult inpatients	1980-1981	Stool culture on selective medium + cytotoxicity assay	Active	CDI incidence (%) UC: 5; CD: 7.7
Greenfield <i>et al</i> <sup>[21]</sup> (1983)	IBD adult inpatients and outpatients	1980-1981	Stool culture on selective medium + cytotoxicity assay	Mixed	CDI incidence (%) UC: 13.7; CD: 13.2
Burke <i>et al</i> <sup>[94]</sup> (1987)	IBD adult outpatients	1984-1986	Stool culture on selective medium + cytotoxicity assay	Active	CDI incidence (%) IBD 3.2
Gryboski <sup>[95]</sup> (1991)	IBD pediatric inpatients and outpatients	1986-1990	Stool culture on selective medium + cytotoxicity assay	Active	CDI incidence (%) IBD 16; UC: 18; CD 14
Meyer <i>et al</i> <sup>[22]</sup> (2004)	IBD adult inpatients and outpatients	2000-2001	Immunoassay for Toxin A until 2001 then EIA for Toxin A/B	Active	CDI incidence (%) IBD: 16.7; UC: 12.5; CD: 23.8; IC: 11.1
Mylonaki <i>et al</i> <sup>[23]</sup> (2004)	IBD adult inpatients and outpatients	1997-2001	ELISA for Toxins A/B	Active	CDI incidence (%) IBD: 5.5; CD: 13.2
Issa <i>et al</i> <sup>[24]</sup> (2007)	IBD adult inpatients and outpatients	2005	ELISA for Toxins A/B	Active	CDI incidence (%) UC: 6.1; CD: 4.1 IBD patients accounted for 4% of the total CDI patient cohort in 2003, 7% in 2004, and 16% in 2005
Rodemann <i>et al</i> <sup>[16]</sup> (2007)	IBD pediatric and adult inpatients (United States)	1998-2004	Cell cytotoxic culture	Active	CDI incidence (%) UC: 3.9; CD: 1.6
			2002 onwards <i>C. difficile</i> Toxin A/B immunoassay		CDI incidence increase: UC > CD > non-IBD Non-IBD population: 8.5 to 15.9/1000 admissions CD: 9.5 to 22.3/1000 admissions UC: 18.4 to 57.6/1000 admissions
Shen <i>et al</i> <sup>[33]</sup> (2008)	UC adult outpatients with IPAA	2005-2006	ELISA for Toxin A/B	Mixed	CDI incidence (%) UC: 18.3
Bossuyt <i>et al</i> <sup>[20]</sup> (2009)	IBD and non-IBD CDI adult inpatients	2000-2008	EIA for Toxin A until 2005, then EIA for Toxins A/B	Active	All patients: 3.75-fold increase in CDI between 2000-2003 and 2004-2008
Balamurugan <i>et al</i> <sup>[96]</sup> (2008)	UC adult outpatients	2004-2005	PCR for <i>C. difficile</i> Toxin A/B ELISA	Mixed	CDI incidence (%) UC: 92
Ananthakrishnan <i>et al</i> <sup>[18]</sup> (2008)	IBD and non-IBD CDI adult inpatients	1998-2004	N/R	N/R	CDI incidence increase: UC: 24 to 39/1000 discharge ; CD: 8 to 12/1000 discharges
Nguyen <i>et al</i> <sup>[17]</sup> (2008)	IBD and non-IBD adult inpatients	1998-2004	N/R	N/R	CDI incidence increase: UC: 26.6 to 51.2/1000 discharges
Pascarella <i>et al</i> <sup>[35]</sup> (2009)	IBD pediatric inpatients	2005-2007	Enzyme immunoassay for toxins A/B	Mixed	CDI incidence (%) UC: 21.3; CD: 35
Ricciardi <i>et al</i> <sup>[27]</sup> (2009)	IBD adult inpatients	1993-2003	N/R	Active	CDI incidence (%) UC: 2.8; CD: 1.0 CDI incidence increase: IBD: 12.2 to 21/1000 discharges; CD + colonic involvement: 12.2 to 23.1/1000 discharges
Wultańska <i>et al</i> <sup>[36]</sup> (2010)	IBD pediatric outpatients	2005-2007	EIA for Toxins A/B or PCR	Mixed	CDI incidence (%) IBD: 60; UC: 61; CD: 59
Ananthakrishnan <i>et al</i> <sup>[38]</sup> (2011)	IBD adult inpatients	1998, 2004, 2007	N/R	N/R	CDI incidence increase: CD: 0.8 to 1.5% of hospitalizations; UC: 2.4 to 5.3% of hospitalizations Absolute mortality increase in CDI + IBD (5.9% to 7.2%)
Kaneko <i>et al</i> <sup>[46]</sup> (2011)	UC pediatric and adult inpatients and outpatients	2006-2009	ELISA for Toxin A	Active	CDI incidence (%) UC inpatient: 36.6; UC outpatient: 41.7
Mezoff <i>et al</i> <sup>[37]</sup> (2011)	IBD pediatric patients	2007-2008	EIA for Toxins A and B	Mixed	CDI incidence (%) UC: 5.8; CD: 7.8; IC: 11.1
Ott <i>et al</i> <sup>[28]</sup> (2011)	IBD adult inpatients	2001-2008	ELISA for Toxins A/B or characteristic histology	Active	CDI incidence (%) IBD: 4.0; CD: 13.2; UC: 4.7
Banaszkiewicz <i>et al</i> <sup>[38]</sup> (2012)	IBD pediatric inpatients	2007-2010	EIA for Toxins A and B	Mixed	CDI incidence (%) IBD: 47
Antonelli <i>et al</i> <sup>[29]</sup> (2012)	IBD adult inpatients	2007-2010	N/R	Active	CDI incidence (%) UC: 11.1; CD: 1.7
Murthy <i>et al</i> <sup>[31]</sup> (2012)	UC adult inpatients	2002-2008	N/R	Active	CDI incidence (%) UC: 9.0
Lamoué-Smith <i>et al</i> <sup>[97]</sup> (2013)	IBD pediatric inpatients and outpatients (United States)	2006-2012	PCR for Toxin B +/- ELISA for Toxin A/B	Mixed	CDI incidence (%) UC: 18.4; CD: 11.6



Masclee <i>et al</i> <sup>[47]</sup> (2013)	IBD adult outpatients	2009-2010	PCR for <i>C. difficile</i> and Toxin A/B	Active	CDI incidence (%) IBD: 4.9; UC: 3.4; CD: 5.9
Mir <i>et al</i> <sup>[39]</sup> (2013)	IBD pediatric patients	2010-2012	EIA or PCR for Toxin A/B	N/R	CDI incidence (%) IBD: 8.1; UC: 5.6; CD: 9.3; IBUD: 11.1 No significant variation in IBD incidence over 3 yr
Pant <i>et al</i> <sup>[98]</sup> (2013)	IBD pediatric inpatients	2000, 2003, 2006, 2009	N/R	N/R	CDI incidence increase: IBD: 21.7 to 28 cases/1000 IBD cases per year; UC: 28.1 to 42.2/1000 cases per year; CD: 18.3 to 20.3/1000 cases per year
Li <i>et al</i> <sup>[34]</sup> (2013)	IBD adult outpatients with IPAA	2010-2011	PCR for Toxin B gene	Active	CDI incidence (%) IBD: 10.7; UC: 10.4; CD: 0; IC: 25.0
Martinelli <i>et al</i> <sup>[40]</sup> (2014)	IBD pediatric inpatients and outpatients	2010-2011	EIA for Toxins A/B	Mixed	CDI incidence (%): IBD: 10.0; UC: 7.5; CD: 11.9
Regnault <i>et al</i> <sup>[30]</sup> (2014)	IBD adult inpatients	2008-2010	Stool culture on selective medium + cytotoxicity assay +/- toxigenic culture	Active	CDI incidence (% hospitalizations): IBD: 7.0; UC: 6.8; CD: 7.2
Negrón <i>et al</i> <sup>[32]</sup> (2014)	UC adult inpatients	2000-2009	EIA for Toxins A/B	Active	CDI incidence (%) UC: 6.1
Hourigan <i>et al</i> <sup>[99]</sup> (2014)	IBD and non-IBD pediatric and adult inpatients	1993-2012	N/R	N/R	CDI incidence increase: IBD: 19.9 to 67/1000 admissions Rate of increase in CDI not significantly different between patients with or without IBD
Krishnarao <i>et al</i> <sup>[25]</sup> (2015)	IBD adult inpatients and outpatients	2008-2011	EIA and PCR	Mixed	CDI incidence (%) IBD: 5.1
Sandberg <i>et al</i> <sup>[19]</sup> (2015)	IBD pediatric inpatients	1997-2011	N/R	N/R	Hospitalization rate increase: CDI + IBD: 2.8 to 14.4 per million population per year Rate of increase for UC + CDI = CD + CDI
Simian <i>et al</i> <sup>[100]</sup> (2016)	IBD adult and pediatric inpatients and outpatients	2014-2015	PCR	N/R	CDI incidence (%) UC: 5.0; CD: 5.0
Roy <i>et al</i> <sup>[101]</sup> (2016)	CD adult outpatients on chronic antibiotic therapy > 6 mo	1992-2015	N/R	N/R	CDI incidence (%) CD: 2.0

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's Disease; IC: Indeterminate colitis; IBUD: Inflammatory bowel disease unclassified; IPAA: Ileal anal-pouch anastomosis; EIA: Enzyme immunoassay; ELISA: Enzyme linked immunosorbent assay; PCR: Polymerase chain reaction; N/R: Not reported.

to 11.1%<sup>[26-32]</sup>. In adult outpatients with ileal-anal pouch anastomosis (IPAA) for IBD, incidence of CDI is 10.7%-18.3%<sup>[33,34]</sup>. The incidence of CDI in IBD among pediatric patients is 7.8%-69%, similarly with a higher incidence among patients with UC as opposed to CD<sup>[35-40]</sup>.

### Risk factors for CDI in IBD

In patients with CDI and IBD, risk factors are categorized into environmental and host risk factors, including those specific to IBD. Several studies have demonstrated that IBD itself is an independent risk factor for CDI in both adult and pediatric populations<sup>[16,35,41]</sup>.

In the general population, many host and environmental risk factors have been identified. These include antibiotic exposure, specifically broad-spectrum antibiotics, as well as recent hospitalization, immunosuppression, increased age, and comorbidities<sup>[42]</sup>.

In IBD populations, risk factors for CDI appear to be partly distinct (Table 2). Evidence is contradictory regarding antibiotic use as a risk factor for CDI in IBD patients. Three retrospective studies identified

recent antibiotic use as a risk factor for CDI and recurrent CDI in both CD and UC<sup>[23,43,44]</sup>. In one study, antibiotic exposure within 30 d prior to *C. difficile* testing was associated with a twelve-fold risk of CDI in UC patients (95%CI: 1.2-124.2)<sup>[43]</sup>. Several others contradict this<sup>[30,34,35,43,45-47]</sup>. Scarce evidence supports nonsteroidal anti-inflammatories (NSAIDs) and proton pump inhibitors (PPIs) as risk factors for CDI in IBD. One retrospective cohort study of 480 IBD patients hospitalized for a flare who also underwent *C. difficile* testing, describes NSAID use within two months prior to admission as a predisposing factor for CDI (OR = 3.8, 95%CI: 1.2-12.3,  $P = 0.02$ )<sup>[30]</sup>. No studies have identified gastric acid-suppressive therapy as a risk factor for CDI in the IBD population<sup>[30,34,43-46]</sup>.

Most studies demonstrate ongoing steroid, biologic, or immunomodulator therapy does not increase the risk of CDI in IBD patients<sup>[30,34,35,43,45-47]</sup>, however, some contradictory evidence exists. A retrospective cohort study of 999 IBD inpatients (737 CD and 262 UC) report a greater than two-fold increased risk of CDI with maintenance immunomodulator use, defined as azathioprine, 6-mercaptopurine, or methotrexate

**Table 2** Risk factors for *Clostridium difficile* infection in inflammatory bowel disease

Ref.	Sampling time frame	Setting	Diagnosis method	Identified risk factors	
				HOST	ENVIRONMENT
Razik <i>et al</i> <sup>[44]</sup> (2016)	2010-2013	Inpatient	PCR	Non-ileal CD	Hospitalisation for CDI; recent antibiotic use; biologic therapy; 5-ASA; Steroids
McCurdy <i>et al</i> <sup>[54]</sup> (2016)	2005-2011	Inpatient and outpatient	PCR	CMV infection	N/A
Seril <i>et al</i> <sup>[45]</sup> (2014)	2010-2013	Inpatient and outpatient	PCR for Toxin B	Post-surgery mechanical intestinal complications; low serum immunoglobulin level	None identified
Regnault <i>et al</i> <sup>[30]</sup> (2014)	2008-2010	Inpatient	Stool culture on selective medium + cytotoxicity assay +/- toxigenic culture	None identified	NSAIDs
Connelly <i>et al</i> <sup>[52]</sup> (2014)	N/R	N/R	PCR for Toxin A gene	<i>IL-4</i> gene associated SNP rs2243250	Not studied
Ananthakrishnan <i>et al</i> <sup>[102]</sup> (2014)	1998-2010	Inpatient	N/R	Low vitamin D concentration	Not studied
Ananthakrishnan <i>et al</i> <sup>[56]</sup> (2013)	N/R	Inpatient and outpatient	ELISA for Toxin A/B	Female sex; pancolitis; IBD-related SNPs	Protective : Anti-TNF therapy
Monaghan <i>et al</i> <sup>[53]</sup> (2013)	2009-2012	N/R	Toxigenic culture	Impaired ability to generate: toxin-specific antibody, memory B-cell responses	Not studied
Li <i>et al</i> <sup>[34]</sup> (2013)	2010-2011	Outpatient	PCR for Toxin B	None identified	Recent hospitalization
Masclée <i>et al</i> <sup>[47]</sup> (2013)	2009-2010	Outpatient	PCR for <i>C. difficile</i> and Toxins A/B	None identified	None identified
Kaneko <i>et al</i> <sup>[46]</sup> (2011)	2006-2009	Inpatient and outpatient	ELISA for Toxin A	None identified	None identified
Kariv <i>et al</i> <sup>[43]</sup> (2011)	2000-2006	Inpatient and outpatient	EIA for Toxin A/B	Recent surgery	Recent antibiotic use; recent hospitalization
Ricciardi <i>et al</i> <sup>[27]</sup> (2009)	1993-2003	Inpatient	N/R	Colonic involvement	Not studied
Schneeweiss <i>et al</i> <sup>[49]</sup> (2009)	2001-2006	Inpatient and outpatient	N/R	Not studied	Corticosteroid initiation
Nguyen <i>et al</i> <sup>[17]</sup> (2008)	1998-2004	Inpatient	N/R	Colonic involvement	Not studied
Issa <i>et al</i> <sup>[24]</sup> (2007)	2005	Inpatient	ELISA for Toxin A/B	Comorbidity	Maintenance immunomodulator use
Rodemann <i>et al</i> <sup>[16]</sup> (2007)	1998-2004	Inpatient	Cell cytotoxic culture 2002 onwards <i>C. difficile</i> Toxin A/B immunoassay	Age	Not studied
Mylonaki <i>et al</i> <sup>[23]</sup> (2004)	1997-2001	Inpatient	ELISA for Toxin A/B	Comorbidity	Recent antibiotic use

CDI: *Clostridium difficile* infection; rCDI: Recurrent *Clostridium difficile* infection; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's Disease; IPAA: Ileal anal-pouch anastomosis; CMV: Cytomegalovirus; CF: Cystic fibrosis; EIA: Enzyme immunoassay; ELISA: Enzyme linked immunosorbent assay; NSAID: Non-steroidal anti-inflammatories PCR: Polymerase chain reaction; N/R: Not reported.

(OR = 2.56, 95%CI: 1.28-5.12,  $P = 0.008$ )<sup>[24]</sup>. In the general population, corticosteroid use increases the risk of CDI<sup>[48]</sup>. However, when analyzing CDI risk in IBD patients using corticosteroids, studies were observational and did not control for underlying disease activity. A large retrospective cohort study of 10662 IBD inpatients noted a greater than three times increased risk of CDI within 90 d of corticosteroid initiation (RR = 3.4; 95%CI: 1.9-6.1) but no increased risk with preceding biologic therapy. This risk remained constant after 90 d of corticosteroid therapy and was not dose-dependent<sup>[49]</sup>. Risk factors for recurrent CDI (rCDI), in addition to recent antibiotic use, included preceding steroid and biologic therapy. However, when further stratified, rCDI was associated with infliximab use but not adalimumab or immunomodulator therapy<sup>[44]</sup>.

Although there appears to be more community-

acquired CDI in the IBD population compared to the general population, recent hospitalization has also been identified as a risk factor for CDI and rCDI<sup>[43,44]</sup>. Patients who have undergone colectomy are still at risk of CDI. Ten point seven percent of symptomatic IBD patients with ileal anal-pouch anastomosis (IPAA) were found to be positive for *C. difficile* toxin in a prospective cohort of 196 patients<sup>[34]</sup>. A retrospective observational study of 284 UC patients who underwent IPAA found that 64 patients developed pouchitis. Three of the four patients in this cohort with antibiotic-refractory pouchitis were discovered to have CDI that responded to oral vancomycin<sup>[50]</sup>.

Genetic and immunologic risk factors have been identified in IBD patients for the development of CDI<sup>[51]</sup>. In a retrospective cohort study of 172 IBD patients, an interleukin-4-associated single nucleotide polymorphism (rs2243250) is associated with CDI

in IBD<sup>[52]</sup>. Monaghan *et al.*<sup>[53]</sup> studied the humoral response to *C. difficile* toxins A and B in patients with IBD, cystic fibrosis, and healthy controls, finding that an impaired ability to sustain or generate strong toxin-specific antibody and B-cell responses could play a role in CDI development in IBD patients. Furthermore, low serum immunoglobulins were reported as a risk factor for CDI in IBD patients with IPAA<sup>[34]</sup>. A retrospective case control study of 306 IBD inpatients and outpatients, found that those with CMV infection were at higher risk of being co-infected with *C. difficile*<sup>[54]</sup>. As in the general population, patient comorbidities increase the risk of CDI in the IBD population<sup>[16,17,55]</sup>. While adult IBD patients affected by CDI are younger than those in the general population, increasing age has also been reported as a risk factor for CDI<sup>[16]</sup>.

IBD disease activity is difficult to differentiate from CDI. Therefore, it is not clear that disease activity is an independent risk factor for the development of CDI. Disease location may affect patient risk. CDI is more often identified in those with UC and CD patients with colonic involvement<sup>[16,24]</sup>. In a retrospective nested case-control analysis of a national hospital discharge database, the prevalence of CDI among IBD patients with only small bowel disease was significantly lower than UC patients or CD patients with ileocolonic disease and only slightly higher than non-IBD patients<sup>[17]</sup>. Extent of disease in UC patients may be a risk factor for CDI. A prospective cohort study of 319 UC patients found pancolitis to be a risk factor for CDI (OR = 2.52, 95%CI: 1.03-6.17)<sup>[56]</sup>.

### Impact of CDI in IBD

CDI negatively impacts short and long-term IBD-related outcomes, including rates of colectomy, escalation in IBD therapy, and mortality. It also results in longer hospitalizations, increased readmission rates, and increased in-hospital expenditures (Table 3).

Increased mortality among IBD patients with CDI has been reported in numerous adult inpatient studies compared to non-IBD patients with CDI<sup>[17]</sup> and IBD patients without CDI<sup>[31,55,57,58]</sup>. Furthermore, it appears that this excess mortality is not limited to the index hospitalization. A retrospective cohort study of 2016 adult UC inpatients described increased mortality among patients with CDI compared to those without CDI in the five years post-discharge (HR = 2.41, 95%CI: 1.37-4.22)<sup>[31]</sup>.

Colectomy rates have been reported to be higher in IBD patients with CDI. A retrospective case control study of 99 adult UC inpatients reported CDI at index admission significantly predicted colectomy within one year<sup>[59]</sup>. Higher rates of colectomy among IBD patients with CDI have been similarly reported in other large adult inpatient studies compared to non-IBD patients with CDI (6.4% vs 0.3%)<sup>[44]</sup> and IBD patients without CDI (OR = 1.87-10.0)<sup>[32,57,59,60]</sup> during index admission and up to one year following the initial episode.

IPAA failure also is associated with a history of CDI. A retrospective chart-review study of 417 IBD patients undergoing IPAA found that a history of CDI prior to colectomy in IBD patients was independently associated with IPAA failure (HR = 3.02, 95%CI: 1.23-7.44)<sup>[61]</sup>.

While CDI alone is associated with significant morbidity and mortality, it is thought that CDI may actually lead to a flare in IBD activity resulting in further morbidity. This is supported by a retrospective cohort study of 146 adult UC inpatients and outpatients reporting increased escalation in therapy among patients with CDI in the year after index admission compared to the year prior<sup>[60]</sup>. A retrospective nested case control study of 238 pediatric IBD inpatients with and without CDI similarly demonstrated significant escalation in therapy among those with CDI as compared to those without after the infection<sup>[62]</sup>.

### Diagnosis of CDI in IBD

The overlap in symptomatology between CDI and isolated IBD flare complicates the diagnosis of CDI in IBD patients. CDI and acute inflammatory colitis are clinically indistinguishable. Therefore, a diagnosis relies primarily on laboratory findings, and to a lesser degree endoscopic or histologic findings.

It is recommended to test all patients with acute flares presenting with diarrhea for CDI<sup>[63]</sup>. Despite its impact on outcome and management, many patients with newly diagnosed IBD or flaring IBD are not tested for CDI. A retrospective cohort study of adult IBD inpatients report that *C. difficile* testing within 48 h for patients hospitalized for an IBD flare was only performed on 59% of 813 consecutive hospitalizations. A diagnosis of UC or CD with colonic involvement was noted to be independent predictors of CDI testing<sup>[30]</sup>. In a retrospective cohort study of pediatric patients with newly diagnosed IBD, only 42% of 290 cases had testing for *C. difficile* around the time of diagnosis<sup>[39]</sup>.

Compared to previously discussed diagnostic methods, pseudomembranes on colonoscopy are specific but not sensitive to diagnose CDI in IBD patients. In a multi-center retrospective study of 93 IBD patients hospitalized with CDI who underwent colonoscopy, only 13% were noted to have pseudomembranes. The presence of pseudomembranes was not found to significantly impact clinical outcomes<sup>[64]</sup>. A retrospective case-control study of CDI in IBD and non-IBD patients found that none of the IBD-CDI patients had pseudomembranes on endoscopy compared to nearly half of the non-IBD-CDI group<sup>[20]</sup>. A retrospective study of 37 flaring UC patients assessed histological changes on colonic biopsies with or without CDI. They reported that although those with CDI had significantly more microscopic pseudomembranes than the controls without CDI, less than half of the specimens of CDI patients had this finding<sup>[65]</sup>.

Testing *via* PCR should only be performed on

**Table 3 Outcomes of inflammatory bowel disease patients with *Clostridium difficile* infection**

Ref.	Patient population	Sampling time frame	Study design	n	Outcomes
Razik <i>et al</i> <sup>[44]</sup> (2016)	Adult CDI IBD + CDI  Inpatient	2010-2013	Retrospective, single-center, cohort study	503	Incidence of rCDI IBD > non-IBD [2.04/100 person-months (95%CI: 1.55-2.64) <i>vs</i> 1.25 episodes per 100 person-months (95%CI: 1.05-1.48)] Colectomy IBD > non-IBD (6.4% <i>vs</i> 0.3%)
Skowron <i>et al</i> <sup>[61]</sup> (2016)	Adult IBD + IPAA Inpatient (United States)	2000-2010	Retrospective, observational, single-center cohort study	417	CDI pre-colectomy associated with post-reconstruction pouch failure (HR = 3.02 95%CI: 1.23-7.44)
McCurdy <i>et al</i> <sup>[54]</sup> (2016)	Adult IBD IBD + CMV  IBD + CMV + CDI  IBD + CDI Inpatient and outpatient (United States)	2005-2011	Retrospective, case-control, single-center, study	248	Colectomy-free survival at 1 yr IBD + CDI > IBD + CMV + CDI (71.5% <i>vs</i> 30%) IBD + CMV controls > IBD + CMV + CDI (57.1% <i>vs</i> 30%)
Negrón <i>et al</i> <sup>[32]</sup> (2014)	Adult UC Inpatient (Canada)	2000-2009	Retrospective, case-control, multi-center, database study	481	Emergent surgery CDI + UC > UC alone [OR = 3.39 (95%CI: 1.02-11.23)] Development of new infectious postoperative complication CDI + UC > UC alone (OR = 4.76, 95%CI: 1.10-20.63)
Horton <i>et al</i> <sup>[70]</sup> (2014)	Adult IBD Inpatient (United States)	2006-2010	Retrospective, observational, single-center study	114	Readmission: UC + CDI > CD + CDI (24% <i>vs</i> 10%, <i>P</i> = 0.04) IBD + steroids > no-steroids (29% <i>vs</i> 8%, <i>P</i> < 0.01) Colectomy: UC + CDI > CD + CDI, index admission (27.4% <i>vs</i> 0%, <i>P</i> < 0.01) IBD + steroids > no-steroids (32% <i>vs</i> 6%, <i>P</i> < 0.01)
Pant <i>et al</i> <sup>[98]</sup> (2013)	Pediatric IBD Inpatient (United States)	2000, 2003, 2006, 2009	Retrospective, nested case-control, nationwide database study	12610	LOS: CDI + IBD > IBD (8.0 <i>vs</i> 6.0, aRC = 2.1 d, 95%CI: 1.4-2.8) Hospitalization cost: CDI + IBD > IBD alone (\$45126 <i>vs</i> \$34703, aRC = \$11506, 95%CI: 6192-16829) Parenteral nutrition: CDI + IBD > IBD alone (15.9% <i>vs</i> 12.1% aOR = 1.5, 95%CI: 1.1-2.0) Blood transfusions: CDI + IBD > IBD alone (17.7% <i>vs</i> 9.8%, aOR = 1.8, 95%CI: 1.4-2.4).
Li <i>et al</i> <sup>[34]</sup> (2013)	Adult IBD + IPAA  Outpatient (United States)	2010-2011	Prospective, single-center, cohort study	196	42.9% cured by single course of Vancomycin 57.1% recurrent/refractory CDI
Chu <i>et al</i> <sup>[103]</sup> (2013)	Adult UC + CDI Inpatient (United States)	2002-2012	Retrospective, single-center, observational study	23	Morbidity and mortality after colectomy: UC + CDI + full antibiotic course pre-op = UC + CDI + incomplete antibiotic course pre-op
Ananthakrishnan <i>et al</i> <sup>[55]</sup> (2013)	Adult IBD Inpatient (United States)	2007	Retrospective, nested case-control, nationwide database study	67221 hospitalizations	Mortality: CDI + IBD <i>vs</i> IBD alone (OR = 3.23, 95%CI: 2.55-4.03).
Murthy <i>et al</i> <sup>[31]</sup> (2012)	Adult UC Inpatient (Canada)	2002-2008	Retrospective, database, cohort study	2016	Mortality: CDI + UC > UC alone, 5-yr risk (aHR = 2.40, 95%CI: 1.37-4.20) CDI + UC > UC alone, index hospitalization (aHR = 8.90, 95%CI: 2.80-28.3) CDI + UC > UC alone, 5 years post-discharge (aHR = 2.41, 95%CI: 1.37-4.22)



Navaneethan <i>et al</i> <sup>[60]</sup> (2012)	Adult UC Inpatient and outpatient (United States)	2002-2007	Retrospective, single-center, cohort study	146	UC-related ER visits: CDI + UC <i>vs</i> UC alone, 1 yr post index infection (37.8% <i>vs</i> 4%, $P < 0.001$ ) Colectomy: CDI + UC <i>vs</i> UC alone, 1 yr post index infection (35.6% <i>vs</i> 9.9%, $P < 0.001$ ) CDI associated with colectomy within 1 yr (OR = 10, 95%CI: 2.7-36.3) Escalation in therapy: CDI + UC year after CDI admission <i>vs</i> year prior (55.8% <i>vs</i> 12.9%, $P < 0.0001$ )
Jen <i>et al</i> <sup>[57]</sup> (2011)	Adult IBD Inpatient (England)	2002-2008	Retrospective, nested case-control, nationwide database study	241478 hospitalizations	Mortality: IBD + CDI (defined as hospital-acquired > IBD alone (aOR = 6.32, 95%CI: 5.67-7.04) LOS: IBD + CDI > IBD alone (27.9 d longer) GI surgery: IBD + CDI > IBD alone (aOR = 1.87, 95%CI: 0.60-5.85)
Kariv <i>et al</i> <sup>[43]</sup> (2011)	Adult UC Inpatient and outpatient (United States)	2000-2006	Single-center	78	Colectomy within 3 mo not associated with CDI No UC or CDI associated mortality identified
Ananthakrishnan <i>et al</i> <sup>[58]</sup> (2011)	Adult IBD Inpatient (United States)	1998, 2004, 2007	Retrospective, nested case-control, nationwide database study	-	Mortality: IBD + CDI > IBD alone, from 1998 to 2007 (OR = 2.38, 95%CI: 1.52-3.72 to OR = 3.38, 95%CI: 2.66-4.29).
Kelsen <i>et al</i> <sup>[62]</sup> (2011)	Pediatric IBD Inpatient (United States)	1997-2007	Retrospective, nested case-control, single-center study	315	rCDI: CDI + IBD > CDI-alone (34% <i>vs</i> 7.5%, $P < 0.0001$ ) Escalation in therapy: IBD + CDI > IBD alone (67% <i>vs</i> 30%, $P < 0.001$ )
Jodorkovsky <i>et al</i> <sup>[59]</sup> (2010)	Adult UC Inpatient (United States)	2004-2005	Retrospective, single-center, case-control study	99	UC-related hospitalizations: CDI + IBD > IBD alone, over 1 yr Colectomy: CDI at index admission predictor for colectomy within 1 yr (OR = 2.38, 95%CI: 1.01-5.6) CDI status not a significant predictor for requirement for emergent colectomy at index admission LOS: CDI + IBD = IBD alone
Ben-Horin <i>et al</i> <sup>[64]</sup> (2010)	Adult IBD + CDI Inpatient (Europe/Israel)	2000-2008	Retrospective, multi-center, cohort study	93	Morbidity and mortality: IBD + CDI patients + pseudomembranes on endoscopy = IBD + CDI without pseudomembranes
Nguyen <i>et al</i> <sup>[17]</sup> (2008)	IBD and non-IBD controls Inpatient (United States)	1998-2004	Retrospective, nested case-control, nationwide database study	116842 hospitalizations	Mortality: UC + CDI > CDI alone (OR = 3.79, 95%CI: 2.84-5.06) LOS: CD + CDI > CDI alone Hospitalization cost: UC + CDI > CDI alone

CDI: Clostridium difficile infection; rCDI: Recurrent clostridium difficile infection; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; IPAA: Ileal anal-pouch anastomosis; CMV: Cytomegalovirus; OR: Odds ratio; aOR Adjusted odds ratio; aRC: Adjusted regression coefficient; LOS: Length of stay.

unformed stools to limit false positives. Asymptomatic carriers of toxigenic *C. difficile* exist in both IBD patients and the general population. Asymptomatic carriage rates vary significantly with the patient population under study<sup>[66]</sup>. A rate of 8.2% has been reported in an adult outpatient IBD population with stable disease compared to 1.0% in healthy controls, with higher rates in UC patients compared

to those with CD<sup>[67]</sup>. A prospective case-control study of 163 pediatric outpatients reports a significantly higher carriage rate in those with IBD than in healthy controls (17% *vs* 3%), which was not associated with recent hospitalization<sup>[68]</sup>. There are no studies evaluating treatment of the asymptomatic carriage of *C. difficile*. Evidence is lacking to suggest that treating asymptomatic *C. difficile* carriers has any future

impact on IBD disease activity or the development of symptomatic CDI. However, in the general population, carriage of *C. difficile* in the absence of symptoms carries a protective effect against future symptomatic CDI<sup>[7]</sup>. This protective effect has not been studied in the IBD population.

It has been demonstrated that the asymptomatic shedding of *C. difficile* spores can continue for weeks following the resolution of symptoms<sup>[69]</sup>. Therefore, test of cure is not recommended. However, in patients with IBD and CDI where symptom overlap creates both diagnostic and therapeutic challenges, repeat testing in patients with ongoing diarrhea may guide management, despite the risk of false-positive results.

### **Treatment of CDI in IBD patients**

In patients with confirmed CDI, distinguishing between symptoms resulting from infection, as opposed to a flare of underlying IBD, creates a management dilemma. There are no randomized controlled trials (RCT) of therapy in IBD patients with CDI to help guide practice. Guidelines outlining the approach to eradication of *C. difficile* via antibiotic therapy or fecal microbiota transplant (FMT) in the setting of recurrent CDI also include recommendations for the IBD population<sup>[3]</sup>. IBD outpatients with non-severe CDI can be initially treated with metronidazole, however IBD inpatients regardless of disease severity should receive a vancomycin-containing regimen as first-line therapy (Table 4)<sup>[70]</sup>. In addition to medical therapy, specific infection control measures should also be put in place, including hand-washing to minimize fecal-oral transmission of *C. difficile* spores, as well as isolation of patients with CDI under contact-precautions.

### **Management of IBD flares in patients with CDI**

While the treatment of isolated CDI is well studied, the initiation, maintenance or escalation of corticosteroid, immunomodulator or biologic therapy in IBD patient with CDI is not delineated and relies heavily on expert opinion.

### **Corticosteroids**

In the setting of suspected IBD flare in a patient with known CDI, concurrent corticosteroid therapy is reasonable and supported by expert opinion<sup>[3,71]</sup>. Nevertheless, significant uncertainty exists among practitioners with regards to the initiation of corticosteroid therapy and its safety in the context of an ongoing CDI-mediated colitis. A survey of 169 North American gastroenterologists demonstrated divergence among clinicians with regards to initiating therapy in hospitalized UC patients with CDI; 54% opted for antibiotic monotherapy compared to 46% opting for a combination of antibiotics with either azathioprine or corticosteroids<sup>[71]</sup>. This concern originates from findings of several observational studies, detailed

above, demonstrating increased risk of CDI, rCDI, and worse outcomes among IBD patients receiving corticosteroids<sup>[44,49,70]</sup>. However, these patients were receiving corticosteroids prior to CDI, and no analysis has been performed for initiation of corticosteroids in IBD patients with CDI on appropriate antimicrobial therapy.

Literature on initiating corticosteroids for IBD flares in patients with concomitant CDI is limited to case reports yielding promising results with patients experiencing remission of symptoms after starting corticosteroid therapy when appropriate antibiotics had failed to do so (Table 5). Similarly, data regarding the initiation of corticosteroids in patients with CDI in the general population is scarce. Corticosteroids have been successfully used as adjunctive therapy to antibiotics in infectious processes such as meningitis, pneumonia, and sepsis<sup>[72-74]</sup>. While the benefit of corticosteroids seen in these infections may not predict an effect in CDI, it does confer biologic plausibility.

Conversely, a European retrospective, non-randomized, multi-center study of 155 IBD patients hospitalized with CDI evaluated the effects of antibiotics and immunomodulators compared to antibiotics alone. Immunomodulators were defined as any of the following: corticosteroids at a dose equal to or above 20 mg of prednisone daily, thiopurines at any dose, methotrexate, cyclosporine, tacrolimus, or biologics of any kind. Furthermore, there was no indication of whether therapy was for induction or maintenance of IBD. Conclusions are thus limited by the heterogeneity in the definition of immunomodulator use and antibiotic regimens. Nonetheless, combination of antibiotic and immunomodulator therapy was associated with higher morbidity and mortality compared to antibiotic monotherapy<sup>[75]</sup>. Most recent AGA practice guidelines suggest postponing escalation of steroids in the setting of acute CDI until 72 to 96 h after the initiation of appropriate antibiotic therapy. However, they refrain from providing further guidance on when to withhold, continue, or escalate corticosteroid therapy given the current absence of prospective data<sup>[76]</sup>.

### **Immunomodulators and biologic therapy**

Recent CDI guidelines suggest, in IBD patients with CDI, maintaining, but not escalating, existing immunosuppressive therapy, including immunomodulators such as azathioprine and methotrexate, as well as biologic agents<sup>[3]</sup>. Guidelines for the management of opportunistic infections in IBD make no explicit recommendations regarding these therapies in this setting, citing the lack of data available<sup>[77]</sup>. As described above, conflicting evidence exists regarding immunomodulator and biologic therapies as risk factors for the development of CDI or rCDI. No published data exists regarding when initiation of immunomodulating therapy or biologic therapy is

**Table 4 Treatment of clostridium difficile infection in inflammatory bowel disease<sup>[3,4]</sup>**

Severity	Criteria	Treatment	Comments
First episode			
Stop all non-CDI related antibiotic therapy if possible			
Mild to moderate disease	Diarrhea and symptoms not meeting criteria for severe disease	Metronidazole 500 mg by mouth 3 times per day for 10 d to 14 d or Vancomycin 125 mg by mouth 4 times per day for 10 to 14 d	In hospitalized patients with UC and nonsevere CDI, treatment with a vancomycin-containing regimen <i>vs</i> metronidazole alone resulted in fewer readmissions and shorter LOS <sup>[70]</sup>
Severe disease	Serum albumin < 3 g/dL AND one of the following: WBC $\geq$ 15000 cells/mm <sup>3</sup> Abdominal tenderness Creatinine $\geq$ 133 $\mu$ mol/L	Vancomycin 125 mg by mouth 4 times per day for 10 to 14 d	
Severe, complicated disease	Admission to intensive care unit  Hypotension $\pm$ vasopressor requirement Fever $\geq$ 38.5 °C Ileus Mental status changes  WBC $\geq$ 35000 cells/mm <sup>3</sup> or $\leq$ 2000 cells/mm <sup>3</sup> Serum lactate $\geq$ 2.2 mmol/L End organ failure	Vancomycin 500 mg by mouth or nasogastric tube 4 times per day and  Metronidazole 500 mg IV every 8 h and, if ileus, Vancomycin 500 mg in 500 mL saline as enema 4 times per day	Consider early surgical consultation
Recurrent CDI			
First recurrence		Metronidazole 500 mg by mouth 3 times per day for 10 to 14 d or Vancomycin 125 mg by mouth 4 times per day for 10 to 14 d or Fidaxomicin 200 mg by mouth 2 times per day for 10 d	
Second recurrence		-Tapered and pulsed vancomycin or Fidaxomicin 200 mg by mouth 2 times per day for 10 d	
Subsequent recurrence		-Fecal microbiota transplant	

LOS: Length of stay; CDI: Clostridium difficile infection; UC: Ulcerative colitis.

safe in patients with both IBD and CDI. In a study of 14 pediatric patients with predominantly CD being treated with methotrexate and anti-TNF therapy, four patients developed CDI. They were treated with antibiotics with successful clearance of *C. difficile* but ultimately failed combination therapy<sup>[78]</sup>. It is difficult to draw conclusions regarding the safety of biologic and immunomodulator therapy from this due to the sample size. Figure 2 summarizes our approach to the patient with IBD who presents with an acute flare in symptoms for which a *C. difficile* assay is sent, based on existing literature.

#### **Fecal microbiota transplant and recurrent CDI**

Existing therapeutic options for rCDI in the general population include vancomycin pulsed and tapered regimens, fidaxomicin, as well as fecal microbiota transplant (FMT). FMT is appealing given the potential to treat both CDI and IBD simultaneously. The risk of rCDI increases with each episode and is higher in

IBD patients, as demonstrated in a large retrospective cohort study (32% *vs* 24%,  $P < 0.01$ )<sup>[44]</sup>. FMT has been demonstrated to be a safe and effective therapy for rCDI in the general population on the basis of several large RCTs<sup>[79-81]</sup>. Several studies have analyzed treatment of rCDI in IBD patients. A retrospective study of immunosuppressed patients with CDI undergoing FMT included 36 IBD patients, of which 86% were cured of CDI after one transplant and 14% worsened in disease activity<sup>[82]</sup>. Another retrospective multicenter study of 67 IBD patients (35 CD; 31 UC; 1 IBUD), of which 64% were receiving immunosuppressive therapy at the time of FMT, found that 79% had either resolution of their diarrhea and/or negative CDI testing at week 12 and 46% had improved disease activity at 3 mo. Disease activity at 3 mo remained the same or worsened in 36%, and 18% of patients, respectively<sup>[83]</sup>. Adverse events occurred in 12% of patients at 3 mo. One patient received a colectomy and two had IBD related hospitalizations. In

**Table 5 Case reports of corticosteroid initiation in *Clostridium difficile* infection**

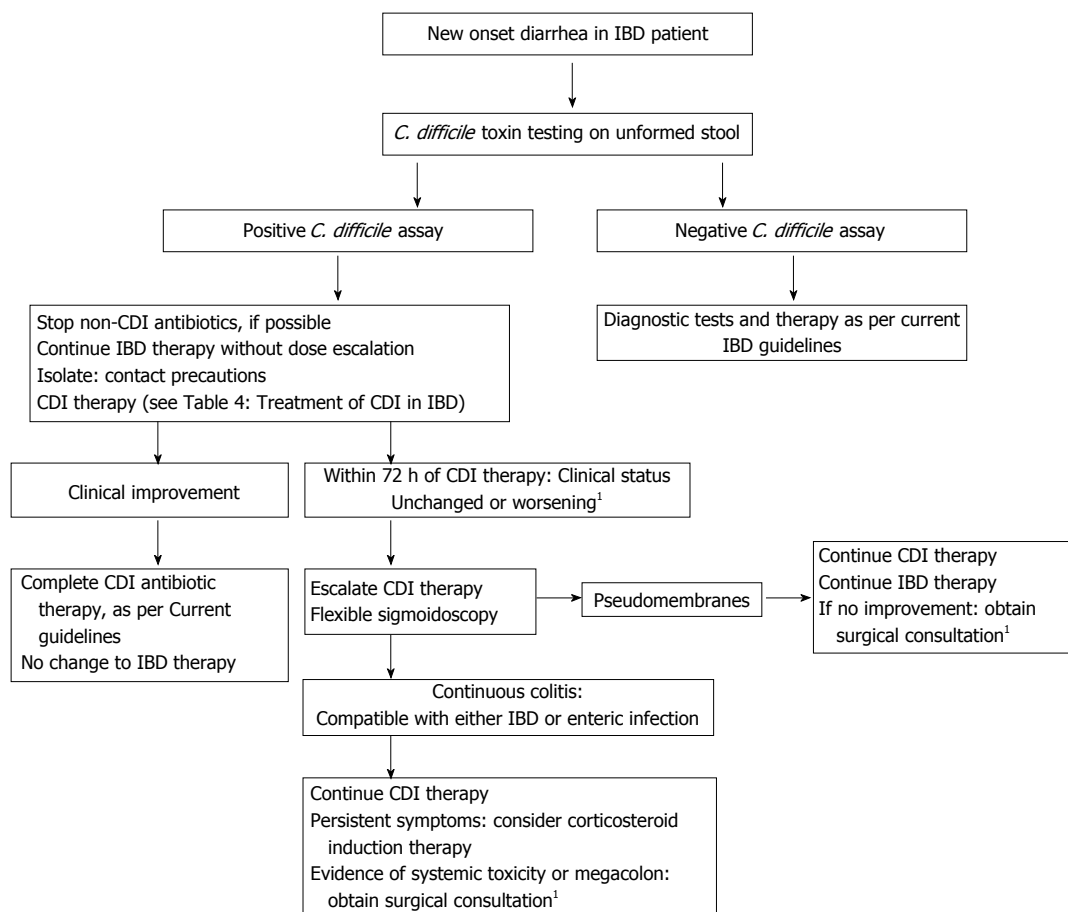
Reference (year of publication)	Patient data		Treatment regimen	Outcome
	Demographics	Clinical presentation		
Cavagnaro <i>et al</i> <sup>[104]</sup> (2003)	5M	Bloody diarrhea (> 10 loose stools/d), tenesmus, abdominal tenderness, fever  WBC 19000 cells/mm <sup>3</sup> , albumin 21 g/L Positive <i>C. difficile</i> toxin	Oral vancomycin (40 mg/kg per day divided in 6-hourly doses) and IV metronidazole (20 mg/kg per day divided in 8-hourly doses) × 14 d  IV methylprednisolone (2 mg/kg per day in two divided doses) on day 14 × 3 d	Resolution of diarrhea within 24 h of steroid initiation  Resolution of endoscopic changes at 6 wk
Sykes <i>et al</i> <sup>[105]</sup> (2012)	54F	Pseudomembranous colitis on flexible sigmoidoscopy on day 14 Moderate CDI that resolved with 10-d course antibiotics  Recurrent diarrhea and abdominal pain 10 d after completion of antibiotics with left colonic thickening on CT and positive <i>C. difficile</i> toxin  Fever, tachycardia on day 4	Prednisone 2 mg/kg per day tapered over one month Oral metronidazole × 10 d with resolution of symptoms (doses not specified)  Oral vancomycin and metronidazole upon admission (doses not specified) × 4 d	Decreased stool frequency, normalization of vital signs, reduction in CRP to 132 within 48 h of steroid initiation Resolution of diarrhea, further reduction in CRP to 15 after 9 d of steroid therapy Resolution of endoscopic changes at 1 mo  Sustained clinical response at 5 mo
	73F	Moderate-severe CDI that resolved with 10-d course antibiotics  Recurrent moderate CDI 1 wk after completion of antibiotics that resolved with another 10-d course of antibiotics Recurrent CDI 10 d after completion of antibiotics with fever, tachycardia, increased CRP 87 Slow response to antibiotics with flexible sigmoidoscopy on day 8 with pseudomembranous colitis	Metronidazole 400 mg every 8 h × 10 d with resolution of symptoms  Oral vancomycin 125 mg every 6 h × 10 d with resolution of symptoms  Oral vancomycin 125 mg every 6 h × 8 d with tapering regimen over 14 d followed by tapering regimen	Resolution of diarrhea, normalization of vital signs, reduction in CRP to 7 within 48 h of steroid initiation Complete clinical response at 14 d with no further relapses
	91F	Moderate CDI with persistent diarrhea despite courses of metronidazole and vancomycin CRP 11 Flexible sigmoidoscopy with pseudomembranous colitis	Oral metronidazole 400 mg every 8 h × 10 d without resolution of symptoms  Oral vancomycin 125 mg every 6 h for prolonged course without resolution of symptoms Prednisolone 30 mg daily × 14 d with continued vancomycin tapering regimen over 4 wk	Resolution of diarrhea and normalization of CRP within 72 h of steroid initiation No further relapses

CDI: *Clostridium difficile* infection; CRP: C-reactive protein.

a prospective study of 35 IBD patients (13 CD; 22 UC) undergoing FMT for rCDI, 54% of patients required escalation of IBD therapy, despite disappearance of *C. difficile* toxin from the stool<sup>[84]</sup>. Another retrospective

study of 272 IBD and non-IBD patients undergoing one FMT for rCDI demonstrated IBD patients had lower CDI clearance rates than non-IBD patients (74% vs 92%  $P = 0.0018$ ), independent of immunosuppressive





**Figure 2 Approach to potential *Clostridium difficile* infection in inflammatory bowel disease patients.** <sup>1</sup>Obtain surgical consultation earlier, as dictated by CDI guidelines, should there be evidence of toxic megacolon, or concern for rapid deterioration despite medical therapy. CDI: *Clostridium difficile* infection; IBD: Inflammatory bowel disease.

therapy<sup>[85]</sup>. In follow-up, despite *C. difficile* toxin clearance, 50% of UC patients worsened in disease activity requiring escalation of therapy<sup>[86]</sup>.

FMT appears to effectively treat rCDI in IBD patients, albeit less-so than in the general population. However, subsequent worsening of disease activity is consistent throughout the literature. Furthermore, the effects of FMT on IBD activity are unclear. Outcomes are heterogeneous regarding FMT as treatment for IBD alone<sup>[87,88]</sup>. Although several meta-analysis exist<sup>[89,90]</sup> only 2 RCTs with conflicting results regarding UC patients are included. While one RCT of 70 patients showed FMT induced clinical remission compared to placebo<sup>[88]</sup>, the other did not achieve a stringent composite primary end point of clinical remission and a > 1 point decrease in the endoscopic mayo score in 37 UC patients<sup>[87]</sup>. More recently, an RCT of intensive multidonor FMT (colonoscopic infusion followed by 5 enemas weekly for 8 wk) in 85 UC patients achieved a primary endpoint of steroid free clinical remission with endoscopic remission or response at week 8<sup>[91]</sup>. These results, combined with the efficacy of FMT in the treatment of rCDI in IBD patients, necessitates future RCTs analyzing intensive multidonor FMT for rCDI in IBD patients.

In conclusion, CDI commonly complicates the course of IBD but the lack of data precludes formal strong recommendations on the management of IBD in patients with CDI. Initiation of corticosteroids in IBD flares in the context of acute CDI is understudied but seems to be safe. Initiation or resumption of immunosuppressive therapy within 48 to 72 h of targeted antibiotic therapy may be appropriate. To better understand the treatment of IBD flares in the context of acute CDI, further studies are needed to determine the optimal timing and dosing of IBD-specific therapies.

## COMMENTS

### Background

*Clostridium difficile* (*C. difficile*) has been identified as an important nosocomial infection whose traditional risk factors include recent antibiotic use and exposure to a health care institution. Inflammatory bowel disease (IBD) is another important risk factor for *Clostridium difficile* infection (CDI), likely related to the decreased intestinal microbial diversity and disordered immune response seen in this population. Many observational studies have explored the epidemiology, risk factors, and outcomes of CDI in those with IBD and have reported its negative impact. CDI in IBD patients has been linked to excess morbidity, including longer hospitalization, higher risk of colectomy, and escalation in IBD therapy, as well increased mortality. IBD and CDI-related symptoms are often difficult to distinguish and beyond *C. difficile* eradication,

the appropriate IBD therapy is unclear. This review explored the existing evidence regarding the management of IBD in patients with CDI.

### Research frontiers

Prospective studies evaluating the initiation and maintenance of IBD therapeutics in patients with CDI are lacking and are needed to help guide practice.

### Innovations and breakthroughs

While the negative impact of developing CDI in those with IBD has been well established, the appropriate management of CDI in the IBD population is less well-defined. Risk factors for the development of CDI in IBD patients identified in this review include recent antibiotic exposure, hospitalization, and colonic involvement. Contradictory evidence exists as to whether maintenance immunosuppressive therapy is a risk factor for the development of CDI. On the basis of data presented in this study, vancomycin should be used as a first-line regimen for CDI. Case reports suggest that corticosteroid initiation, after appropriate antibiotic coverage, may be safe in those with CDI and IBD flare.

### Applications

The symptoms of an IBD flare and CDI are often indistinguishable. As such, stool testing for *C. difficile* should be sent in every flaring IBD patient. Once CDI is diagnosed, a vancomycin-containing antibiotic regimen should be initiated. In the setting of ongoing symptoms, not warranting surgical intervention, it remains unclear when IBD-specific therapy can be initiated. However, case reports and expert opinion may allow for corticosteroid initiation after 3 d of appropriate CDI therapy.

### Peer-review

It's a well done and well written extensive review on the epidemiology and therapy of CDI in IBD patients.

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