

ORIGINAL PAPERS

Risk factors for *Clostridium difficile* diarrhea in patients with inflammatory bowel disease

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ABSTRACT

Background: Despite the growing incidence of *Clostridium difficile* diarrhea (CCD) in patients with inflammatory bowel disease (IBD), little is known about the associated risk factors.

Method: A retrospective study comparing cases of CCD in patients with IBD to IBD carriers who did not develop CCD. A comparison was also made with patients who developed CCD but did not suffer IBD.

Results: Three cases (20 %) with IBD and CCD had received antibiotics during the previous three months versus none of the controls (IBD without CCD, $p = 0.22$). Ten cases (67 %) received treatment with proton pump inhibitors (PPIs) versus 2 (13 %) in the control group (IBD without CCD, $p = 0.001$). Seven cases underwent colonoscopy and pseudomembranes were seen in one (14 %). Fourteen (93 %) patients demonstrated a favourable response to metronidazole. Patients with IBD and CCD presented with younger age (36 ± 10 years), a higher degree of community-acquired infection (13 patients, 87 %), immunosuppressive treatment (7 patients, 47 %) and less patients had received previous antibiotic treatment (3 patients, 20 %) than those with CCD without IBD. The proportion of patients who received treatment with PPIs was similar (66 % and 80 %, respectively $p = 0.266$).

Conclusions: CCD in IBD carriers affects younger patients, the majority are community acquired (less nosocomial) and it is more related to previous treatment with PPIs than with the antibiotic treatment. Clinical evolution is also favourable.

Key words: *Clostridium difficile*. Inflammatory bowel disease. Ulcerative colitis. Crohn's disease. Antibiotic-associated diarrhea. Metronidazole.

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INTRODUCTION

The incidence of diarrhea due to *C. difficile* associated to IBD has increased over the last few years, being higher than the incidence found in the general population (1-5). This anaerobic, spore-forming bacterium is capable of producing toxins that give rise to disruption and inflammation of the colonic mucosa and, occasionally, can cause extraintestinal infection (6). It has been suggested that this infection could contribute to the development of some IBD outbreaks, overall in hospitalized patients (5,7). CCD in patients with IBD usually appears in the hospital setting and affects younger patients (9,10). Once *C. difficile* intestinal colonization has occurred, the risk of developing diarrhea, or remaining as a carrier, depends, among other circumstances, on the patient's immunological status and serum concentration of antibodies against *C. difficile* toxins (8).

The adequate use of suitable drugs and hospital epidemiological measures to prevent *C. difficile* dissemination are the principal means to reduce its incidence (5,9). Included among the CCD risk factors identified within the general population are advanced age, comorbidities, hospitalization and previous use of antibiotics (6,9). It has been shown that systemic corticosteroid treatment favours its appearance in patients with IBD, however the relationship

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between previous exposure to antibiotics and CCD is lower than in other groups (10,11). Until now, few studies have analyzed the circumstances that trigger CCD in patients with IBD (6). For this reason, it was decided to analyze the risk factors for the development of CCD in patients with IBD and, specifically, improve our understanding of the role of proton pump inhibitors (PPIs) in the appearance of this infection.

METHOD

A retrospective, observational study was performed in patients with inflammatory bowel disease. The study cohort corresponded to IBD patients who were regularly attended by a system of appointments in a specialist consultation unit of a tertiary hospital in Madrid (Spain) between January 2005 and February 2014.

Cases were defined as those patients who had three or more daily bowel motions for a period of at least 48 hours and were found to be positive for *C. difficile* in stool samples. For each case, another patient (control), paired for the period (month) and the environment of the episode (ambulatory or hospitalized), was randomly assigned from hospital patients with IBD that had not presented CCD during follow-up. Because two cases acquired the infection while hospitalized for other reasons, two controls (without CCD) were randomly chosen from IBD carriers who had been admitted to the gastroenterology ward during the same month as the cases. The other controls (13 patients) were IBD patients who did not present CCD and were examined in the gastroenterology service during the same month that the cases were diagnosed. Patients were not paired by age or gender in case these demographic variables could have a bearing on the risk of CCD. Subsequently, a comparison was made between a sample of 30 IBD patients with CCD and two controls per case selected from among patients treated for CCD in our hospital during the last 10 years.

The variables studied were age, gender, IBD type, duration of disease, diabetes, prior colectomy, residence in a nursing home, hospital admission during the previous 3 months, comorbidity, treatment for IBD and administration of omeprazole (or other proton pump inhibitor) during the previous 3 months, systemic antibiotic during the previous month, clinical presentation, evolution, recurrence of infection or onset of diarrhea during the 2 months following the episode studied.

The diagnosis of CCD was performed using detection of the glutamate dehydrogenase antigen (GHD) and toxins A and B through enzyme immunoassays (*C. DiffQuikChek Complete Techlab®*, Blacksburg, Vancouver). In the cases that were GHD antigen positive but toxin negative, the presence of the toxin B gene was determined by polymerase chain reaction (PCR) using the GenomEra CDX *C. difficile* assay (Abacus Diagnostica, Finland).

Statistical analysis

The Mann Whitney U test was used to compare quantitative variables. The chi-square test, with Yates' correction was used (when necessary) to compare qualitative variables. *p* values less than 0.05 were considered statistically significant. Given the limited number of patients, a multivariate analysis was not considered appropriate.

RESULTS

Fifteen patients with IBD who presented CCD (cases) were included during the study period. The mean age was 36 ± 10 years, which was lower than that of the controls without IBD (41 ± 10 years, *p* = 0.039). Eleven cases (73 %) were male *versus* five among the controls (33 %, *p* = 0.028). None of the patients resided in a nursing home.

Eight cases (53 %) had ulcerative colitis and seven (47 %) Crohn's disease (Table I). The median duration of the disease was 55 months in cases and 84 months in controls (*p* = 0.647). Two cases (13 %), who presented granulomatous colitis, had undergone colectomy due to failure to control inflammatory activity. Ten cases (66 %) received chronic treatment with omeprazole (20 mg daily, with the exception of one with 40 mg) *versus* two control patients (13 %, *p* = 0.009). Eight cases (53 %) received oral corticosteroid treatment with a mean dose equivalent of 25 mg/24 hours prednisone (*p* = 0.052). None of the cases was treated with rectally administered corticosteroids. Six cases (40 %) received continuous treatment with infliximab and one (6 %) with adalimumab.

Three cases had been admitted during the previous three months. In addition, three cases (20 %) had received systemic antibiotics during the previous month compared to none of the controls (*p* = 0.222) (Table I). In two cases (13 %) the CCD appeared after one week of hospital admission and therefore was considered nosocomial acquisition. Thirteen patients with IBD and CCD (87 %) presented abdominal pain and four patients (27 %) vomiting. Fever was only detected in four patients (27 %) and weight loss in three (20 %). A decision had been taken to admit nine of the thirteen cases of community-acquired CCD (60 %) to hospital.

Nine patients with IBD and CCD (60 %) presented leukocyte counts higher than $10,000/\text{mm}^3$ (mean leukocyte count $13,545/\text{mm}^3$). In seven cases (47 %), colonoscopy was performed during the episode of CCD. Pseudomembranes were seen in one of these (14 %), signs suggestive of moderately active IBD in another (14 %), and mild affection in three cases (42 %). Six cases (40 %) presented diarrhea, which was attributed to their underlying disease, during the 2 months prior to diagnosis of the infection. Two patients with IBD and CCD (13 %) presented diarrhea after infection but without microbiological demonstration of *C. difficile* infection relapse.

Table I. Clinical characteristics of patients with inflammatory bowel disease (IBD) and diarrhea due to *Clostridium difficile* (CCD) compared with IBD patients without CCD (controls)

	Cases (n = 15)	Controls (n = 15)	OR (95 % CI)	p
Age (years) ¹	35.8 (6.8)	41.2 (7.6)		0.039
Male gender	11 (73)	5 (33)	2.5 (1.01-6.2)	0.028
Ulcerative colitis	8 (53)	7 (47)		0.715
Duration of IBD (months) ¹	55 (114)	84 (144)		0.647
Diabetes	1 (7)	1 (7)		0.464
Previous colectomy	2 (13)	2 (13)		0.591
Omeprazole previous 3 months	10 (66)	2 (13)	13 (2-81)	0.009
Salicylates	8 (53)	5 (33)		0.461
Corticosteroids ²	8 (53)	2 (13)	7.4 (1-45)	0.052
Anti-TNF	7 (47)	9 (60)		0.714
Antibiotics previous 30 days	3 (20)	0 (0)		0.224
Hospitalization previous 3 months	3 (20)	0 (0)		0.224
Fever	4 (27)	0 (0)		0.049
Abdominal pain	13 (87)	4 (27)	17.8 (2-116)	0.002
Death	1 (7)	1 (7)		0.464

¹Median and interquartile range. Figures in brackets are qualitative variables expressed as percentages. ²Equivalent dose of prednisone higher than 10 mg/day. IBD: Inflammatory bowel disease; anti-TNF: Tumor necrosis factor inhibitors (infliximab, adalimumab).

The diagnosis was made by toxin detection in 8 patients (53 %) and toxin-producing gene detection by PCR in the remaining seven cases (47 %). All patients were treated with 500 mg metronidazole every 8 hours. Only one case had a poor response that required a switch to fidaxomicin 200 mg/12 hours for 10 days. None of the patients with IBD and CCD required admittance to the ICU. One patient died in the case group (due to advanced chronic liver disease) and another in the control group (secondary to disseminated colorectal carcinoma), however these deaths were not related to the CCD.

Comparing cases (CCD and IBD) with patients with CCD but without IBD, it was seen that the former were younger (36 ± 10 and 73 ± 17 years, respectively, $p = 0.007$). They also had a higher proportion community-acquired CCD (87 %) and immunosuppression therapy (including anti-TNF drugs), but less previous antibiotic therapy (Table II). No significant differences were observed in relation to previous treatment with PPIs, being 66 % in case IBD carriers and 80% in the comparison group ($p = 0.266$).

DISCUSSION

The majority of CCD cases in IBD patients appeared in the community as has been observed in similar series (5,6). Only 20 % of the patients had been admitted

during the previous months and, in 13 % of the cases, the CCD appeared during a hospital stay which was due to another disease. By contrast, the majority of the patients without IBD (53 %) suffered a nosocomial *C. difficile* infection (12).

Patients with IBD and CCD were somewhat younger and were predominantly male compared to the controls. None of these findings were identified in previous series and should be interpreted with caution given the low power of the study (6). Advanced age has been identified as a risk factor for CCD in the general population, which is congruent with the older age of the patients without IBD (13).

It should be noted that only 20 % of the cases had received antibiotics during the month preceding the episode of CCD. This epidemiological difference suggests the existence of intestinal flora alterations in IBD patients that could facilitate the spread of *C. difficile* (4,12,14-16). IBD patients may show a certain degree of immune stimulation, epithelial dysfunction and increased mucosal permeability which could also allow *C. difficile* colonization and proliferation (5,6,17).

Consistent with other studies, no increased risk of infection was found among patients receiving anti-TNF drugs (17). Different previous studies have shown mixed results in the relationship between corticosteroid therapy and the risk of CCD. Various series have demonstrated an increased risk with systemic administration (18,19), others

Table II. Clinical characteristics of patients with inflammatory bowel disease (IBD) and diarrhea due to *Clostridium difficile* (CCD) and controls (CCD without IBD)

	Cases (n = 15)	Controls (n = 30)	OR (95 % CI)	p
Age (years) ¹	35.8 (6.8)	73.2 (55-89)		0.007
Male gender	11 (73)	16 (53)		0.446
Nosocomial acquisition	2 (13)	16 (53)	0.13 (0.02-0.8)	0.010
Diabetes	1 (7)	5 (17)		0.335
Previous colectomy	2 (13)	0 (0)		0.106
Omeprazole previous 3 months	10 (66)	24 (80)		0.266
Immunosuppressors	7 (47)	5 (17)	4.3 (0.9-22)	0.038
Antibiotics previous 30 days	3 (20)	27 (90)	0.03 (0-0.2)	< 0.001
Hospitalization previous 3 months	3 (20)	13 (43)		0.127
Fever	4 (27)	6 (20)		0.440
Abdominal pain	13 (87)	19 (63)		0.097
Death	1 (7)	5 (17)		0.336

¹Median and interquartile range. Figures in brackets are qualitative variables expressed as percentages. Immunosuppression: Immunosuppressive drugs including tumor necrosis factor inhibitors.

only with rectal application (5) and others have found no relationship between different types of treatment and the risk of CCD (4). The cases analyzed showed that systemic steroid therapy showed a trend toward statistical significance ($p = 0.052$) as a risk factor for CCD (18,19). It is possible that the immune impairment secondary to steroids and the subsequent reduction in antibody synthesis could be related to this result (20).

The most significant finding of this study was the relationship between the administration of PPIs and the risk of CCD. The protective role of gastric acidity against vegetative forms of *C. difficile*, which limits its intrusion into more distal regions of the gastrointestinal tract, is well known (21). PPI treatment was initially associated with the carrier state and recurrences rather than the risk of the first episode of CCD (11,22). Subsequently it was also associated with the appearance of the first episode in general CCD series (23), but only in one of a series of patients with IBD (17). Even taking into account the small number of patients analyzed in this series, the use of these drugs should be questioned for patients with IBD, especially in cases with doubtful indications (24).

The low mortality detected in patients with IBD and CCD is an expected result considering the relatively young patients and low comorbidity (6,12). None of the cases required colectomy or admission to the ICU (12,25). The response to metronidazole was adequate in most IBD cases which suggests the validity of metronidazole as treatment of choice in initial, non-serious episodes of CCD (26-28). Also noteworthy was the low risk of recurrence which is consistent with some previous experiences (29), but differs from that shown in other reports that have

observed increased severity and recurrence in patients with IBD (30,31).

C. difficile infection in IBD patients will pose a major problem in the coming years due to its growing incidence and the use of increasingly sensitive microbiological techniques, such as PCR, which can determine the capacity to produce toxins. Although the majority studies based on the general population and IBD have not shown any relevant significant clinical differences with respect to the diagnostic test used (17,32), others found lower severity when PCR was used (33). A subgroup of patients has been identified with diarrhea due to an outbreak of their disease in which *C. difficile* may have played a role as a mere contaminant (6,33,34). We cannot definitely rule out the possibility that some of our patients belong to this group, although the temporary response to specific treatment does not support this theory.

Some authors have observed a higher incidence of CCD in active IBD patients (4) and it has been suggested that CD infection could participate in the initial pathogenesis of some outbreaks of IBD (3,7). Unfortunately, colonoscopy may not help to confirm CCD because pseudomembranes appear less frequently in patients with IBD (approximately 9 %), especially in the absence of fever (12,28,34,35). In fact, four of our patients exhibited endoscopic signs of activity together with microbiological detection of *C. difficile* infection. This peculiarity may be related to pathogenic differences in the infection associated with chronic IBD inflammation, with lower severity or, as noted previously, with the detection of cases with *C. difficile* colonization but whose diarrhea is due to another cause (12,32,34,35).

Highlighted among the limitations of this study are its retrospective nature and the small number of patients, which may have influenced the lack of detection of other potential risk factors, such as previous antibiotic treatments. A multi-center study with greater statistical power will be necessary to further assess risk factors in these patients.

In summary, CCD in patients with IBD is usually acquired out the hospital setting, is associated more with the administration of BP than with previous antibiotic therapy and usually has a favourable clinical evolution.

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