

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.

Conflict-of-interest statement: D'Aoust J and Battat R confirm that there are no conflicts of interest to declare; Bessissow T has received fees as a speaker for Janssen, Shire, Abbvie, Takeda, Ferring, and Pendopharma; Bessissow T has a research grant from Abbvie, Janssen; Bessissow T has consulted for Abbvie, Takeda, Shire.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

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
Telephone: +1-514-9341934
Fax: +1-514-9348531

Received: March 24, 2017

Peer-review started: March 29, 2017

First decision: April 26, 2017

Revised: May 16, 2017

Accepted: June 18, 2017

Article in press: June 19, 2017

Published online: July 21, 2017

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

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

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^[1,2].

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^[3].

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^[4]. 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^[5-7]. CDI is most commonly defined as the presence of *C. difficile* toxin in the context of characteristic clinical manifestations including diarrhea and abdominal pain^[4]. 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^[8-10]. 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^[11].

Decreased intestinal microbial diversity along with an inadequate immune response is thought to play a causative role in the development CDI^[12-14]. 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^[15]. 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

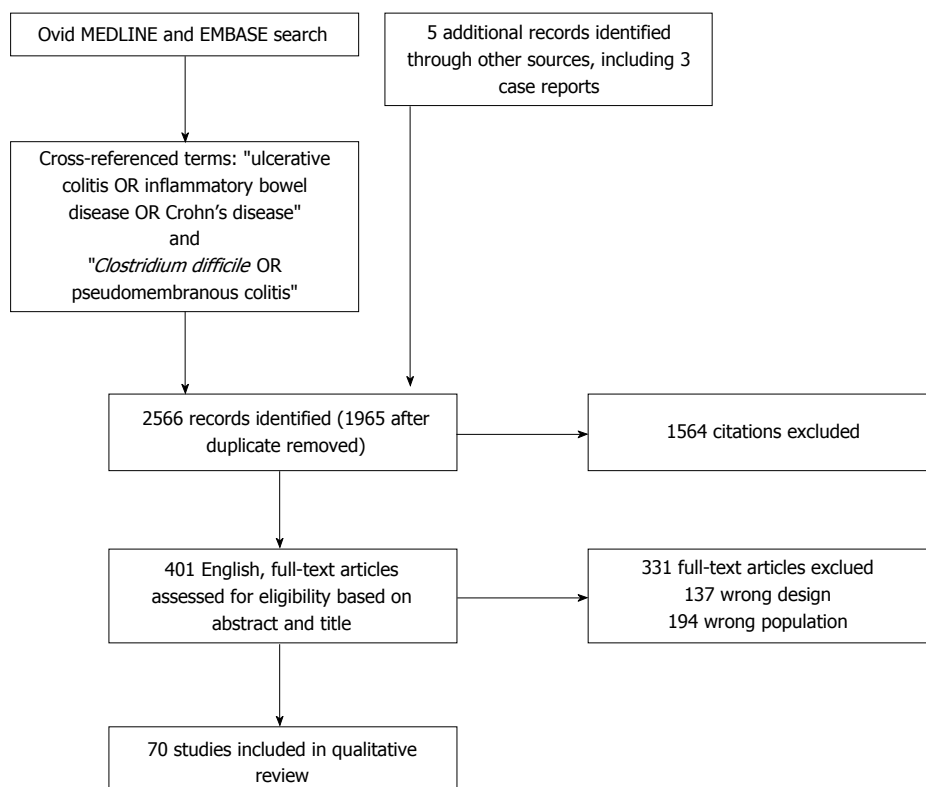


Figure 1 Search strategy for the selection of articles on *Clostridium difficile* infection in inflammatory bowel disease.

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^[16-19]. Several studies demonstrate a disproportionate rise in CDI in the IBD population as compared to the general population^[16,17], while others do not^[20].

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%^[21-25].

Studies report the incidence of CDI in CD adult inpatients between 1.0 and 7.7%^[26-30]. 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 ^[92] (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> ^[93] (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> ^[26] (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> ^[21] (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> ^[94] (1987)	IBD adult outpatients	1984-1986	Stool culture on selective medium + cytotoxicity assay	Active	CDI incidence (%) IBD 3.2
Gryboski ^[95] (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> ^[22] (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> ^[23] (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> ^[24] (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> ^[16] (2007)	IBD pediatric and adult inpatients (United States)	1998-2004	Cell cytotoxic culture 2002 onwards <i>C. difficile</i> Toxin A/B immunoassay	Active	CDI incidence (%) UC: 3.9; CD: 1.6 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 CDI incidence (%) UC: 18.3
Shen <i>et al</i> ^[33] (2008)	UC adult outpatients with IPAA	2005-2006	ELISA for Toxin A/B	Mixed	CDI incidence (%) UC: 18.3
Bossuyt <i>et al</i> ^[20] (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> ^[96] (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> ^[18] (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> ^[17] (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> ^[35] (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> ^[27] (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> ^[36] (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> ^[58] (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> ^[46] (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> ^[37] (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> ^[28] (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> ^[38] (2012)	IBD pediatric inpatients	2007-2010	EIA for Toxins A and B	Mixed	CDI incidence (%) IBD: 47
Antonelli <i>et al</i> ^[29] (2012)	IBD adult inpatients	2007-2010	N/R	Active	CDI incidence (%) UC: 11.1; CD: 1.7
Murthy <i>et al</i> ^[31] (2012)	UC adult inpatients	2002-2008	N/R	Active	CDI incidence (%) UC: 9.0
Lamousé-Smith <i>et al</i> ^[97] (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> ^[47] (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> ^[39] (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; IBDU: 11.1 No significant variation in IBD incidence over 3 yr
Pant <i>et al</i> ^[98] (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> ^[34] (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> ^[40] (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> ^[30] (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> ^[32] (2014)	UC adult inpatients	2000-2009	EIA for Toxins A/B	Active	CDI incidence (%) UC: 6.1
Hourigan <i>et al</i> ^[99] (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> ^[25] (2015)	IBD adult inpatients and outpatients	2008-2011	EIA and PCR	Mixed	CDI incidence (%) IBD: 5.1
Sandberg <i>et al</i> ^[19] (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> ^[100] (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> ^[101] (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; IBDU: 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%^[26-32]. In adult outpatients with ileal-anal pouch anastomosis (IPAA) for IBD, incidence of CDI is 10.7%-18.3%^[33,34]. 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^[35-40].

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^[16,35,41].

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^[42].

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^[23,43,44]. 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)^[43]. Several others contradict this^[30,34,35,43,45-47]. 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, $P = 0.02$)^[30]. No studies have identified gastric acid-suppressive therapy as a risk factor for CDI in the IBD population^[30,34,43-46].

Most studies demonstrate ongoing steroid, biologic, or immunomodulator therapy does not increase the risk of CDI in IBD patients^[30,34,35,43,45-47], 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> ^[44] (2016)	2010-2013	Inpatient	PCR	Non-ileal CD	Hospitalisation for CDI; recent antibiotic use; biologic therapy; 5-ASA; Steroids
McCurdy <i>et al</i> ^[54] (2016)	2005-2011	Inpatient and outpatient	PCR	CMV infection	N/A
Seril <i>et al</i> ^[45] (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> ^[30] (2014)	2008-2010	Inpatient	Stool culture on selective medium + cytotoxicity assay +/- toxigenic culture	None identified	NSAIDs
Connelly <i>et al</i> ^[52] (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> ^[102] (2014)	1998-2010	Inpatient	N/R	Low vitamin D concentration	Not studied
Ananthakrishnan <i>et al</i> ^[56] (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> ^[53] (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> ^[34] (2013)	2010-2011	Outpatient	PCR for Toxin B	None identified	Recent hospitalization
Maslee <i>et al</i> ^[47] (2013)	2009-2010	Outpatient	PCR for <i>C. difficile</i> and Toxins A/B	None identified	None identified
Kaneko <i>et al</i> ^[46] (2011)	2006-2009	Inpatient and outpatient	ELISA for Toxin A	None identified	None identified
Kariv <i>et al</i> ^[43] (2011)	2000-2006	Inpatient and outpatient	EIA for Toxin A/B	Recent surgery	Recent antibiotic use; recent hospitalization
Ricciardi <i>et al</i> ^[27] (2009)	1993-2003	Inpatient	N/R	Colonic involvement	Not studied
Schneeweiss <i>et al</i> ^[49] (2009)	2001-2006	Inpatient and outpatient	N/R	Not studied	Corticosteroid initiation
Nguyen <i>et al</i> ^[17] (2008)	1998-2004	Inpatient	N/R	Colonic involvement	Not studied
Issa <i>et al</i> ^[24] (2007)	2005	Inpatient	ELISA for Toxin A/B	Colonic involvement	Maintenance immunomodulator use
Rodemann <i>et al</i> ^[16] (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> ^[23] (2004)	1997-2001	Inpatient	ELISA for Toxin A/B	None identified	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, $P = 0.008$)^[24]. In the general population, corticosteroid use increases the risk of CDI^[48]. 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^[49]. 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^[44].

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^[43,44]. 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^[34]. 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^[50].

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

in IBD^[52]. Monaghan *et al.*^[53] 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^[34]. 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*^[54]. As in the general population, patient comorbidities increase the risk of CDI in the IBD population^[16,17,55]. 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^[16].

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^[16,24]. 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^[17]. 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)^[56].

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^[17] and IBD patients without CDI^[31,55,57,58]. 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)^[31].

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^[59]. 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%)^[44] and IBD patients without CDI (OR = 1.87-10.0)^[32,57,59,60] 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)^[61].

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^[60]. 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^[62].

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^[63]. 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^[30]. 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^[39].

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^[64]. 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^[20]. 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^[65].

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> ^[44] (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) vs 1.25 episodes per 100 person-months (95%CI: 1.05-1.48)] Colectomy IBD > non-IBD (6.4% vs 0.3%)
Skowron <i>et al</i> ^[61] (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> ^[54] (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% vs 30%) IBD + CMV controls > IBD + CMV + CDI (57.1% vs 30%)
Negrón <i>et al</i> ^[32] (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> ^[70] (2014)	Adult IBD Inpatient (United States)	2006-2010	Retrospective, observational, single-center study	114	Readmission: UC + CDI > CD + CDI (24% vs 10%, <i>P</i> = 0.04) IBD + steroids > no-steroids (29% vs 8%, <i>P</i> < 0.01) Colectomy: UC + CDI > CD + CDI, index admission (27.4% vs 0%, <i>P</i> < 0.01) IBD + steroids > no-steroids (32% vs 6%, <i>P</i> < 0.01)
Pant <i>et al</i> ^[98] (2013)	Pediatric IBD Inpatient (United States)	2000, 2003, 2006, 2009	Retrospective, nested case-control, nationwide database study	12610	LOS: CDI + IBD > IBD (8.0 vs 6.0, aRC = 2.1 d, 95%CI: 1.4-2.8) Hospitalization cost: CDI + IBD > IBD alone (\$45126 vs \$34703, aRC = \$11506, 95%CI: 6192-16829) Parenteral nutrition: CDI + IBD > IBD alone (15.9% vs 12.1% aOR = 1.5, 95%CI: 1.1-2.0) Blood transfusions: CDI + IBD > IBD alone (17.7% vs 9.8%, aOR = 1.8, 95%CI: 1.4-2.4).
Li <i>et al</i> ^[34] (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> ^[103] (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 Mortality: CDI + IBD vs IBD alone (OR = 3.23, 95%CI: 2.55-4.03).
Ananthkrishnan <i>et al</i> ^[55] (2013)	Adult IBD Inpatient (United States)	2007	Retrospective, nested case-control, nationwide database study	67221 hospitalizations	Mortality: CDI + IBD vs IBD alone (OR = 3.23, 95%CI: 2.55-4.03).
Murthy <i>et al</i> ^[31] (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> ^[60] (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%, <i>P</i> < 0.001) Colectomy: CDI + UC <i>vs</i> UC alone, 1 yr post index infection (35.6% <i>vs</i> 9.9%, <i>P</i> < 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%, <i>P</i> < 0.0001) 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)
Jen <i>et al</i> ^[57] (2011)	Adult IBD Inpatient (England)	2002-2008	Retrospective, nested case-control, nationwide database study	241478 hospitalizations	IBD + CDI > IBD alone (aOR = 1.87, 95%CI: 0.60-5.85) Colectomy within 3 mo not associated with CDI No UC or CDI associated mortality identified
Kariv <i>et al</i> ^[43] (2011)	Adult UC Inpatient and outpatient (United States)	2000-2006	Single-center	78	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). rCDI: CDI + IBD > CDI-alone (34% <i>vs</i> 7.5%, <i>P</i> < 0.0001) Escalation in therapy: IBD + CDI > IBD alone (67% <i>vs</i> 30%, <i>P</i> < 0.001)
Ananthkrishnan <i>et al</i> ^[58] (2011)	Adult IBD Inpatient (United States)	1998, 2004, 2007	Retrospective, nested case-control, nationwide database study	-	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
Kelsen <i>et al</i> ^[62] (2011)	Pediatric IBD Inpatient (United States)	1997-2007	Retrospective, nested case-control, single-center study	315	Morbidity and mortality: IBD + CDI patients + pseudomembranes on endoscopy = IBD + CDI without pseudomembranes
Jodorkovsky <i>et al</i> ^[59] (2010)	Adult UC Inpatient (United States)	2004-2005	Retrospective, single-center, case-control study	99	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
Ben-Horin <i>et al</i> ^[64] (2010)	Adult IBD + CDI Inpatient (Europe/Israel)	2000-2008	Retrospective, multi-center, cohort study	93	
Nguyen <i>et al</i> ^[17] (2008)	IBD and non-IBD controls Inpatient (United States)	1998-2004	Retrospective, nested case-control, nationwide database study	116842 hospitalizations	

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^[66]. 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^[67]. 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^[68]. 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^[7]. 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^[69]. 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^[3]. 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)^[70]. 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^[3,71]. 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^[71]. 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^[44,49,70]. 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^[72-74]. 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^[75]. 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^[76].

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^[3]. 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^[77]. 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^[3,4]

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 ^[70]
Severe disease	Serum albumin < 3 g/dL AND one of the following: WBC \geq 15000 cells/mm ³ Abdominal tenderness Creatinine \geq 133 μ 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 ³ or \leq 2000 cells/mm ³ 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^[78]. 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%, $P < 0.01$)^[44]. FMT has been demonstrated to be a safe and effective therapy for rCDI in the general population on the basis of several large RCTs^[79-81]. 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^[82]. Another retrospective multicenter study of 67 IBD patients (35 CD; 31 UC; 1 IBDU), 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^[83]. 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> ^[104] (2003)	5M	Bloody diarrhea (> 10 loose stools/d), tenesmus, abdominal tenderness, fever	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	Resolution of diarrhea within 24 h of steroid initiation
		WBC 19000 cells/mm ³ , albumin 21 g/L Positive <i>C. difficile</i> toxin	IV methylprednisolone (2 mg/kg per day in two divided doses) on day 14 × 3 d	Resolution of endoscopic changes at 6 wk
Sykes <i>et al</i> ^[105] (2012)	54F	Pseudomembranous colitis on flexible sigmoidoscopy on day 14	Prednisone 2 mg/kg per day tapered over one month	
		Moderate CDI that resolved with 10-d course antibiotics	Oral metronidazole × 10 d with resolution of symptoms (doses not specified)	Decreased stool frequency, normalization of vital signs, reduction in CRP to 132 within 48 h of steroid initiation
		Recurrent diarrhea and abdominal pain 10 d after completion of antibiotics with left colonic thickening on CT and positive <i>C. difficile</i> toxin	Oral vancomycin and metronidazole upon admission (doses not specified) × 4 d	Resolution of diarrhea, further reduction in CRP to 15 after 9 d of steroid therapy
		Fever, tachycardia on day 4		Resolution of endoscopic changes at 1 mo
		with pseudomembranous colitis on flexible sigmoidoscopy CRP increased from 149 on admission to 236 on day 4	Oral vancomycin 125 mg every 6 h × 9 d IV hydrocortisone 100 mg every 6 h × 9 d Prednisolone 30 mg daily with tapering regimen	Sustained clinical response at 5 mo
	73F	Moderate-severe CDI that resolved with 10-d course antibiotics	Metronidazole 400 mg every 8 h × 10 d with resolution of symptoms	Resolution of diarrhea, normalization of vital signs, reduction in CRP to 7 within 48 h of steroid initiation
		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	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 Prednisolone 30 mg daily × 7 d followed by tapering regimen	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^[84]. 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

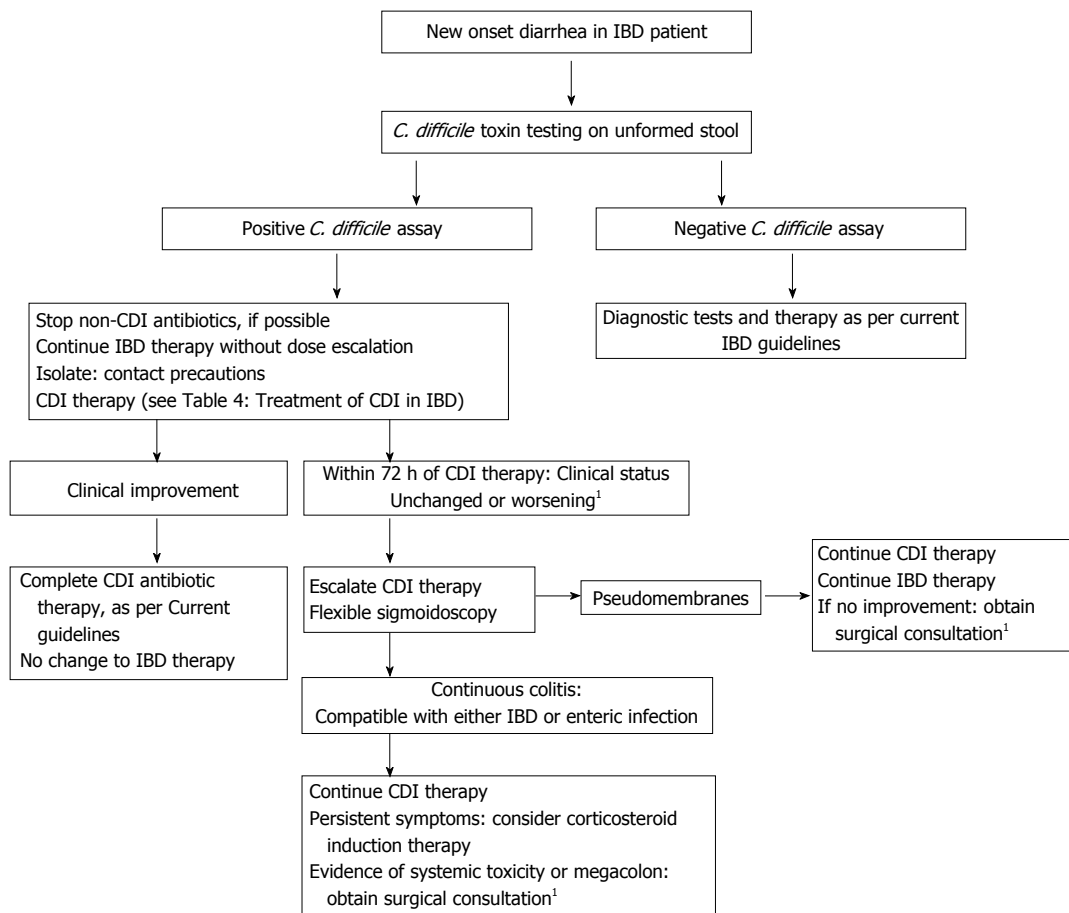


Figure 2 Approach to potential *Clostridium difficile* infection in inflammatory bowel disease patients. ¹Obtain surgical consultation earlier, as dictated by CDI guidelines, should there be evidence of toxic megacolon, or concern for rapid deterioration despite medical therapy. CDI: *Clostridium difficile*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

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

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^[87,88]. Although several meta-analysis exist^[89,90] 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^[88], 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^[87]. 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^[91]. 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.

REFERENCES

- Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011; **365**: 1713-1725 [PMID: 22047562 DOI: 10.1056/NEJMra1102942]
- Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, Gendre JP. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002; **8**: 244-250 [PMID: 12131607]
- Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol* 2013; **108**: 478-498; quiz 499 [PMID: 23439232 DOI: 10.1038/ajg.2013.4]
- Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; **31**: 431-455 [PMID: 20307191 DOI: 10.1086/651706]
- Viscidi R, Laughon BE, Yolken R, Bo-Linn P, Moench T, Ryder RW, Bartlett JG. Serum antibody response to toxins A and B of Clostridium difficile. *J Infect Dis* 1983; **148**: 93-100 [PMID: 6886489]
- Jangi S, Lamont JT. Asymptomatic colonization by Clostridium difficile in infants: implications for disease in later life. *J Pediatr Gastroenterol Nutr* 2010; **51**: 2-7 [PMID: 20512057 DOI: 10.1097/MPG.0b013e3181d29767]
- Shim JK, Johnson S, Samore MH, Bliss DZ, Gerding DN. Primary symptomless colonisation by Clostridium difficile and decreased risk of subsequent diarrhoea. *Lancet* 1998; **351**: 633-636 [PMID: 9500319 DOI: 10.1016/S0140-6736(97)08062-8]
- Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S, Dewar K, Hudson TJ, Horn R, René P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005; **353**: 2442-2449 [PMID: 16322602 DOI: 10.1056/NEJMoa051639]
- McDonald LC, Killgore GE, Thompson A, Owens RC Jr, Kazakova SV, Sambol SP, Johnson S, Gerding DN. An epidemic, toxin gene-variant strain of Clostridium difficile. *N Engl J Med* 2005; **353**: 2433-2441 [PMID: 16322603 DOI: 10.1056/NEJMoa051590]
- Freeman J, Bauer MP, Baines SD, Corver J, Fawley WN, Goorhuis B, Kuijper EJ, Wilcox MH. The changing epidemiology of Clostridium difficile infections. *Clin Microbiol Rev* 2010; **23**: 529-549 [PMID: 20610822 DOI: 10.1128/CMR.00082-09]
- Lessa FC, Winston LG, McDonald LC; Emerging Infections Program C. difficile Surveillance Team. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015; **372**: 2369-2370 [PMID: 26061850 DOI: 10.1056/NEJM1505190]
- Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of Clostridium difficile and serum levels of IgG antibody against toxin A. *N Engl J Med* 2000; **342**: 390-397 [PMID: 10666429 DOI: 10.1056/NEJM200002103420604]
- Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent Clostridium difficile diarrhoea. *Lancet* 2001; **357**: 189-193 [PMID: 11213096 DOI: 10.1016/S0140-6736(00)03592-3]
- Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, Schmidt TM, Young VB. Decreased diversity of the fecal Microbiome in recurrent Clostridium difficile-associated diarrhea. *J Infect Dis* 2008; **197**: 435-438 [PMID: 18199029 DOI: 10.1086/525047]
- Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology* 2014; **146**: 1489-1499 [PMID: 24560869 DOI: 10.1053/j.gastro.2014.02.009]
- Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007; **5**: 339-344 [PMID: 17368233 DOI: 10.1016/j.cgh.2006.12.027]
- Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008; **103**: 1443-1450 [PMID: 18513271 DOI: 10.1111/j.1572-0241.2007.01780.x]
- Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. *Gut* 2008; **57**: 205-210 [PMID: 17905821]
- Sandberg KC, Davis MM, Gebremariam A, Adler J. Disproportionate rise in Clostridium difficile-associated hospitalizations among US youth with inflammatory bowel disease, 1997-2011. *J Pediatr Gastroenterol Nutr* 2015; **60**: 486-492 [PMID: 25419679 DOI: 10.1097/MPG.0000000000000636]
- Bossuyt P, Verhaegen J, Van Assche G, Rutgeerts P, Vermeire S. Increasing incidence of Clostridium difficile-associated diarrhea in inflammatory bowel disease. *J Crohns Colitis* 2009; **3**: 4-7 [PMID: 21172241 DOI: 10.1016/j.crohns.2008.09.003]
- Greenfield C, Aguilar Ramirez JR, Pounder RE, Williams T, Danvers M, Marper SR, Noone P. Clostridium difficile and inflammatory bowel disease. *Gut* 1983; **24**: 713-717 [PMID: 6135648]
- Meyer AM, Ramzan NN, Loftus EV Jr, Heigh RI, Leighton JA. The diagnostic yield of stool pathogen studies during relapses of inflammatory bowel disease. *J Clin Gastroenterol* 2004; **38**: 772-775 [PMID: 15365403 DOI: 10.1097/01.mcg.0000139057.05297.d6]
- Mylonaki M, Langmead L, Pantes A, Johnson F, Rampton DS. Enteric infection in relapse of inflammatory bowel disease: importance of microbiological examination of stool. *Eur J*

- Gastroenterol Hepatol* 2004; **16**: 775-778 [PMID: 15256979]
- 24 **Issa M**, Vijayapal A, Graham MB, Beaulieu DB, Otterson MF, Lundeen S, Skaros S, Weber LR, Komorowski RA, Knox JF, Emmons J, Bajaj JS, Binion DG. Impact of Clostridium difficile on inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007; **5**: 345-351 [PMID: 17368234 DOI: 10.1016/j.cgh.2006.12.028]
 - 25 **Krishnarao A**, de Leon L, Bright R, Moniz H, Law M, Leleiko N, Sands BE, Merrick M, Shapiro J, Wallenstein S, Giacalone J, Shah SA. Testing for Clostridium difficile in patients newly diagnosed with inflammatory bowel disease in a community setting. *Inflamm Bowel Dis* 2015; **21**: 564-569 [PMID: 25581825 DOI: 10.1097/MIB.0000000000000309]
 - 26 **Rolny P**, Järnerot G, Möllby R. Occurrence of Clostridium difficile toxin in inflammatory bowel disease. *Scand J Gastroenterol* 1983; **18**: 61-64 [PMID: 6144171]
 - 27 **Ricciardi R**, Ogilvie JW Jr, Roberts PL, Marcello PW, Concannon TW, Baxter NN. Epidemiology of Clostridium difficile colitis in hospitalized patients with inflammatory bowel diseases. *Dis Colon Rectum* 2009; **52**: 40-45 [PMID: 19273954 DOI: 10.1007/DCR.0b013e31819733df]
 - 28 **Ott C**, Girlich C, Klebl F, Plentz A, Iesalnieks I, Schölmerich J, Obermeier F. Low risk of Clostridium difficile infections in hospitalized patients with inflammatory bowel disease in a German tertiary referral center. *Digestion* 2011; **84**: 187-192 [PMID: 21646782 DOI: 10.1159/000324617]
 - 29 **Antonelli E**, Baldoni M, Giovenali P, Villanacci V, Essatari M, Bassotti G. Intestinal superinfections in patients with inflammatory bowel diseases. *J Crohns Colitis* 2012; **6**: 154-159 [PMID: 22325169 DOI: 10.1016/j.crohns.2011.07.012]
 - 30 **Regnault H**, Bourrier A, Lalande V, Nion-Larmurier I, Sokol H, Seksik P, Barbut F, Cosnes J, Beaugerie L. Prevalence and risk factors of Clostridium difficile infection in patients hospitalized for flare of inflammatory bowel disease: a retrospective assessment. *Dig Liver Dis* 2014; **46**: 1086-1092 [PMID: 25294795]
 - 31 **Murthy SK**, Steinhart AH, Tinmouth J, Austin PC, Daneman N, Nguyen GC. Impact of Clostridium difficile colitis on 5-year health outcomes in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2012; **36**: 1032-1039 [PMID: 23061526 DOI: 10.1111/apt.12073]
 - 32 **Negrón ME**, Barkema HW, Rioux K, De Buck J, Checkley S, Proulx MC, Frolkis A, Beck PL, Dieleman LA, Panaccione R, Ghosh S, Kaplan GG. Clostridium difficile infection worsens the prognosis of ulcerative colitis. *Can J Gastroenterol Hepatol* 2014; **28**: 373-380 [PMID: 25157528]
 - 33 **Shen BO**, Jiang ZD, Fazio VW, Remzi FH, Rodriguez L, Bennett AE, Lopez R, Queener E, Dupont HL. Clostridium difficile infection in patients with ileal pouch-anal anastomosis. *Clin Gastroenterol Hepatol* 2008; **6**: 782-788 [PMID: 18467184 DOI: 10.1016/j.cgh.2008.02.021]
 - 34 **Li Y**, Qian J, Queener E, Shen B. Risk factors and outcome of PCR-detected Clostridium difficile infection in ileal pouch patients. *Inflamm Bowel Dis* 2013; **19**: 397-403 [PMID: 23328770 DOI: 10.1097/MIB.0b013e318280fcb9]
 - 35 **Pascarella F**, Martinelli M, Miele E, Del Pezzo M, Roscetto E, Staiano A. Impact of Clostridium difficile infection on pediatric inflammatory bowel disease. *J Pediatr* 2009; **154**: 854-858 [PMID: 19230908 DOI: 10.1016/j.jpeds.2008.12.039]
 - 36 **Wultańska D**, Banaszekiewicz A, Radzikowski A, Obuch-Woszczyński P, Młynarczyk G, Brazier JS, Pituch H, van Belkum A. Clostridium difficile infection in Polish pediatric outpatients with inflammatory bowel disease. *Eur J Clin Microbiol Infect Dis* 2010; **29**: 1265-1270 [PMID: 20577773 DOI: 10.1007/s10096-010-0997-9]
 - 37 **Mezoff E**, Mann EA, Hart KW, Lindsell CJ, Cohen MB. Clostridium difficile infection and treatment in the pediatric inflammatory bowel disease population. *J Pediatr Gastroenterol Nutr* 2011; **52**: 437-441 [PMID: 21407116 DOI: 10.1097/MPG.0b013e3181f97209]
 - 38 **Banaszkiewicz A**, Kowalska-Duplaga K, Pytrus T, Pituch H, Radzikowski A. Clostridium difficile infection in newly diagnosed pediatric patients with inflammatory bowel disease: prevalence and risk factors. *Inflamm Bowel Dis* 2012; **18**: 844-848 [PMID: 21936029 DOI: 10.1002/ibd.21837]
 - 39 **Mir SA**, Kellermayer R. Clostridium difficile infection in newly diagnosed pediatric inflammatory bowel disease in the mid-southern United States. *J Pediatr Gastroenterol Nutr* 2013; **57**: 487-488 [PMID: 23783013 DOI: 10.1097/MPG.0b013e3182a027c5]
 - 40 **Martinelli M**, Strisciuglio C, Veres G, Paerregaard A, Pavic AM, Aloï M, Martin-de-Carpi J, Levine A, Turner D, Del Pezzo M, Staiano A, Miele E; Porto IBD Working Group of European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). Clostridium difficile and pediatric inflammatory bowel disease: a prospective, comparative, multicenter, ESPGHAN study. *Inflamm Bowel Dis* 2014; **20**: 2219-2225 [PMID: 25268634 DOI: 10.1097/MIB.0000000000000219]
 - 41 **Kuntz JL**, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM. Incidence of and risk factors for community-associated Clostridium difficile infection: a nested case-control study. *BMC Infect Dis* 2011; **11**: 194 [PMID: 21762504 DOI: 10.1186/1471-2334-11-194]
 - 42 **Leffler DA**, Lamont JT. Clostridium difficile infection. *N Engl J Med* 2015; **372**: 1539-1548 [PMID: 25875259 DOI: 10.1056/NEJMra1403772]
 - 43 **Kariv R**, Navaneethan U, Venkatesh PG, Lopez R, Shen B. Impact of Clostridium difficile infection in patients with ulcerative colitis. *J Crohns Colitis* 2011; **5**: 34-40 [PMID: 21272802 DOI: 10.1016/j.crohns.2010.09.007]
 - 44 **Razik R**, Rumman A, Bahreini Z, McGeer A, Nguyen GC. Recurrence of Clostridium difficile Infection in Patients with Inflammatory Bowel Disease: The RECIDIVISM Study. *Am J Gastroenterol* 2016; **111**: 1141-1146 [PMID: 27215924 DOI: 10.1038/ajg.2016.187]
 - 45 **Seril DN**, Ashburn JH, Lian L, Shen B. Risk factors and management of refractory or recurrent clostridium difficile infection in ileal pouch patients. *Inflamm Bowel Dis* 2014; **20**: 2226-2233 [PMID: 25222656 DOI: 10.1097/MIB.0000000000000205]
 - 46 **Kaneko T**, Matsuda R, Taguri M, Inamori M, Ogura A, Miyajima E, Tanaka K, Maeda S, Kimura H, Kunisaki R. Clostridium difficile infection in patients with ulcerative colitis: investigations of risk factors and efficacy of antibiotics for steroid refractory patients. *Clin Res Hepatol Gastroenterol* 2011; **35**: 315-320 [PMID: 21435967 DOI: 10.1016/j.clinre.2011.02.004]
 - 47 **Masclee GM**, Penders J, Jonkers DM, Wolffs PF, Pierik MJ. Is clostridium difficile associated with relapse of inflammatory bowel disease? results from a retrospective and prospective cohort study in the Netherlands. *Inflamm Bowel Dis* 2013; **19**: 2125-2131 [PMID: 23867869]
 - 48 **Furuya-Kanamori L**, Stone JC, Clark J, McKenzie SJ, Yakob L, Paterson DL, Riley TV, Doi SA, Clements AC. Comorbidities, Exposure to Medications, and the Risk of Community-Acquired Clostridium difficile Infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol* 2015; **36**: 132-141 [PMID: 25632995 DOI: 10.1017/ice.2014.39]
 - 49 **Schneeweiss S**, Korzenik J, Solomon DH, Canning C, Lee J, Bressler B. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. *Aliment Pharmacol Ther* 2009; **30**: 253-264 [PMID: 19438424 DOI: 10.1111/j.1365-2036.2009.04037.x]
 - 50 **Suzuki H**, Ogawa H, Shibata C, Haneda S, Watanabe K, Takahashi K, Funayama Y, Sasaki I. The long-term clinical course of pouchitis after total proctocolectomy and IPAA for ulcerative colitis. *Dis Colon Rectum* 2012; **55**: 330-336 [PMID: 22469801 DOI: 10.1097/DCR.0b013e3182417358]
 - 51 **Hughes M**, Qazi T, Berg A, Weinberg J, Chen X, Kelly CP, Farraye FA. Host Immune Response to Clostridium difficile

- Infection in Inflammatory Bowel Disease Patients. *Inflamm Bowel Dis* 2016; **22**: 853-861 [PMID: 26954708 DOI: 10.1097/MIB.0000000000000696]
- 52 **Connelly TM**, Koltun WA, Sangster W, Berg AS, Hegarty JP, Harris L 3rd, Deiling S, Stewart DB. An interleukin-4 polymorphism is associated with susceptibility to Clostridium difficile infection in patients with inflammatory bowel disease: results of a retrospective cohort study. *Surgery* 2014; **156**: 769-774 [PMID: 25239315 DOI: 10.1016/j.surg.2014.06.067]
- 53 **Monaghan TM**, Robins A, Knox A, Sewell HF, Mahida YR. Circulating antibody and memory B-Cell responses to C. difficile toxins A and B in patients with C. difficile-associated diarrhoea, inflammatory bowel disease and cystic fibrosis. *PLoS One* 2013; **8**: e74452 [PMID: 24058568 DOI: 10.1371/journal.pone.0074452]
- 54 **McCurdy JD**, Enders FT, Khanna S, Bruining DH, Jones A, Killian JM, Tariq R, Smyrk TC, Loftus EV Jr. Increased Rates of Clostridium difficile Infection and Poor Outcomes in Patients with IBD with Cytomegalovirus. *Inflamm Bowel Dis* 2016; **22**: 2688-2693 [PMID: 27755270 DOI: 10.1097/MIB.0000000000000939]
- 55 **Ananthkrishnan AN**, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. *J Crohns Colitis* 2013; **7**: 107-112 [PMID: 22440891 DOI: 10.1016/j.crohns.2012.02.015]
- 56 **Ananthkrishnan AN**, Oxford EC, Nguyen DD, Sauk J, Yajnik V, Xavier RJ. Genetic risk factors for Clostridium difficile infection in ulcerative colitis. *Aliment Pharmacol Ther* 2013; **38**: 522-530 [PMID: 23848254 DOI: 10.1111/apt.12425]
- 57 **Jen MH**, Saxena S, Bottle A, Aylin P, Pollok RC. Increased health burden associated with Clostridium difficile diarrhoea in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33**: 1322-1331 [PMID: 21517920]
- 58 **Ananthkrishnan AN**, McGinley EL, Saeian K, Binion DG. Temporal trends in disease outcomes related to Clostridium difficile infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 976-983 [PMID: 20824818 DOI: 10.1002/ibd.21457]
- 59 **Jodorkovsky D**, Young Y, Abreu MT. Clinical outcomes of patients with ulcerative colitis and co-existing Clostridium difficile infection. *Dig Dis Sci* 2010; **55**: 415-420 [PMID: 19255850 DOI: 10.1007/s10620-009-0749-9]
- 60 **Navaneethan U**, Mukewar S, Venkatesh PG, Lopez R, Shen B. Clostridium difficile infection is associated with worse long term outcome in patients with ulcerative colitis. *J Crohns Colitis* 2012; **6**: 330-336 [PMID: 22405170 DOI: 10.1016/j.crohns.2011.09.005]
- 61 **Skowron KB**, Lapin B, Rubin M, Hurst RD, Rubin DT, Hyman NH, Umanskiy K. Clostridium Difficile Infection in Ulcerative Colitis: Can Alteration of the Gut-associated Microbiome Contribute to Pouch Failure? *Inflamm Bowel Dis* 2016; **22**: 902-911 [PMID: 26891259 DOI: 10.1097/MIB.0000000000000710]
- 62 **Kelsen JR**, Kim J, Latta D, Smathers S, McGowan KL, Zaoutis T, Mamula P, Baldassano RN. Recurrence rate of clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 50-55 [PMID: 20722068 DOI: 10.1002/ibd.21421]
- 63 **Bitton A**, Buie D, Enns R, Feagan BG, Jones JL, Marshall JK, Whittaker S, Griffiths AM, Panaccione R; Canadian Association of Gastroenterology Severe Ulcerative Colitis Consensus Group. Treatment of hospitalized adult patients with severe ulcerative colitis: Toronto consensus statements. *Am J Gastroenterol* 2012; **107**: 179-194; author reply 195 [PMID: 22108451 DOI: 10.1038/ajg.2011.386]
- 64 **Ben-Horin S**, Margalit M, Bossuyt P, Maul J, Shapira Y, Bojic D, Chermesh I, Al-Rifai A, Schoepfer A, Bosani M, Allez M, Lakatos PL, Bossa F, Eser A, Stefanelli T, Carbonnel F, Katsanos K, Checchin D, de Miera IS, Reinisch W, Chowers Y, Moran GW; European Crohn's and Colitis Organization (ECCO). Prevalence and clinical impact of endoscopic pseudomembranes in patients with inflammatory bowel disease and Clostridium difficile infection. *J Crohns Colitis* 2010; **4**: 194-198 [PMID: 21122505 DOI: 10.1016/j.crohns.2009.11.001]
- 65 **Wang T**, Matukas L, Streutker CJ. Histologic findings and clinical characteristics in acutely symptomatic ulcerative colitis patients with superimposed Clostridium difficile infection. *Am J Clin Pathol* 2013; **140**: 831-837 [PMID: 24225751 DOI: 10.1309/AJCP2LBRTTJBF3KD]
- 66 **Viscidi R**, Willey S, Bartlett JG. Isolation rates and toxigenic potential of Clostridium difficile isolates from various patient populations. *Gastroenterology* 1981; **81**: 5-9 [PMID: 7239125]
- 67 **Clayton EM**, Rea MC, Shanahan F, Quigley EM, Kiely B, Hill C, Ross RP. The vexed relationship between Clostridium difficile and inflammatory bowel disease: an assessment of carriage in an outpatient setting among patients in remission. *Am J Gastroenterol* 2009; **104**: 1162-1169 [PMID: 19319128 DOI: 10.1038/ajg.2009.4]
- 68 **Hourigan SK**, Chirumamilla SR, Ross T, Golub JE, Rabizadeh S, Saed SA, Elson CO, Kelly CP, Carroll KC, Oliva-Hemker M, Sears C. Clostridium difficile carriage and serum antitoxin responses in children with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 2744-2752 [PMID: 24145927 DOI: 10.1097/OI.MIB.0000435434.53871.36]
- 69 **Sethi AK**, Al-Nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ. Persistence of skin contamination and environmental shedding of Clostridium difficile during and after treatment of C. difficile infection. *Infect Control Hosp Epidemiol* 2010; **31**: 21-27 [PMID: 19929371 DOI: 10.1086/649016]
- 70 **Horton HA**, Dezfoli S, Berel D, Hirsch J, Ippoliti A, McGovern D, Kaur M, Shih D, Dubinsky M, Targan SR, Fleshner P, Vasiliauskas EA, Grein J, Murthy R, Melmed GY. Antibiotics for Treatment of Clostridium difficile Infection in Hospitalized Patients with Inflammatory Bowel Disease. *Antimicrob Agents Chemother* 2014; **58**: 5054-5059 [PMID: 24913174 DOI: 10.1128/AAC.02606-13]
- 71 **Yanai H**, Nguyen GC, Yun L, Lebwahl O, Navaneethan U, Stone CD, Ghazi L, Moayyedi P, Brooks J, Bernstein CN, Ben-Horin S. Practice of gastroenterologists in treating flaring inflammatory bowel disease patients with clostridium difficile: antibiotics alone or combined antibiotics/immunomodulators? *Inflamm Bowel Dis* 2011; **17**: 1540-1546 [PMID: 21674710 DOI: 10.1002/ibd.21514]
- 72 **Brouwer MC**, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev* 2015; (9): CD004405 [PMID: 26362566 DOI: 10.1002/14651858.CD004405.pub5]
- 73 **Siemieniuk RA**, Meade MO, Alonso-Coello P, Briel M, Evaniew N, Prasad M, Alexander PE, Fei Y, Vandvik PO, Loeb M, Guyatt GH. Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Ann Intern Med* 2015; **163**: 519-528 [PMID: 26258555 DOI: 10.7326/M15-0715]
- 74 **Annane D**. Corticosteroids for severe sepsis: an evidence-based guide for physicians. *Ann Intensive Care* 2011; **1**: 7 [PMID: 21906332 DOI: 10.1186/2110-5820-1-7]
- 75 **Ben-Horin S**, Margalit M, Bossuyt P, Maul J, Shapira Y, Bojic D, Chermesh I, Al-Rifai A, Schoepfer A, Bosani M, Allez M, Lakatos PL, Bossa F, Eser A, Stefanelli T, Carbonnel F, Katsanos K, Checchin D, Miera IS, Chowers Y, Moran GW; European Crohn's and Colitis Organization (ECCO). Combination immunomodulator and antibiotic treatment in patients with inflammatory bowel disease and clostridium difficile infection. *Clin Gastroenterol Hepatol* 2009; **7**: 981-987 [PMID: 19523534 DOI: 10.1016/j.cgh.2009.05.031]
- 76 **Khanna S**, Shin A, Kelly CP. Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute. *Clin Gastroenterol Hepatol* 2017; **15**: 166-174 [PMID: 28093134 DOI: 10.1016/j.cgh.2016.10.024]
- 77 **Rahier JF**, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, Domènech E, Eliakim R, Eser A, Frater J, Gassull M,

- Giladi M, Kaser A, Lémann M, Moreels T, Moschen A, Pollok R, Reinisch W, Schunter M, Stange EF, Tilg H, Van Assche G, Vietg N, Vucelic B, Walsh A, Weiss G, Yazdanpanah Y, Zabana Y, Travis SP, Colombel JF; European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009; **3**: 47-91 [PMID: 21172250 DOI: 10.1016/j.crohns.2009.02.010]
- 78 **Absah I**, Faubion WA Jr. Concomitant therapy with methotrexate and anti-TNF- α in pediatric patients with refractory crohn's colitis: a case series. *Inflamm Bowel Dis* 2012; **18**: 1488-1492 [PMID: 21882301 DOI: 10.1002/ibd.21885]
- 79 **Cammarota G**, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G, Sanguinetti M, Gasbarrini A. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2015; **41**: 835-843 [PMID: 25728808 DOI: 10.1111/apt.13144]
- 80 **Lee CH**, Steiner T, Petrof EO, Smieja M, Roscoe D, Nematallah A, Weese JS, Collins S, Moayyedi P, Crowther M, Ropeleski MJ, Jayaratne P, Higgins D, Li Y, Rau NV, Kim PT. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent *Clostridium difficile* Infection: A Randomized Clinical Trial. *JAMA* 2016; **315**: 142-149 [PMID: 26757463 DOI: 10.1001/jama.2015.18098]
- 81 **van Nood E**, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kujper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; **368**: 407-415 [PMID: 23323867 DOI: 10.1056/NEJMoa1205037]
- 82 **Kelly CR**, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, Aroniadis O, Barto A, Borody T, Giovanelli A, Gordon S, Gluck M, Hohmann EL, Kao D, Kao JY, McQuillen DP, Mellow M, Rank KM, Rao K, Ray A, Schwartz MA, Singh N, Stollman N, Suskind DL, Vindigni SM, Youngster I, Brandt L. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol* 2014; **109**: 1065-1071 [PMID: 24890442 DOI: 10.1038/ajg.2014.133]
- 83 **Fischer M**, Kao D, Kelly C, Kuchipudi A, Jafri SM, Blumenkehl M, Rex D, Mellow M, Kaur N, Sokol H, Cook G, Hamilton MJ, Phelps E, Sipe B, Xu H, Allegretti JR. Fecal Microbiota Transplantation is Safe and Efficacious for Recurrent or Refractory *Clostridium difficile* Infection in Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2016; **22**: 2402-2409 [PMID: 27580384 DOI: 10.1097/MIB.0000000000000908]
- 84 **Chin SM**, Sauk J, Mahabamunage J, Kaplan JL, Hohmann EL, Khalili H. Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection in Patients With Inflammatory Bowel Disease: A Single-Center Experience. *Clin Gastroenterol Hepatol* 2017; **15**: 597-599 [PMID: 27923723 DOI: 10.1016/j.cgh.2016.11.028]
- 85 **Khoruts A**, Rank KM, Newman KM, Viskocil K, Vaughn BP, Hamilton MJ, Sadowsky MJ. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection. *Clin Gastroenterol Hepatol* 2016; **14**: 1433-1438 [PMID: 26905904 DOI: 10.1016/j.cgh.2016.02.018]
- 86 **Newman KM**, Rank KM, Vaughn BP, Khoruts A. Treatment of recurrent *Clostridium difficile* infection using fecal microbiota transplantation in patients with inflammatory bowel disease. *Gut Microbes* 2017; **8**: 303-309 [PMID: 28102756 DOI: 10.1080/19490976.2017.1279377]
- 87 **Rossen NG**, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflo A, Löwenberg M, van den Brink GR, Mathus-Vliegen EM, de Vos WM, Zoetendal EG, D'Haens GR, Ponsioen CY. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology* 2015; **149**: 110-118.e4 [PMID: 25836986 DOI: 10.1053/j.gastro.2015.03.045]
- 88 **Moayyedi P**, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, Armstrong D, Marshall JK, Kassam Z, Reinisch W, Lee CH. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* 2015; **149**: 102-109.e6 [PMID: 25857665 DOI: 10.1053/j.gastro.2015.04.001]
- 89 **Sun D**, Li W, Li S, Cen Y, Xu Q, Li Y, Sun Y, Qi Y, Lin Y, Yang T, Xu P, Lu Q. Fecal Microbiota Transplantation as a Novel Therapy for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *Medicine* (Baltimore) 2016; **95**: e3765 [PMID: 27281075 DOI: 10.1097/MD.00000000000003765]
- 90 **Shi Y**, Dong Y, Huang W, Zhu D, Mao H, Su P. Fecal Microbiota Transplantation for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *PLoS One* 2016; **11**: e0157259 [PMID: 27295210 DOI: 10.1371/journal.pone.0157259]
- 91 **Paramsothy S**, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, Samuel D, Leong RWL, Connor S, Ng W, Paramsothy R, Xuan W, Lin E, Mitchell HM, Borody TJ. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017; **389**: 1218-1228 [PMID: 28214091 DOI: 10.1016/S0140-6736(17)30182-4]
- 92 **Keighley MR**. *Clostridium difficile* and inflammatory bowel disease. *J Antimicrob Chemother* 1983; **11**: 493-494 [PMID: 6885673]
- 93 **Gurian L**, Klein K, Ward TT. Role of *Clostridium difficile* and *Campylobacter jejuni* in relapses of inflammatory bowel disease. *West J Med* 1983; **138**: 359-360 [PMID: 6858121]
- 94 **Burke DA**, Axon AT. *Clostridium difficile*, sulphasalazine, and ulcerative colitis. *Postgrad Med J* 1987; **63**: 955-957 [PMID: 2897683]
- 95 **Gryboski JD**. *Clostridium difficile* in inflammatory bowel disease relapse. *J Pediatr Gastroenterol Nutr* 1991; **13**: 39-41 [PMID: 1919950]
- 96 **Balamurugan R**, Balaji V, Ramakrishna BS. Estimation of faecal carriage of *Clostridium difficile* in patients with ulcerative colitis using real time polymerase chain reaction. *Indian J Med Res* 2008; **127**: 472-477 [PMID: 18653911]
- 97 **Lamousé-Smith ES**, Weber S, Rossi RF, Neinstedt LJ, Mosammaparast N, Sandora TJ, McAdam AJ, Bousvaros A. Polymerase chain reaction test for *Clostridium difficile* toxin B gene reveals similar prevalence rates in children with and without inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2013; **57**: 293-297 [PMID: 23698022 DOI: 10.1097/MPG.0b013e3182999990]
- 98 **Pant C**, Anderson MP, Deshpande A, Altaf MA, Grunow JE, Atreja A, Sferra TJ. Health care burden of *Clostridium difficile* infection in hospitalized children with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 1080-1085 [PMID: 23478808 DOI: 10.1097/MIB.0b013e3182807563]
- 99 **Hourigan SK**, Oliva-Hemker M, Hutfless S. The prevalence of *Clostridium difficile* infection in pediatric and adult patients with inflammatory bowel disease. *Dig Dis Sci* 2014; **59**: 2222-2227 [PMID: 24788321]
- 100 **Simian D**, Fluxá D, Flores L, Lubascher J, Ibáñez P, Figueroa C, Kronberg U, Acuña R, Moreno M, Quera R. Inflammatory bowel disease: A descriptive study of 716 local Chilean patients. *World J Gastroenterol* 2016; **22**: 5267-5275 [PMID: 27298570 DOI: 10.3748/wjg.v22.i22.5267]
- 101 **Roy A**, Lichtiger S. *Clostridium difficile* Infection: A Rarity in Patients Receiving Chronic Antibiotic Treatment for Crohn's Disease. *Inflamm Bowel Dis* 2016; **22**: 648-653 [PMID: 26650148 DOI: 10.1097/MIB.0000000000000641]
- 102 **Ananthakrishnan AN**, Cagan A, Gainer VS, Cheng SC, Cai T, Szolovits P, Shaw SY, Churchill S, Karlson EW, Murphy SN, Kohane I, Liao KP. Higher plasma vitamin D is associated with reduced risk of *Clostridium difficile* infection in patients with inflammatory bowel diseases. *Aliment Pharmacol Ther* 2014; **39**: 1136-1142 [PMID: 24641590 DOI: 10.1111/apt.12706]
- 103 **Chu EW**, Ecker BL, Garg M, Divino CM. The surgical

- management of active ulcerative colitis complicated by Clostridium difficile infection. *J Gastrointest Surg* 2013; **17**: 392-396 [PMID: 23135837 DOI: 10.1007/s11605-012-2031-2]
- 104 **Cavagnaro C**, Berezin S, Medow MS. Corticosteroid treatment of severe, non-responsive Clostridium difficile induced colitis. *Arch Dis Child* 2003; **88**: 342-344 [PMID: 12651766]
- 105 **Sykes E**, McDonald P, Flanagan PK. Corticosteroids in the Treatment of Pseudomembranous Colitis: A Report of 3 Cases. *Gastroenterology Res* 2012; **5**: 211-214 [PMID: 27785209 DOI: 10.4021/gr469w]
- P- Reviewer:** Begun J, Matowicka-Karna J, Tambuwala M, Zhulina Y
S- Editor: Qi Y **L- Editor:** A **E- Editor:** Zhang FF





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgooffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



ISSN 1007-9327

