Journal of Crohn's and Colitis (2009) **3**, 4–7

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Increasing incidence of *Clostridium difficile*-associated diarrhea in inflammatory bowel disease

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Received 10 August 2008; received in revised form 8 September 2008; accepted 16 September 2008

KEYWORDS
Clostridium difficile;
Inflamamatory bowel disease;
Ribotype NAP1/027;
Immunomodulators;
Post antibiotic diarrhea

Abstract

Introduction and aim: Over the last decade a rise in *Clostridium difficile*-associated diarrhea (CDAD) has been observed. A higher incidence of CDAD has also been suggested in patients with inflammatory bowel disease (IBD), and may be a challenging factor in the differential diagnosis of flares. It is unclear if the increase is caused by the enhanced use of immunosuppressive therapy in IBD. We investigated if CDAD infection is increasing in IBD patients and evaluated outcome and possible predisposing factors.
Methods: Through an electronic database of the Laboratory of Microbiology of our hospital (tertiary referral center), all stool samples from patients admitted for diarrhea and hospitalized on gastroenterology wards between January 2000 and January 2008 were reviewed for diagnosis of CDAD. For analysis, we compared two periods of equal duration.
Results: A total of 57 patients were diagnosed with CDAD, of whom 26.3% had concomitant IBD. A 3.75-fold increase in CDAD was observed between period 1 and period 2, irrespective of underlying IBD and with a comparable total number of analyzed stool samples between both periods. Non-IBD patients were significantly older. Antibiotic use three months prior to the infection was higher in non-IBD (29/42 or 69%) than in IBD patients (6/15 or 42%) ($p=0.047$). Nine IBD patients were on concomitant immunomodulators, and this was not different between period 1 and period 2. Most patients had a successful outcome and only one patient with ulcerative colitis needed semi-urgent colectomy. Two patients died in the non-IBD group. The duration of hospital stay was significantly lower in IBD patients.
Conclusion: We observed a significant rise in CDAD in both IBD and non-IBD. The clinical outcome was favorable with only one IBD patient needing semi-urgent colectomy. Because *C. difficile* can mimic an IBD flare, it is essential that clinicians are vigilant to this complication. The use of immunosuppressive drugs in IBD does not influence the risk.
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doi:10.1016/j.crohns.2008.09.003

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1. Introduction

Clostridium difficile is an anaerobic, rod-shaped, gram-positive bacteria which exists in two forms, a toxin-producing vegetative form and a dormant spore form. The toxins produced by the bacteria may cause colitis. There are two types of toxins: a more potent toxin A (enterotoxin) and a less severe toxin B (cytotoxin).[1–4] *C. difficile* can be divided by polymerase chain reaction (PCR) into more than 150 ribotypes of which the ribotype NAP1/027 appears to be more virulent than other PCR ribotypes.[5]

The typical clinical presentation of *C. difficile*-associated diarrhea (CDAD) has been described over 30 years ago and may vary from mild diarrhea to toxic megacolon with severe sepsis and multiorgan failure. CDAD is associated with a substantial mortality varying between 4.5%–22% depending on the studies.[6–7] A recent report demonstrated that more than 2% of all in-hospital deaths were linked to *C. difficile* infection.[8] Prior antibiotic use is the most important risk factor. Other risk factors which have been reported include older age, prolonged hospital stay, poor immunity, chemotherapy and acid suppression.[1–4] Endoscopic documentation of pseudomembranes is almost pathognomonic but is seen in only a third of the patients.[9]

Recently, an increase in CDAD has been described in North America.[6–7,10] Until now no studies have been published about the evolution of the incidence of CDAD in Europe and especially not in patients with inflammatory bowel disease (IBD). In patients affected with IBD, the diagnosis of CDAD may be blurred since the clinical symptoms may mimic a flare of the disease. Furthermore, most IBD patients are young and do not carry risk factors, this being on of the reasons why stool cultures for CDAD are not often obtained during follow up of these patients. Based on the literature and also on our clinical observation, we investigated if the rise in CDAD is also observed in IBD patients particularly in Europe and studied clinical outcome and risk factors.

2. Methods

2.1. Patients

Since January 2000, the laboratory of microbiology of our hospital (tertiary referral center) holds an electronic database of all received specimens. Through this database, all stool samples from patients admitted to the gastroenterology ward with diarrhea between January 2000 and January 2008 were reviewed for diagnosis of CDAD. It is the policy in our hospital that patients admitted with diarrhea and no travel history, will be hospitalized on the gastroenterology ward. We analysed the samples in two periods of equal duration: January 2000 to December 2003 (period 1) and January 2004 to December 2007 (period 2). Patients were analysed for concomitant diagnosis of IBD, Crohn's disease (CD) or ulcerative colitis (UC). By review of all clinical charts, co-morbidity was assessed, as well as concomitant immunomodulators (in case of IBD patients), previous antibiotic use, treatment and duration of treatment for CDAD, duration of hospital stay and outcome. Characteristics of the patient population is provided in Table 1. In 2000 on CDAD was defined as diarrhea with positive toxin A of *C. difficile* (*C. difficile* Toxin A Test, Oxoid Ltd, Basingstoke, Hampshire, United Kingdom) and from 2005 positive A/B toxin of *C. difficile* (Immunocard A&B, Meridian Diagnostics, Inc., Cincinnati, Ohio, United States). It has to be mentioned that some isolates have been shown to produce only toxin B. Although such strains are very rarely observed it has been found to account for 3% of the strains referred to the reference laboratory.[11] Analyses for ribotype NAP1/027 were done in an out hospital reference lab (Laboratory of microbiology, Hôpital Saint-Luc, Université Catholique de Louvain, Belgium).

Table 1 Patient's characteristics. Both the total study population, as well as the IBD and non-IBD patients separately are shown (IBD = inflammatory bowel disease)

	Total $n=57$	IBD $n=15$	No IBD $n=42$	p (IBD vs non-IBD)
Gender (male/female)	21/36	5/10	16/26	ns
Age (years)				
•Mean	57.5	42.5	62.8	0.001
•Range	16–93	16–81	17–93	
Comorbidity (n)				
•cerebrovascular accident	7	0	7	ns
•malignancy	10	2	8	ns
Hospital stay (days)	24.4	15.2	27.7	<0.001
Mortality (n)	2	0	2	ns
Colectomy (n)	1	1	0	ns
Risk factors				
•Antibiotic use	35	6	29	0.047
•Immunosuppression	10	9	1	<0.001
•Acid suppression	24	5	19	ns

2.2. Statistical analysis

Continuous data are expressed as means (normal distribution) or medians and interquartile ranges (non-Gaussian distribution). Chi square test or Fisher's exact where appropriate were performed to compare frequencies using SPSS 15.0. A p value (two-tailed) of <0.05 was considered as threshold for significance.

3. Results

3.1. Incidence of CDAD

During the total study period, a total of 57 patients were admitted with a diagnosis of CDAD of whom 15 (26.3%) had concomitant IBD. Among the IBD patients, 9 had CD, 5 had UC and one patient had indeterminate colitis. In the whole study period a 3.75-fold increase in CDAD was observed from period 1 ($n=12$) to period 2 ($n=45$) (Fig. 1). The increase in incidence was not significantly different between IBD and non-IBD patients: in the non-IBD group, the total number of CDAD infections increased from 9 (period 1) to 33 (period 2), and in the IBD group, from three (period 1) to 12 (period 2). Between both periods there was only a 1.2-fold increase in the total number of analysed stool samples ($n=1.348$ in period 1,ie 1 positive sample/112 analyses to $n=1.659$ in period 2,ie 1 positive sample/37 analyses). In period one, 1.048 patients were tested with a mean of 1.36 stool samples

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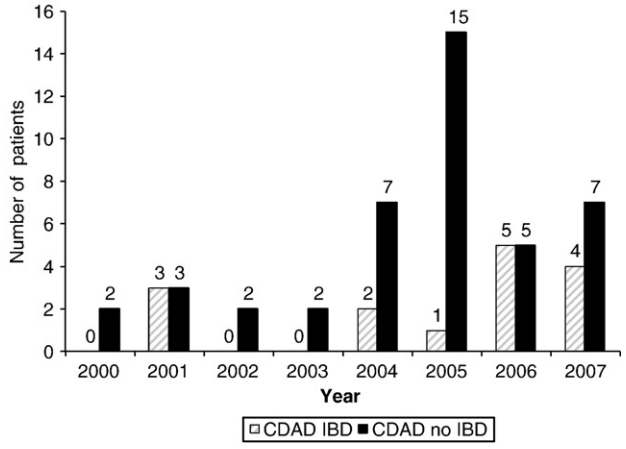

Figure 1 Evolution of the incidence of *C. difficile*-associated diarrhea over years (CDAD=*C. difficile*-associated diarrhea; IBD= Inflammatory bowel disease).

per patient and a median of 1 (range 1–11). In the second period, 1.150 patients were tested with a mean of 1.48 stool samples per patient and a median of 1 (range 1–12). Concerning the number of patients tested and the number of stool samples per patient no differences were seen between period 1 and period 2.

There was no indication that a specific ribotype of CDAD was responsible for the increase over time, and more precisely, there was no indirect indication of an outbreak of ribotype NAP1/027 subgroup CDAD.

3.2. Risk factors for CDAD infection

Risk factors are shown in Table 1. It was noted that the IBD patients were significantly younger (mean 42.5 years, range 16–81 years) than the non-IBD patients (mean 62.8 years, range 17–93 years) ($p=0.001$). Among IBD patients, most acquired CDAD in an outpatient setting ($n=11/15$; 73%) as compared to the non-IBD patients where half ($n=21/42$) developed CDAD during hospitalisation for other reasons, although this strictly lacked significance ($p=0.14$). The latter might have been explained in part by the fact that the non-IBD group carried more co-morbidity including cerebrovascular accidents ($n=7$) and concomitant malignancies ($n=8$) than the IBD patients (no cerebrovascular accidents and only 2 malignancies).

Antibiotic (AB) use 3 months prior to the CDAD episode was reported in 35 patients (61.4%) and was higher in non-IBD patients (29/42 or 69%) than in the IBD patients (6/15 or 40%) ($p=0.047$). Forty-five percent of the non-IBD patients were taking proton pump inhibitors (PPI) or H2-blockers and in the IBD group 33% was treated with PPI or H2-blockers ($p=$ns). Only one patient in the non-IBD group was on immunomodulatory drugs (low dose steroids), whereas 60% ($n=9$) of the IBD patients were taking immunomodulation (steroids $n=6$, azathioprine $n=5$, anti-TNF $n=4$). However, we did not observe a significant difference in the use of these drugs in the IBD patients between both periods (2/3 in period 1 and 7/12 in period 2).

3.3. Outcome

Surprisingly, none of the IBD patients had pseudomembranes on endoscopy whereas almost half of the non-IBD patients which underwent endoscopy had pseudomembranes ($n=9/19$, 47%). Most patients (81%) were started on AB but in 18% symptoms resolved without therapy after stopping AB taken prior to the onset of diarrhea. The choice of AB for treatment of CDAD included metronidazole or ornidazole in 72% of patients ($n=33$) and in 28% ($n=13$) oral vancomycin was started. There was a successful outcome in most patients. In cases of failure of therapy (no negativation of toxins) with imidazole derivatives vancomycin was started. This was needed in 8/33 (24%) patients. One patient with UC needed a semi-urgent colectomy one month after CDAD infection due to a persistent colitis despite disappearance of *C. difficile* A/B toxin in the stools. In the non-IBD group two patients died, one patient from an undefined systemic disease and another patient due to a sudden cardiac arrest in palliative setting. The duration of hospital stay was significantly shorter in IBD patients (mean 15.2 days, range 1–37 days) compared to non-IBD patients (mean 27.7 days, range 3–106 days) ($p<0.001$).

4. Discussion

A global increase in CDAD has been documented over the last decade, and has drawn the attention of clinicians given the excess in morbidity and mortality associated with the condition.[6,10] Specifically the ribotype NAP1/027 has been linked with severe outbreaks and epidemics.[12]

The diagnosis of CDAD may be particularly obscured in patients with IBD, since the clinical presentation often mimics a flare. Stool cultures are not always performed in patients presenting with a flare of CD or CU unless symptoms do not improve despite appropriate anti-inflammatory therapy.

In this study, we observed an almost four-fold increase of CDAD over the past 8 years in both IBD and non-IBD patients which could not be linked to a specific ribotype. This rise in incidence is similar to what has been reported in earlier recent studies.[13–15]

The subgroup of IBD patients with CDAD needs special attention for several reasons. We found that IBD patients with CDAD are younger and acquire the infection mostly in an outpatient setting. We also observed that they do not present with a clear cut endoscopic picture, since none had pseudomembranes on endoscopy. This is in accordance with a previous study which reported similar findings.[14] Another aspect to point out is that IBD patients may present with CDAD following total proctocolectomy and ileostomy as shown in one of our patients. When assessing risk factors for CDAD, we observed less prior AB use in IBD patients compared to non-IBD patients.[16] Overall, all these factors make that IBD patients carry less suspicion for CDAD which can result in a delay of the diagnosis. Therefore, the diagnosis of CDAD in IBD patients warrants *systematic* microbiological stool examinations in patients presenting with a flare. Repeated examinations are not indicated unless in case of refractory symptoms.

Once the diagnosis of CDAD is established antimicrobial therapy is mandatory in most patients although in our cohort, symptoms resolved without AB therapy in 18% of patients.

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The treatments of choice includes imidazole derivatives or vancomycin orally. Both antimicrobial substances have equal efficacy as first line treatment for moderate CDAD, but higher cure rates have been observed with vancomycin in severe CDAD.[17] Current recommendations from Centers for Disease Control and Prevention (CDC) propose oral metronidazole for mild and vancomycin for severe disease.[18] Some caution is needed when vancomycin is started as first line treatment due to the risk of selecting vancomycin-resistant enterococci.[1–3] In our opinion, in IBD patients presenting with a flare, CDAD needs to be treated adequately with antibiotic therapy and if needed anti-inflammatory therapy has to be stopped or adapted depending on the clinical presentation.

We also observed some discrepant findings compared to previous studies. First, we observed only one semi-urgent colectomy whereas other centers reported less favourable outcomes with colectomy rates approaching 20%.[19] Second, the duration of hospital stay in the IBD patients with CDAD in our study was significantly shorter (almost half the time) than that observed in 2 North-American studies.[13,15] Previous studies also revealed a higher mortality in CDAD with coexisting IBD compared to CDAD alone.[15,20] This trend was also not confirmed in our study. On the contrary, we found a more favorable outcome for CDAD in IBD patients. The different results may be explained by the selection of the patient cohort and the younger age of the IBD patients in our study.

Finally, the increasing use of immunomodulatory drugs did not influence the risk of mortality or longer hospitalization. This is an important and reassuring finding given that the use of thiopurine analogues, methotrexate or anti-TNF agents has been associated with a substantial risk of infections.[21] Nevertheless, careful assessment of an IBD patient who presents with a flare, and consideration of potential infections remains necessary.

In conclusion, we demonstrated that the incidence of CDAD is growing also in Europe but that the evolution is comparable in patients with inflammatory bowel disease as well as in the general population. It is essential that clinicians are vigilant to identify this infectious complication also in IBD patients presenting with symptoms of a flare of their disease. A rapid and adequate diagnosis and therapy lead to a favorable evolution in most patients without excess in hospital stay or mortality. The increasing use of immunosuppressive drugs in IBD does not seem to influence the risk.

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