***Clostridium difficile* and inflammatory bowel disease: implications for current clinical practice**

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Abstract

Clostridium difficile infection should always be included in the differential diagnosis of patients with refractory inflammatory bowel disease (IBD) symptoms, as it is well known to induce or mimic a flare of IBD. There is currently an alarming increase in the incidence of *C. difficile* infection in Europe and North America. Current epidemiologic data suggest that more virulent strains, such as *C. difficile* 027/ NAPI/BI, are emerging. Testing for both *C. difficile* toxins A and B should be done, and often serial stool samples may be required, especially if the index of suspicion is high. Patients with IBD do not necessarily require a history of antibiotic use or hospitalization to acquire the infection and most do not have pseudomembranes on sigmoidoscopy. *C. difficile* infection is associated with longer hospital stays, increased mortality, and higher complication rates, including colectomy. Treatment with oral vancomycin is probably the drug of choice as one study suggests that patients had lower colectomy rates on this drug. Further work is required to clarify the best management strategies for *C. difficile* in IBD patients, and more effort is needed to halt the rising incidence of this infection, perhaps with adherence to safer antibiotic prescribing guidelines, hand washing, and cleaner hospital environments, which should reduce the risk of acquiring and spreading this preventable infection.

Introduction and context

Issues in *Clostridium difficile* infection and inflammatory bowel disease

Clostridium difficile infection has gained recent attention because of its rising incidence in hospitalized patients. *C. difficile* complicates the management of inflammatory bowel disease (IBD) and often can be overlooked in a patient who presents with an exacerbation of symptoms. The dilemma facing physicians is when, how often, and in whom to order expensive stool tests for *C. difficile*. The other issue is how to differentiate faecal carriage of *C. difficile* from an infection in patients with IBD. The association of *C. difficile* with IBD is neither novel nor recent. In a series of case reports in the early 1980s, LaMont and Trnka [1] identified an association between the presence of *C. difficile* toxin and IBD exacerbation. Subsequently, a prospective study by the same

investigators showed that *C. difficile* toxin was found in the stool of 19% of IBD patients, suggesting that *C. difficile* can cause worsening of disease activity in patients with IBD [2]. In that study, *C. difficile* was not necessarily associated with antibiotic use. In contrast, a second group of investigators found that *C. difficile* toxin was present mostly in the stool of IBD patients exposed to antibiotics, and concluded that there was no association with IBD activity [3]. More recently, Meyer and colleagues [4] showed that 20% of patients with IBD who relapsed had a positive stool test for *C. difficile* toxin. *C. difficile* was observed in 10 of 12 patients whose stool specimens were positive for any pathogen, all 10 of whom improved clinically with treatment for *C. difficile*. Furthermore, antibiotic use was associated with 90% of the patients who tested positive for *C. difficile* [4].

What has changed since these early reports is the rising incidence of *C. difficile* infections in hospitalized patients in North America [5,6] and Europe [6] noted mostly since the turn of this century. Data from US hospital discharges have revealed a doubling of *C. difficile*-associated disease (CDAD) between 1996 and 2003 [7], and the proportion of patients diagnosed with *C. difficile* increased by 26% from 2000 to 2001 in non-federal US hospitals [8]. Patients recently treated with broad-spectrum antibiotics, hospitalized patients, immunocompromised individuals, the elderly, and patients with cancer are all at increased risk for CDAD. IBD patients are frequently on long-term immunosuppressants, are more likely to be hospitalized, often require antibiotics, and have many of the risk factors for acquiring CDAD. This brief report will look at the impact of rising *C. difficile* rates on the IBD population and the implications for the clinical management of these patients in this era of epidemic rates of *C. difficile* infections.

Recent advances

***C. difficile* is an escalating problem in IBD patients**

Data from two tertiary referral centres from the US showed that the incidence of CDAD has not only risen among hospitalized patients, but was disproportionately higher in those with IBD [9,10]. A study from St Louis, Missouri, examined all admissions to a tertiary medical centre from 1998 to 2004 and found that the incidence of *C. difficile* infection had increased among both IBD and non-IBD patients, with the greatest increase occurring among those with ulcerative colitis (UC) [10]. The odds ratio for CDAD in Crohn's disease (CD) was 2.1 [95% confidence interval (CI) 1.3 to 3.4], and the odds ratio for CDAD in UC was 4.0 (95% CI 2.4 to 6.6). The median numbers of days from admission to acquiring CDAD were 0.5 days for UC, 0.8 days for CD, and 4.0 days for all non-IBD diagnoses. While 63% of IBD patients who acquired CDAD did so within 48 hours of admission, 63% of non-IBD patients did so only after 48 hours [10].

Another study, from Milwaukee, Wisconsin, reviewed data from all patients who were followed at this tertiary IBD centre between 2000 and 2005 [9]. During the last 2 years of the study, the incidence of *C. difficile* infection rose from 1.8 to 4.6%. The proportions of IBD patients within the total number of patients diagnosed with CDAD were 4% in 2003, 7% in 2004, and 16% in 2005. Of these, 76% of individuals with IBD contracted CDAD as an outpatient and 61% of IBD patients with *C. difficile* infection had prior antibiotic exposure (most commonly, ciprofloxacin). Community-acquired CDAD occurred three times as often as nosocomial disease.

None of the IBD patients with CDAD had pseudomembranes [9]. Also, data from Leuven, Belgium, have shown a 3.75-fold increase in CDAD between January 2000 and January 2008 [11]. Considerably fewer IBD patients (42%) had been noted to have taken prior antibiotics compared with non-IBD patients (69%).

Impact of *C. difficile* infection on IBD outcomes

In the Milwaukee study, more than 50% of patients with IBD and *C. difficile* required hospitalization and 20% of hospitalized IBD patients with CDAD required colectomy. Immunosuppression and colonic involvement were independent risk factors for CDAD in IBD [9]. Furthermore, US data from the Nationwide Inpatient Sample (2003) suggested that patients with *C. difficile* and IBD had four times the mortality of those admitted with IBD alone [adjusted odds ratio (aOR) 4.7, 95% CI 2.9 to 7.9] and twice the mortality of those admitted with *C. difficile* but not IBD (aOR 2.2, 95% CI 1.4 to 3.4) [12]. IBD patients with *C. difficile* also stayed in hospital longer by an average of 3 days (95% CI 2.3 to 3.7 days).

Intriguingly, the clinical outcomes in the study from Leuven were better, with IBD patients having a shorter duration of hospitalization and with only one patient with UC needing a colectomy [11]. Similarly, the St Louis, Missouri group also noted no differences in length of stay between CDAD patients with IBD and those without IBD [10].

Unusual aspects of *C. difficile* infection in IBD

Several factors may underlie the increasing incidence of *C. difficile* among patients with IBD. Increased awareness among physicians, more sensitive enzyme-linked immunosorbent assay tests for detection of the toxin in stool samples, and a serendipitous rise unrelated to IBD in hospitalized patients have all been put forward as explanations. However, there seem to be many differences between IBD patients infected with *C. difficile* compared with others. The first is that a relatively larger number of IBD patients have community-acquired infections [9,10]. Second, fewer IBD patients have had prior antibiotic use [9–11]. Third, none of the patients with IBD appear to have developed pseudomembranes [9,13]. The absence of pseudomembranes can be attributed to immunosuppression, as studies suggest that patients with bone marrow or stem cell transplants on immunosuppression, and those with UC on steroids, did not develop pseudomembranes with *C. difficile* infection [13]. Finally, there have been increasing reports of *C. difficile* enteritis complications in patients after recent total colectomy [14], or even, rarely, many years following a protocolectomy, usually presenting as increased ileostomy output or prolonged ileus [15].

While *C. difficile* enteritis is unusual, it may not be surprising as early studies involving autopsies [16] and jejunal aspirates [17] have suggested that the small bowel may in fact be the reservoir for *C. difficile* in humans.

There is considerable debate on whether *C. difficile* is just a colonizer in most patients with IBD or whether the infection does indeed cause an infective colitis superimposed on IBD. An intriguing report from Southern India (where *C. difficile* infection is still an uncommon cause of antibiotic-associated diarrhoea) using quantitative polymerase chain reaction (PCR) of species-specific 16s rDNA of *C. difficile* detected *C. difficile* in 34 of 37 UC patients and 20 of 36 healthy volunteers [18]. However, there were significantly higher numbers of *C. difficile* in UC patients but only eight UC and two healthy volunteers were toxin-positive as well. None of the patients had received antibiotics for at least 2 months prior to the study, and none of the patients were treated for *C. difficile* infection with no adverse events [18]. This suggests that there is an overgrowth of *C. difficile* in UC patients in India detected by PCR, but the clinical significance is uncertain.

Implications for clinical practice

Top tips for management

1. *Always think C. difficile* Have a high index of suspicion for *C. difficile* in symptomatic IBD patients. Patients with unusual symptoms like watery rather than bloody diarrhoea in combination with colonic IBD, fever, non-resolving symptoms with standard treatment, and the presence of risk factors like recent antibiotic use or patients on maintenance immunosuppression should have their stool checked for *C. difficile* and treated if positive.

2. *If in doubt, test and test again.* Testing multiple stool samples may be needed to confirm the diagnosis. Ninety-two percent of patients were detected by the fourth sample in the Milwaukee study, and in one patient the diagnosis was made on only the eighth sample [9].

3. *Never underestimate your foe.* Due to concomitant IBD, it would be difficult to grade the severity of the *C. difficile* colitis but it would be prudent to treat these patients as if they had severe CDAD. The Milwaukee experience suggests a high rate of failure with metronidazole and a lower rate of colectomy with oral vancomycin, therefore oral vancomycin should be the preferred drug of choice [9].

4. *Expect the unexpected.* Consider *C. difficile* in patients with prolonged ileus post-colectomy for IBD or increased ileostomy outputs. Chronic pouchitis has also been attributed to *C. difficile* in patients with ileo anal pouch anastomosis [19].

5. *Prevention is cure.* Concomitant *C. difficile* and IBD has been associated with higher mortality, higher colectomy rates, and longer hospitalization. We, as the medical fraternity, have a responsibility to our patients and should not be lax in adhering to safe antibiotic prescribing guidelines or in implementing simple measures like hand washing between patients to reduce the spread of this infection.

Future directions

Randomized controlled trials are needed to clarify the best management strategy for concomitant *C. difficile* in IBD patients. What dose of vancomycin should be used? Would a tapering schedule of vancomycin help prevent relapse? Are probiotics of any use to prevent or treat this infection in IBD patients? How does one differentiate colonization from infection in patients with already diseased colons? Finally, as already mentioned, a concerted effort is needed to reduce the rising tide of *C. difficile* worldwide with greater emphasis on safer antibiotic prescribing guidelines, hand washing, cleaner hospital environments, and greater physician and community awareness. Until this epidemic is controlled, we will always have tough questions to answer in the management of these seriously ill patients on a daily basis.

Abbreviations

aOR, adjusted odds ratio; CD, Crohn's disease; CDAD, *Clostridium difficile*-associated disease; CI, confidence interval; IBD, inflammatory bowel disease; PCR, polymerase chain reaction; UC, ulcerative colitis.

Competing interests

The author declares that he has no competing interests.

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