Patients with Inflammatory Bowel Disease and the Higher Incidence of Clostridium Difficile Infection

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Abstract
This study aimed at analyzing the patients with inflammatory bowel disease and the higher incidence of clostridium difficile infection by emphasizing the theoretical review of studies discussing the inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis. And by discussing the treatment of CDI in IBD patients, the diagnosis of CDI in IBD, and the risk factors for CDI in IBD. The study concluded that clinicians should be cautious about the chances of CDI in patients who have an exacerbation of IBD. At times the IBD flare cannot be differentiated from CDI requiring a high degree of clinical suspicion and vouching for early stool testing for toxin assay. When CDI in IBD are established primarily within two days of hospital admission it suggests that a good number of the infection was acquired before admission. CDI should, therefore, be suspected in differentiated diagnosis for intractable IBD patients, because many such patients need not present with a history of antibiotic exposure or hospital admission and may largely be receiving outpatient treatment.

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1.1 Introduction

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, affect millions of people around the world, most of whom are diagnosed before age 35. These chronic, life-long conditions can be treated but not cured. Inflammatory bowel diseases (IBD) can significantly affect a patient's quality of life and may have a high financial burden (Strober, Fuss & Mannon, 2007).

Inflammatory bowel disease (IBD) is a term used to describe two main diseases: ulcerative colitis (see figure 1) and Crohn's disease which cause inflammation of the bowel. This inflammation is thought to be due to dysfunction of your immune system, and is not due to an infection. Ulcerative colitis causes inflammation of only the inner lining of the colon and rectum (large bowel). When only the rectum is involved it is sometimes called ulcerative proctitis or just proctitis. When the entire colon is involved it is sometimes called pan-colitis (Stein, 2004).

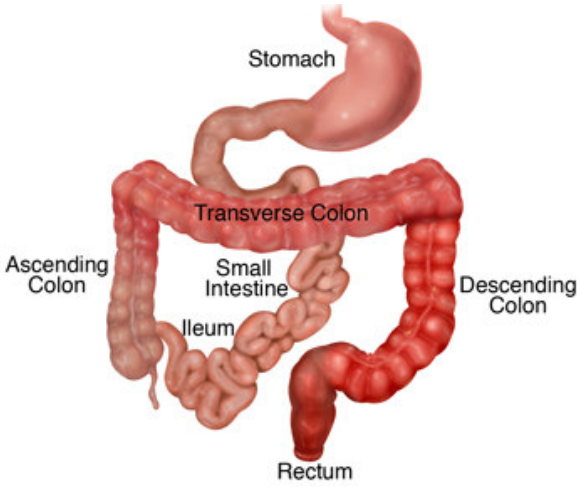

Figure (1): Ulcerative colitis

Crohn's disease (see figure 2) causes inflammation of the full thickness of the bowel wall and may involve any part of the digestive tract from the mouth to the anus (back passage). Most frequently the ileum, which is the last part of the small bowel, the colon or both are involved. These patterns of disease location are referred to as ileitis, colitis and ileo-colitis respectively (Horsthuis, Bipat, Bennink & Stoker, 2008).

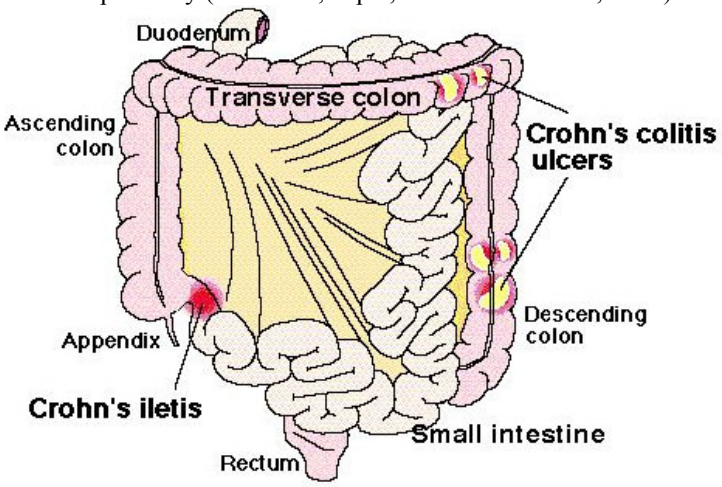

Figure (2): Crohn's disease

Inflammatory bowel disease (IBD) is the collective name for ulcerative colitis (UC) and Crohn's disease (CD), which characteristically run a chronic, and largely unpredictable, relapsing and remitting course in terms of both frequency and severity. Around one in 700 people are affected with IBD in the world, which commonly occurs between the ages of 15 and 40, although any age group can be affected. Treatment of active disease episodes with a combination of drugs, diet and appropriately timed surgery, and maintenance of remission thereafter form the basis of management (Nightingale, 2007).

Clostridium difficile is an anaerobic, gram-positive rod bacterium that may be a normal inhabitant of the human colon, or transmitted exogenously via ingestion (Steele, McCormick, Melton, Paquette, Rivadeneira, Stewart & Rafferty, 2015).

Alterations in the bacterial component of the microbiome, most often due to the use of antibiotics, can lead to bacterial ecological changes that can select for both population growth of C difficile as well as the induction of pathogenic behavior. C difficile is the leading cause of infectious diarrhea in hospitals in the developed world, including up to 20% of reported antibiotic-associated diarrhea and nearly all incidences of pseudomembranous colitis (Bartlett, 2002).

Although the bacteria are present the stool of ~3% of healthy adults, up to 50% of those exposed to an in-patient facility are asymptomatic carriers. Higher rates have been cited in patients following a prolonged duration of exposure to antibiotics, and in those with severe underlying comorbid disease.3–5 Infection can result in a wide range of presentations, from an asymptomatic carrier state or mild C difficile infection (CDI) to a severe and life-threatening condition (Table 1).

Table (1): Terminology associated with Clostridium difficile

Terms	Definitions
Antibiotic-associated diarrhea	Diarrhea in an individual who is currently taking or has recently taken antibiotics (not necessarily from C difficile, although C difficile is a cause of this type of diarrhea). Symptoms include watery diarrhea and abdominal cramping
Asymptomatic colonization/carriage	Patient is colonized with C difficile without signs or symptoms of CDI
CDI	Presence of diarrhea characterized by >3 watery stools per day Other symptoms can include fever, abdominal pain, cramping, nausea, and loss of appetite Typically presents in high-risk patients (elderly, immunocompromised, nursing home residents, or severe underlying disease) with exposure to antibiotics
Pseudomembranous colitis	Presence of plaque formations on colon membranes Considered pathognomonic for CDI in the appropriate clinical setting
Toxic colitis	Extreme inflammation and distention of the colon often resulting from a severe episode of colitis Symptoms include abdominal distension and pain, fever, dehydration, sepsis

Source: Steele, S. R., McCormick, J., Melton, G. B., Paquette, I., Rivadeneira, D. E., Stewart, D & Rafferty, J. (2015).

Clostridium difficile (C. difficile) infection in hospitals in the world continues to be a major public health hazard despite increased control measures including review of antibiotic policies and hygiene measures. Patients with colitis are thought to be particularly vulnerable to C. difficile associated diarrhea (CDAD). Identifying the clinical burden among hospitalized patients admitted with inflammatory bowel disease is an essential first step towards identifying and treating severe C. difficile infection in such individuals (Jen, Saxena, Bottle, Aylin & Pollok, 2011).

Inflammatory bowel disease (IBD) is a chronic condition characterized by unpredictable relapses and periods of remission. The cause is uncertain, but genes interacting with environmental triggers may play a part. Symptoms of IBD vary according to the disease site and severity. Accurate diagnosis is critical and is made through a combination of symptom history review, clinical features and laboratory tests. Treatment strategies focus on resolving symptoms as well as improving quality of life (Nightingale, 2007).

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 (Danese & Fiocchi, 2011).

1.2 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.

1.3 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 2). 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 (Sandberg, Davis, Gebremariam & Adler, 2015).

Several studies demonstrate a disproportionate rise in CDI in the IBD population as compared to the general population, while others do not (Bossuyt, Verhaegen, Van Assche, Rutgeerts & Vermeire, 2009).

Table (2): Epidemiology of *Clostridium difficile* infection in inflammatory bowel disease

Ref.	Patient population	Sampling time frame	Diagnosis method	Disease activity	Conclusions
Meyer *et al* (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
Issa *et al* (2007)	IBD adult inpatients and outpatients	2005	ELISA for Toxins A/B	Active	CDI incidence (%) UC: 6.1; CD: 4.1
Shen *et al* (2008)	UC adult outpatients with IPAA	2005-2006	ELISA for Toxin A/B	Mixed	CDI incidence (%) UC: 18.3
Bossuyt *et al* (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
Wultańska *et al* (2010)	IBD pediatric outpatients	2005-2007	EIA for Toxins A/B	Mixed	CDI incidence (%) IBD: 60; UC: 61; CD: 59
Banaszkiewicz *et al* (2012)	IBD pediatric inpatients	2007-2010	EIA for Toxins A and B	Mixed	CDI incidence (%) IBD: 47
Masclee *et al* (2013)	IBD adult outpatients	2009-2010	PCR for *C. difficile* and Toxin A/B	Active	CDI incidence (%) IBD: 4.9; UC: 3.4; CD: 5.9
Martinelli *et al* (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
Krishnarao *et al* (2015)	IBD adult inpatients and outpatients	2008-2011	EIA and PCR	Mixed	CDI incidence (%) IBD: 5.1
imian *et al* (2016)	IBD adult and pediatric inpatients and outpatients	2014-2015	PCR	N/R	CDI incidence (%) UC: 5.0; CD: 5.0

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. In mixed inpatient and outpatient adult IBD populations, the incidence of CDI ranges between 5.1%-16.7% (Krishnarao, de Leon, Bright, Moniz, Law, Leleiko, Sands, Merrick, Shapiro & Wallenstein, 2015).

Studies report the incidence of CDI in CD adult inpatients between 1.0 and 7.7%. In adult UC inpatients, the incidence of CDI ranges from 2.8% to 11.1%. In adult outpatients with ileal-anal pouch anastomosis (IPAA) for IBD, incidence of CDI is 10.7%-18.3%. 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 (Banaszkiewicz, Kowalska-Duplaga, Pytrus, Pituch & Radzikowski, 2012).

1.4 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.

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.

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. 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). Several others contradict this. 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). No studies have identified gastric acid-suppressive therapy as a risk factor for CDI in the IBD population.

Table (3): Risk factors for *Clostridium difficile* infection in inflammatory bowel disease

Ref.	Sampling time frame	Setting	Diagnosis method	Identified risk factors	
				HOST	ENVIRONMENT
Razik *et al* (2016)	2010-2013	Inpatient	PCR	Non-ileal CD	Hospitalisation for CDI; recent antibiotic use; biologic therapy; 5-ASA; Steroids
McCurdy *et al* (2016)	2005-2011	Inpatient and outpatient	PCR	CMV infection	N/A
Regnault *et al* (2014)	2008-2010	Inpatient	Stool culture on selective medium + cytotoxicity assay +/- toxigenic culture	None identified	NSAIDs
Ananthakrishnan *et al* (2013)	N/R	Inpatient and outpatient	ELISA for Toxin A/B	Female sex; pancolitis; IBD-related SNPs	Protective : Anti-TNF therapy
Kaneko *et al* (2011)	2006-2009	Inpatient and outpatient	ELISA for Toxin A	None identified	None identified
Schneeweiss *et al*] (2009)	2001-2006	Inpatient and outpatient	N/R	Not studied	Corticosteroid initiation
Issa *et al* (2007)	2005	Inpatient	ELISA for Toxin A/B	Colonic involvement	Maintenance immunomodulatory use

Most studies demonstrate ongoing steroid, biologic, or immunomodulatory therapy does not increase the risk of CDI in IBD patients, 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 immunomodulatory use, defined as azathioprine, 6-mercaptopurine, or methotrexate (OR = 2.56, 95%CI: 1.28-5.12, P = 0.008). In the general population, corticosteroid use increases the risk of CDI. 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. 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 immunomodulatory therapy.

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. 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. 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.

Genetic and immunologic risk factors have been identified in IBD patients for the development of CDI. In a retrospective cohort study of 172 IBD patients, an interleukin-4-associated single nucleotide polymorphism (rs2243250) is associated with CDI in IBD. Monaghan et al 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. 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*. As in the general population, patient comorbidities increase the risk of CDI in the IBD population. 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.

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. 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. 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).

1.5 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. 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. 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 (Mir & Kellermayer, 2013).

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. 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. 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 (Wang, Matukas & Streutker, 2013).

Testing *via* PCR should only be performed on 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. 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. 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. 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. 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. 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.

1.6 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 (Surawicz, Brandt, Binion, Ananthakrishnan, Curry, Gilligan, McFarland, Mellow & Zuckerbraun, 2013).

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 as shown in table 4 (Horton, Dezfoli, Berel, Hirsch, Ippoliti, McGovern, Kaur, Shih, Dubinsky & Targan, 2014).

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.

Table (4): Treatment of clostridium difficile infection in inflammatory bowel disease

Severity	Criteria	Treatment
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
Severe disease	Serum albumin < 3 g/dL AND one of the following:	Vancomycin 125 mg by mouth 4 times per day for 10 to 14 d
	WBC ≥ 15000 cells/mm^3	
	Abdominal tenderness	
	Creatinine ≥ 133 μmol/L	
Severe, complicated disease	Admission to intensive care unit	Vancomycin 500 mg by mouth or nasogastric tube 4 times per day
	Hypotension ± vasopressor requirement	
	Fever ≥ 38.5 °C	Metronidazole 500 mg IV every 8 h
	Ileus	and, if ileus,
	Mental status changes	Vancomycin 500 mg in 500 mL saline as enema 4 times per day

1.7 Discussion

In Chetana & Rakesh (2017) study the risk of *C. difficile* acquisition with IBD patients has increased in frequency and severity. The carriage of toxin producing *C. difficile* has been more often found in IBD patients in comparison to the general population. Evidence has been established that IBD patients have gut flora which is *C. difficile* t from patients without IBD, predisposing to colonization with *C. difficile* and other pathogens. This is particularly true because of their innate immune deficiencies, use of antibiotics and immunosuppressive for a long period of time as well as frequent hospitalizations [19]. In the present study 95 (13.2%) IBD patients were on steroids and at least 212 (29%) were hospitalized for treatment. Uncommon features like recurrent bloody stools, younger age-group patients and no previous hospital contact may be found in IBD patients with CDI. In the present study a very large number of patients in the IBD group had bloody stools compared to the non-IBD group and the patients were also significantly younger. However, *C. difficile* toxin positivity was almost similar in both the IBD and the non-IBD groups, contrary to expectations. Ott et al. also reported low risk of CDI in hospitalized patients with IBD in a tertiary referral center in Germany. Low prevalence of *C. difficile* in IBD patients was also reported by Masclee et al. indicating that *C. difficile* does not commonly elicit IBD flare-ups in the Netherlands. In an earlier preliminary investigation we also observed that there was insignificant risk of CDI in IBD cases probably as the hyper virulent strains present in other geographical region has not been detected here so far. Moreover patients in the non-IBD group comprised largely of hospitalized patients suspected of CDI because of diarrhea. An episode of CDI is characterized by watery diarrhea with abdominal cramps and fever. The similar presentation of abdominal pain and diarrhea, makes diagnosis of CDI in IBD patients *C. difficile*. A higher prevalence of asymptomatic CDI is seen in IBD. Watery diarrhea was present in less than one-third of the IBD patients to that present in the non-IBD group. Fever was also similarly present in a little more than one-third of the IBD patients to that present in the non-IBD group. Abdominal pain was However, found to be more frequent in presentation in the IBD group probably because of the inflammatory nature of the disease. Presence of mucus in stool is also a distinguishing aspect of *C. difficile* diarrhea. However, in our IBD patients, the number of stool samples with mucus was much less compared to that of the non-IBD group. The only explanation in this context could be that lesser mucus was produced as the patients were under treatment or because mucus was probably camouflaged due to the presence of blood in stool in many of the IBD patients.

1.8 Conclusion

Clinicians should be cautious about the chances of CDI in patients who have an exacerbation of IBD. At times the IBD flare cannot be differentiated from CDI requiring a high degree of clinical suspicion and vouching for early stool testing for toxin assay. When CDI in IBD are established primarily within two days of hospital admission it suggests that a good number of the infection was acquired before admission. CDI should, therefore, be suspected in differentiated diagnosis for intractable IBD patients, because many such patients need not present with a history of antibiotic exposure or hospital admission and may largely be receiving outpatient treatment. Absence of antibiotic exposure should not decrease the suspicion of CDI in IBD patients. Even when diarrhea is not present, presence of other clinical symptoms and laboratory findings indicate a potential infectious condition, ruling out *C. difficile* would be a practical measure. Careful surveillance for CDI among all IBD patients exhibiting a flare of the disease should be done for early identification and aggressive treatment for reducing the morbidity of CDI among them.

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