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La survenue d'une infection à *Clostridioides difficile* est associée à une aggravation des maladies inflammatoires intestinales à court et moyen terme

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JURY
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Madame le Docteur Marie TITECAT
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Abbreviations

CD	Crohn's disease
CDI	*Clostridoides difficile* infection
CI	Confidence interval
IBD	Inflammatory bowel disease
IQR	Interquartile range
IS	Immunosuppressant
TNF	Tumor necrosis factor
UC	Ulcerative colitis

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RESUME

Introduction : Les patients atteints de maladies inflammatoires chroniques intestinales (MICI) sont plus à risque de développer une infection à *Clostridioides difficile* (ICD), associée à un plus haut risque de mortalité et de chirurgie en comparaison aux patients atteints de MICI seule. Peu d'études ont évalué la prise en charge des ICD chez les patients MICI et leur impact sur le devenir de la MICI à court et moyen terme. Les objectifs de cette étude étaient *(1)* d'évaluer la sévérité, la prise en charge et les conséquences de l'ICD dans une large cohorte de patients MICI, et *(2)* d'évaluer l'impact de l'ICD sur la MICI à court et moyen terme.

Matériel et méthodes : Nous avons mené une étude observationnelle rétrospective et multicentrique incluant consécutivement tous les patients MICI présentant de manière concomitante une ICD, de janvier 2010 à décembre 2018. Chaque patient était suivi un an après l'épisode d'ICD. Les critères de jugement étaient la survenue d'une hospitalisation, d'une modification du traitement de fond de la MICI et/ou d'une chirurgie dans l'année suivant l'ICD.

Résultats : Quatre-vingt-seize échantillons de selles étaient positifs pour le *Clostridioides difficile* chez 86 patients MICI. Quarante-cinq (47%) ICD étaient sévères, 75 (78%) patients étaient hospitalisés pour l'ICD, dont 4 (4%) en unité de soins intensifs. Soixante-dix (70%) patients n'ont reçu qu'une ligne d'antibiotique, 13 (14%) en ont reçu deux ou trois. Trois (3%) patients ont été opérés pendant l'ICD, 2 (2%) sont décédés. Pendant l'année suivant l'ICD, 32 (33%) patients ont été hospitalisés, 45 (47%) ont eu une modification de traitement de fond de la MICI, et 22 (23%) ont subi une chirurgie. En analyse multivariée, le recours à au moins deux lignes d'antibiotiques, contenant systématiquement de la vancomycine ou de la fidaxomicine,

était protecteur de la survenue d'un ou plusieurs évènements péjoratifs associés à la MICI dans l'année suivant la MICI.

Conclusion : Cette étude de vraie vie montre l'impact majeur de l'ICD sur la MICI dans l'année suivant l'ICD, avec des taux d'hospitalisation, de modification de traitement de fond de la MICI et de chirurgie élevés. La MICI devrait être considérée comme un marqueur de sévérité d'ICD, et la vancomycine ou la fidaxomicine devraient être utilisés en première ligne d'antibiothérapie chez ces patients. Après une ICD, ces patients devraient être rigoureusement suivis afin de prévenir la survenue d'une complication liée à la MICI.

SUMMARY

Introduction: Patients with inflammatory bowel disease (IBD) have an increased risk of developing *Clostridioides* difficile infection (CDI), associated with higher risk of mortality, and higher rates of colectomy when compared to patients with IBD alone. Few studies reported the management of CDI in IBD patients and its impact on IBD outcome at short and mid-terms. The aims of this real-life study were to *(1)* evaluate severity, therapeutic management and outcomes of CDI in a large cohort of IBD patients, and to *(2)* assess the impact of CDI on IBD outcomes at short and mid-terms.

Materiel and methods: We performed a retrospective, multicentric, and observational study including all consecutive IBD patients who suffered of concomitant CDI from January 2010 to December 2018. Patients were followed one year after CDI. Primary outcome was the occurrence of IBD related hospitalizations, IBD treatment change, and surgery during the year following CDI. We aimed to identify clinical factors associated with poor outcomes in IBD patients with CDI.

Results: Ninety-six stool samples were positive for *Clostridioides difficile* in 86 IBD patients. Fifty-seven (59%) patients had CD, 36 (41%) had UC. Forty-five (47%) CDI were severe. Seventy-five (78%) patients were hospitalized for CDI, including 4 (4%) patients admitted in intensive care unit. Seventy (70%) patients received a unique line of antibiotics, 13 (14%) patients needed two lines of antibiotics, 2 (2%) patients needed three lines of antibiotics. Three (3%) patients underwent a surgery during CDI, and 2 (2%) died. During the year following CDI, 32 (33%) patients were hospitalized for an IBD flare, 45 (47%) had a modification of their IBD treatment, and 22 (23%)

patients underwent a surgery. The use of at least two lines of antibiotics was associated to a decreased risk of surgery during the year after CDI.

Conclusion: This real-life study reports a major impact of CDI in IBD course during the year following, with high rates of IBD related hospitalizations, IBD treatment modification and surgery. IBD should be considered as a severity marker of CDI, and vancomycin or fidaxomicin should be considered as first-line therapy for CDI in IBD population. After a CDI episode, IBD patients should be closely monitored with careful clinical and biological evaluations.

INTRODUCTION

Clostridioides difficile is an anaerobic, spore-forming, gram-positive bacillus with the ability to produce two exotoxins A and B that cause colitis in susceptible persons (1). Incidence and severity of *C. difficile* infection (CDI) have increased over the past decade (2), especially in patients with inflammatory bowel disease (IBD) (3). Recent studies have shown that patients with IBD have an increased risk and higher incidence of developing CDI with a 3- to 5-fold increase risk of CDI compared to the general population (3,4). Both ulcerative colitis (UC) and Crohn's disease (CD) present high-risk of CDI (5). Several factors are thought to contribute to the increased risk of CDI in IBD patients, including preexisting colonic inflammation, disruption of the intestinal mucosal barrier, dysbiosis, and ongoing immunosuppression (6). Many studies reported that IBD patients infected with CDI present several distinct characteristics when compared to non-IBD patients, including younger age, community acquired CDI, and no previous antibiotics exposure (7). Hospitalized patients with IBD and CDI were reported with higher risk of mortality, longer hospital stays and higher rates of colectomy when compared to patients with IBD alone (5,8–10).

Effectiveness of CDI treatments depends on disease severity and number of CDI episode (11–13). Unfortunately, most of the clinical trials investigating CDI medications have excluded IBD patients because of the inability to identify clinical end points of cure. There are currently no prospective trials comparing antibiotics regimens among patients with CDI and underlying IBD, thus evidences from the non-IBD population are used to guide management (14). Absence of objective measures to stratify CDI severity in IBD patients influences interpretation and generalizability of

such guidelines. Evaluation of therapeutic management of CDI in IBD patients can allow an adapted and timely treatment leading to reach a better clinical evolution for these patients. Moreover, unmet needs also concern the management of CDI in IBD patients and its impact on IBD outcome at short and mid-terms.

The aims of this real-life study were: *(1)* to evaluate severity, therapeutic management and outcomes of CDI in a large cohort of IBD patients, and *(2)* to assess the impact of CDI on IBD outcome at short and mid-terms.

MATERIAL AND METHODS

I. Selection of patients

We performed a retrospective, multicentric, and observational cohort study in three Gastroenterology departments (University Hospital in Lille, hospitals of Valenciennes and Douai, France) from January 2010 to December 2018. Patients were included if they met the following criteria: *(1)* male or female >18 years of age, *(2)* with a diagnosis of IBD according to the European Crohn's and Colitis Organization guidelines (15), *(3)* with a concomitant diagnosis of CDI confirmed presence of *C. difficile* toxin A or B in stools.

II. Data collection

The date of inclusion was defined as the date of CDI diagnosis. The following characteristics were retrospectively recorded for each patient from electronic medical records: gender, age at diagnosis of IBD, age and disease duration at inclusion, smoking status, IBD subtype, IBD location and phenotype according to the Montreal classification (16), previous intestinal resections, prior exposure to IBD treatment (immunosuppressant, biologics), IBD treatment at time of CDI, recent antibiotic treatment (within 8 weeks before CDI). Clinical and biological parameters at CDI diagnosis, community versus hospital acquisition, CDI antibiotic regimen, management of IBD treatment during CDI, hospitalization, length of stay, ICU admission, and mortality were also recorded. Finally, CDI recurrence and CDI reinfection, IBD treatment modifications, IBD related hospitalizations, intestinal resections were recorded during one year of follow-up after CDI.

III. Diagnosis of CDI

Cases of CDI were identified from the microlaboratory database, and the study included only confirmed cases based on either a single-step DNA based PCR test (prior to 1 July 2018) or a two-step algorithm with initial simultaneous detection of both glutamate dehydrogenase (GDH) antigen and toxins A and B by colored chromatographic immunoassay, followed by an optional confirmatory PCR toxin in case of divergent screening tests (after 1 July 2018). Two episodes in the same patient were considered as different.

For each stool sample, electronic patient records were analyzed to determinate IBD status.

IV. Definitions

Severe CDI was defined as an episode with one or more of the following clinical markers of severe, and/or when one or more following unfavourable prognostic favors were presents: *(1)* leucocyte count > 15 x 10^9/L, *(2)* blood albumin < 30g/l, *(3)* serum creatinine $\geqslant$ 1,5 times the premorbide level, according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (11).

Complicated CDI was defined as an episode of CDI with severe colitis or complicated course of disease with significant systemic toxin effects, such as ileus, toxic megacolon or shock, possibly resulting in need for ICU admission, colectomy or death, according to ESCMID (11).

Recurrence was present when CDI re-occurs within 8 weeks after the onset of a previous episode. Reinfection is present when CDI re-occurs later than 8 weeks after the onset of a previous episode.

V. Aims

We aimed to *(1)* evaluate severity and outcomes of CDI in a large cohort of IBD patients, *(2)* identify clinical factors associated with poor outcomes in IBD patients with CDI, *(3)* identify the occurrence of IBD pejorative outcomes during the year following CDI; pejoratives IBD outcomes were defined by IBD related hospitalizations, IBD treatment change, and occurrence of surgery.

VI. Statistical analysis

Descriptive data were presented as frequencies (number) or medians (interquartile range (IQR)). Univariate and multivariate analyses were performed to identify independent predictive factors of IBD pejorative outcomes during the year following CDI, described by the odds ratio (OR) and 95% confidence interval (95%CI). $P<0.05$ was considered to be significant.

RESULTS

I. Patient characteristics

From January 2010 to December 2018, 2378 stool tests were positive for *Clostridioides difficile* in the three involved centers. Ninety-six of these 2378 patients had an IBD and were eligible for the study: 77 in the Hospital of Lille, 13 in Valenciennes, and 6 in Douai.

The demographic and clinical characteristics at inclusion are presented in Table 1. We studied 96 CDI episodes in 86 patients: 10 patients presented a unique recurrence episode during the study period. Fifty-seven (59%) patients had CD, 36 (41%) had UC. Forty-eight patients (50%) were women. Median age at diagnosis of CDI was 34,5 years old (IQR: 23-51), with a median IBD duration of 4 years (IQR: 1-11). Nineteen (20%) patients underwent previous intestinal resection: 3 (8%) UC patients underwent previous surgery (one had an ileostomy, one had an ileo rectal anastomosis, one had a sigmoidectomy with colo-colonic anastomosis). Fifty-four (56%) patients had been previously treated with immunosuppressant treatment, 51 (53%) had been exposed to at least one anti-TNF agent.

Table 1: Patients' characteristics at time of CDI (N = 96)

	All (N = 96)	CD (N = 57)	UC (N = 39)
Female, n (%)	48 (50%)	31 (54%)	17 (44%)
Age at diagnosis of IBD, median (y)	23 (IQR : 17-36)	23 (IQR : 16-29)	25 (IQR : 21,5-50)
Age at diagnosis of CDI, median (y)	34,5 (IQR : 23-51)	33 (IQR : 23-32,5)	43 (IQR : 25,5-61,5)
Median disease duration at diagnostic of CDI (y)	4 (IQR : 1-11)	7,5 (IQR : 3-12,25)	2 (IQR : 0-5,5)
Smoking status, n (%)			
Non smoker	59 (61%)	34 (60%)	25 (64%)
Former smoker	21 (22%)	9 (16%)	12 (31%)
Active smoker	16 (17%)	14 (24%)	2 (5%)
Location of Crohn's disease according to Montreal classification, n (%)			
L1 (ileal)		10 (18%)	
L2 (colonic)		12 (21%)	
L3 (ileocolonic)		35 (61%)	
Location of Ulcerative colitis according to Montreal classification, n (%)			
E1 (proctitis)			3 (8%)
E2 (distal UC)			15 (38%)
E3 (pancolitis)			21 (54%)
History of intestinal surgery related for IBD, n (%)	19 (20%)	16 (28%)	3 (8%)
Previous IBD therapy, n (%)			
5-Aminosalicylates	*54 (56%)*	*25 (44%)*	*29 (74%)*
Immunosuppressants	*61 (64%)*	*43 (75%)*	*18 (46%)*
Anti TNF	*51 (53%)*	*40 (42%)*	*11 (28%)*
1 Anti TNF	*26 (51%)*	*18 (45%)*	*8 731%)*
2 Anti TNF	*18 (35%)*	*15 (38%)*	*3 (27%)*
3 Anti TNF	*6 (12%)*	*6 (15%)*	*0*
4 Anti TNF	*1 (2%)*	*1 (3%)*	*0*
Ustekinumab	*4 (4%)*	*4 (7%)*	*0*
Vedolizumab	*10 (10%)*	*7 (12%)*	*3 (8%)*

Abbreviations: IBD: Inflammatory Bowel Disease, CDI: Clostridium difficile infection, CD: Crohn's Disease, UC: Ulcerative Colitis, TNF: Tumor Necrosis Factor

II. Characteristics and therapeutic management of CDI

The characteristics of CDI and the ongoing treatment at time of CDI are described in Table 2. Eighty-one (84%) CDI were community acquired. Forty-three (45%) had received a recent antibiotic treatment: 21 (49%) received an antibiotic treatment within 8 weeks before CDI, and 22 (51%) received antibiotics for another condition than CDI at time of CDI. Sixteen (36%) patients maintained antibiotic treatments (for another condition than CDI) during CDI episode.

Table 2: Characteristics of CDI and ongoing treatments at time of CDI (N = 96)

	All (N = 96)	CD (N = 57)	UC (N = 39)
Severe CDI [1], n (%)	45 (47%)	22 (39%)	23 (59%)
Complicated CDI [2], n (%)	4 (4%)	3 (5%)	1 (3%)
Community acquired CDI [3], n (%)	81 (84%)	49 (86%)	32 (82%)
Recent antibiotic use [4], n (%)	21 (22%)	12 (21%)	9 (23%)
Concomitant antibiotic use, n (%)	22 (23%)	14 (25%)	8 (21%)
Continuation of antibiotic, n (%)	16 (17%)	10 (18%)	6 (15%)
Treatment of IBD at diagnosis of CDI, n (%)			
Corticosteroids	26 (27%)	10 (18%)	16 (41%)
Immunosupressants	20 (21%)	12 (21%)	8 (21%)
Azathioprine	13 (65%)	8 (67%)	5 (63%)
Methotrexate	5 (25%)	4 (33%)	1 (13%)
Biologics	35 (36%)	27 (47%)	8 (21%)
Anti TNF	26 (74%)	20 (74%)	6 (75%)
Ustekinumab	2 (6%)	2 (7%)	0
Vedolizumab	4 (11%)	3 (11%)	1 (13%)
Other	3 (9%)	2 (7%)	1 (13%)
Combotherapy	9 (9%)	7 (12%)	2 (5%)

Abbreviations: IBD: Inflammatory Bowel Disease, CDI: Clostridium difficile infection, CD: Crohn's Disease, UC: Ulcerative Colitis, TNF: Tumor Necrosis Factor

[1] CDI is defined as severe when one or more of the clinical markers of severe colitis is present, and/or when one or more unfavorable prognostic favors is present: (1) leucocyte count > 15 x 10^9/L, (2) blood albumin < 30g/l, (3) serum creatinine $\geqslant$ 1,5 times the premorbid level, according to ESCMID.

Table 3 summarizes the management of CDI: 45 (47%) CDI were severe, and 4 (4%) CDI were complicated. Seventy-five (78%) patients were hospitalized for CDI, including 4 (4%) patients admitted in intensive care unit. Median length of stay in hospital was 9 days (IQR: 6-12). Twenty-one (22%) patients underwent flexible sigmoidoscopy: mucosal ulcerations were observed in 12 (86%) of them, and pseudomembranous colitis in 3 (3%) patients. Thirty-seven (38%) patients underwent abdominal tomography: colonic wall thickening was found in 29 (30%) patients, distension of large intestine over 6 cm in transverse colon was found in 4 (4%) patients. No colonic perforation was observed.

Figure 1 summarizes antibiotic regimen used for CDI. Eleven (11%) patients were lost to follow-up; 85 (88%) patients received at least one line of antibiotics, 15 (16%) needed a second line of antibiotics, and 2 (2%) required a third one. At the end, 70 (70%) patients received a unique line of antibiotics, 13 (14%) patients needed two lines of antibiotics, and 2 (2%) patients needed three lines of antibiotics.

Therapeutic management of CDI is described in Figure 2: 3 (3%) patients underwent a surgery during CDI, with a median CDI duration of 7 days (IQR: 6,5-20,5) before surgery: 2 subtotal colectomies (one patient with CD and one with UC), and one CD patient had an ileocecal resection. Two (2%) patients died during hospitalization for CDI: a woman aged of 81 years old who unexpectedly died of a cardio respiratory arrest, and a man aged of 77 years with UC and severe Parkinson's disease who died of a pneumopathy of inhalation. In both cases, the patients' IBD was inactive. These two patients died after a median duration of 13,5 days (IQR: 8,75-18,25).

Table 3: Management of CDI (N = 96)

	All (N = 96)	CD (N = 57)	UC (N = 39)
Hospitalisations for CDI, n (%)	75 (78%)	40 (70%)	35 (90%)
ICU admissions for CDI, n (%)	4 (4%)	3 (5%)	1 (3%)
Length of stay, median (d)	9 (6-12)	8 (6-12)	10 (6,5-14,5)
Flexible sigmoidoscopy during CDI, n (%)	21 (22%)	6 (11%)	15 (38%)
Pseudomembrnous colitis, n (%)	*3 (21%)*	*0*	*3 (20%)*
Ulcerations, n (%)	*12 (86%)*	*3 (50%)*	*9 (60%)*
Abdominal tomography during CDI, n (%)	37 (38%)	24 (42%)	13 (33%)
Colonic wall thickening, n (%)	*29 (78%)*	*17 (71%)*	*12 (92%)*
Colectasia [1], n (%)	*4 (11%)*	*3 (13%)*	*1 (8%)*
Perforation, n (%)	*0*	*0*	*0*
Death related to CDI, n (%)	2 (2%)	0	2 (5%)
Surgery during CDI, n (%)	3 (3%)	2 (4%)	1 (3%)
Median CDI duration before surgery (d)	7 (6,5 - 20,5)	20,5 (13,75-27,25)	6
One line of antibiotics, n (%)	70 (73%)	42 (74%)	28 (72%)
Two lines of antibiotics, n (%)	13 (14%)	4 (7%)	9 (23%)
Three lines of antibiotics, n (%)	2 (2%)	1 (2%)	1 (3%)

Abbreviations: IBD: Inflammatory Bowel Disease, CDI: Clostridium difficile infection, CD: Crohn's Disease, UC: Ulcerative Colitis, ICU: Intensive Care Unit, UCEIS: Ulcerative Colitis Endoscopic Index of Severity

[1] Colectasia is defined by a distension of large intestine >6 cm in transverse width of colon.

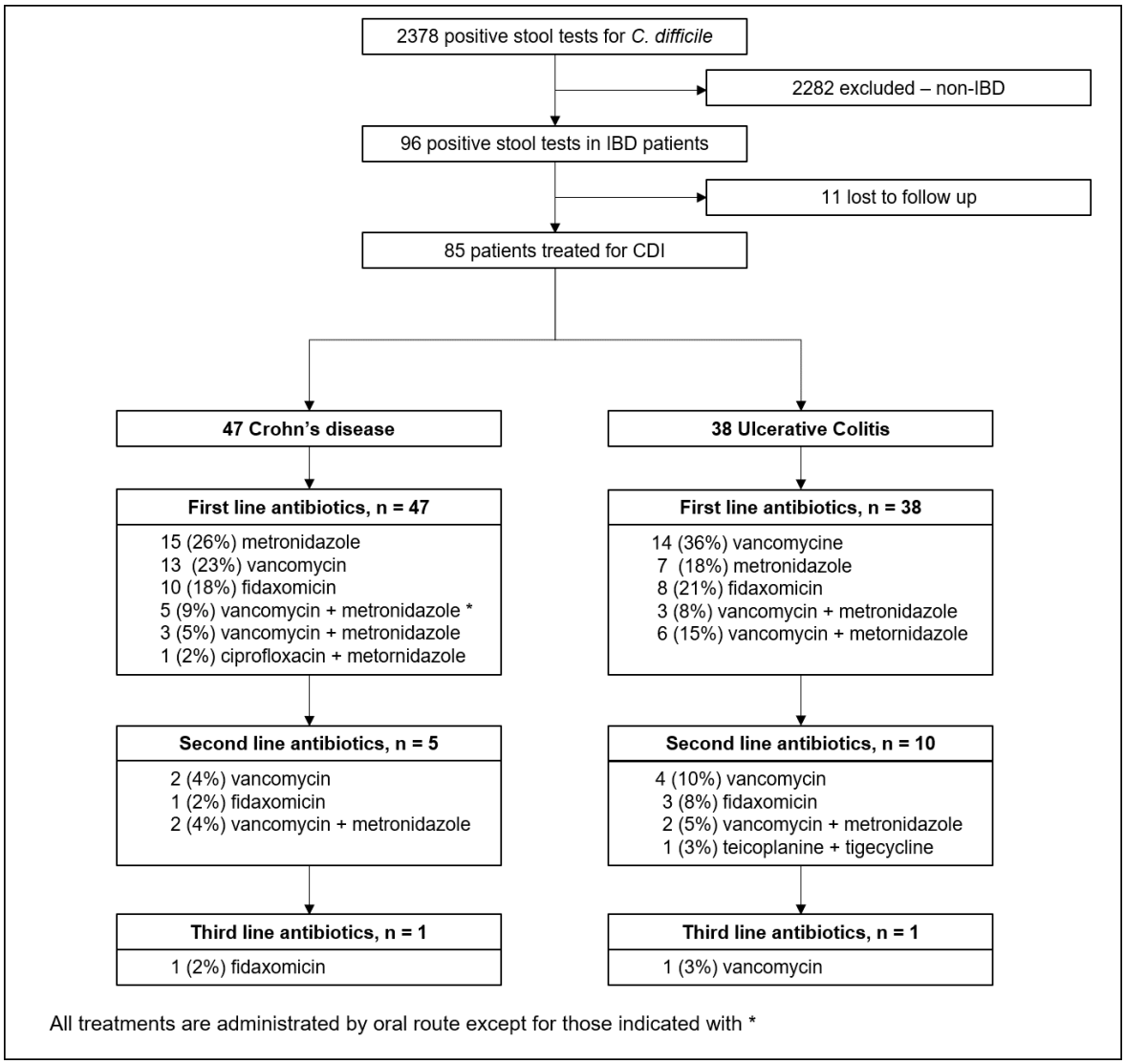

Figure 1: Antibiotic regimen for CDI

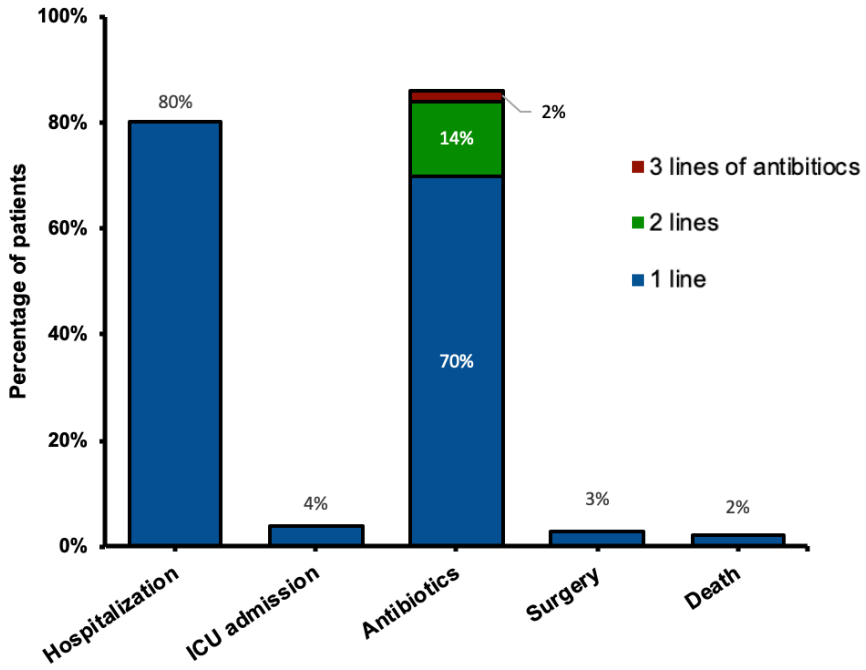

Figure 2: Therapeutic management of CDI

III. Management of IBD treatment during CDI

Figure 3 summarizes the management of IBD treatment during CDI. Twenty-six (27%) patients received with steroids at time of CDI: 18 (69%) patients maintained steroids, and 8 (31%) stopped the treatment. Ten (10%) steroids were introduced during CDI.

Twenty (21%) patients received immunosuppressant therapy (thiopurine in 13 patients, methotrexate in 5 patients, and other immunosuppressant in 2 patients): 14 (70%) were continued, 6 (30%) were stopped. Ten (10%) immunosuppressants were introduced during CDI.

Thirty-five (36%) patients received biologic treatment at time of CDI: 26 (27%) anti-TNF treatments, 2 (2%) ustekinumab, 4 (4%) vedolizumab. Twenty (57%) biologic treatments were continued, 15 (43%) were stopped. Fourteen (15%) biologics were introduced during CDI: 10 (10%) anti-TNF treatments, 2 (2%) ustekinumab, 2 (2%) vedolizumab.

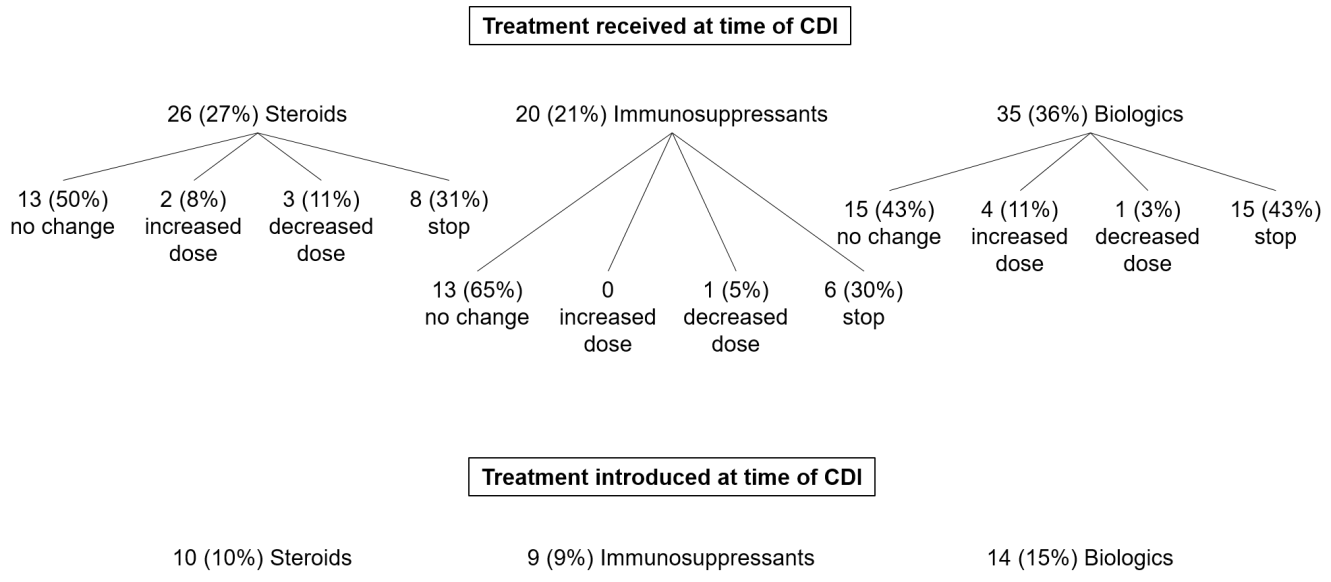

Figure 3: Management of IBD treatments at time of CDI

IV. IBD outcomes during the year after CDI

All patients included had one-year follow-up after CDI episode. Figure 4 summarizes IBD outcomes during the year after CDI in all patients, in UC, and in CD patients. Thirty-two (33%) were hospitalized for an IBD flare, 45 (47%) patients had a modification of their IBD treatment, and 22 (23%) patients underwent a surgery. Figure 5 summarizes surgeries performed in UC and CD patients during the year after CDI: 5 (23%) UC patients underwent surgery, and 17 (77%) CD patients underwent surgery.

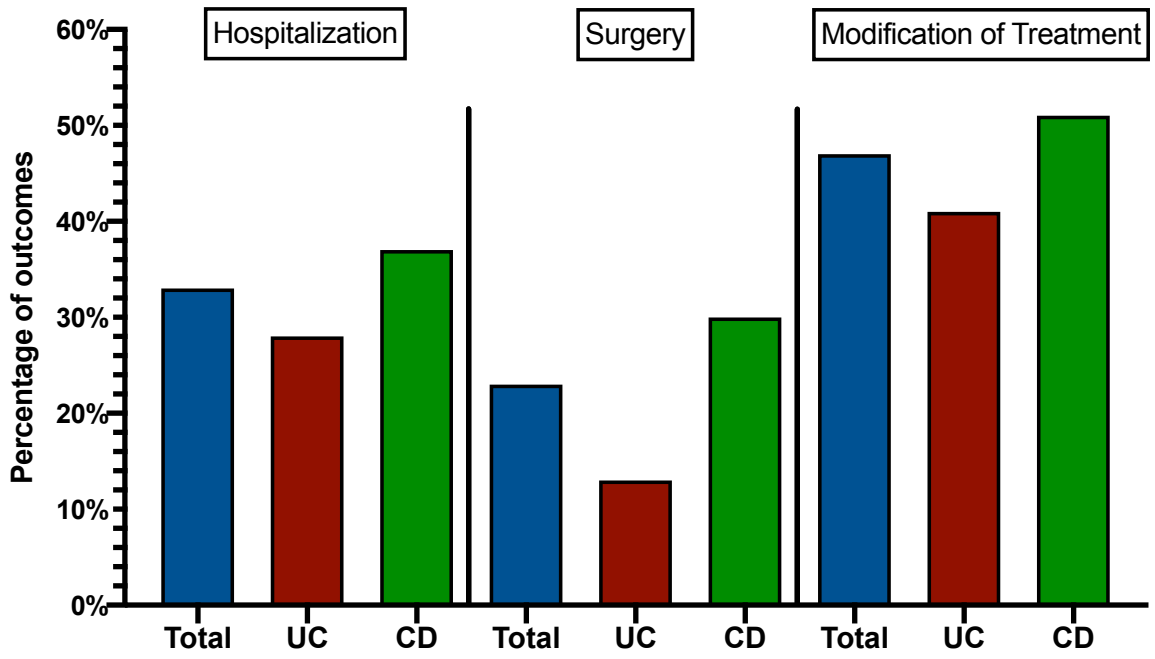

Figure 4: IBD outcomes during the year after CDI

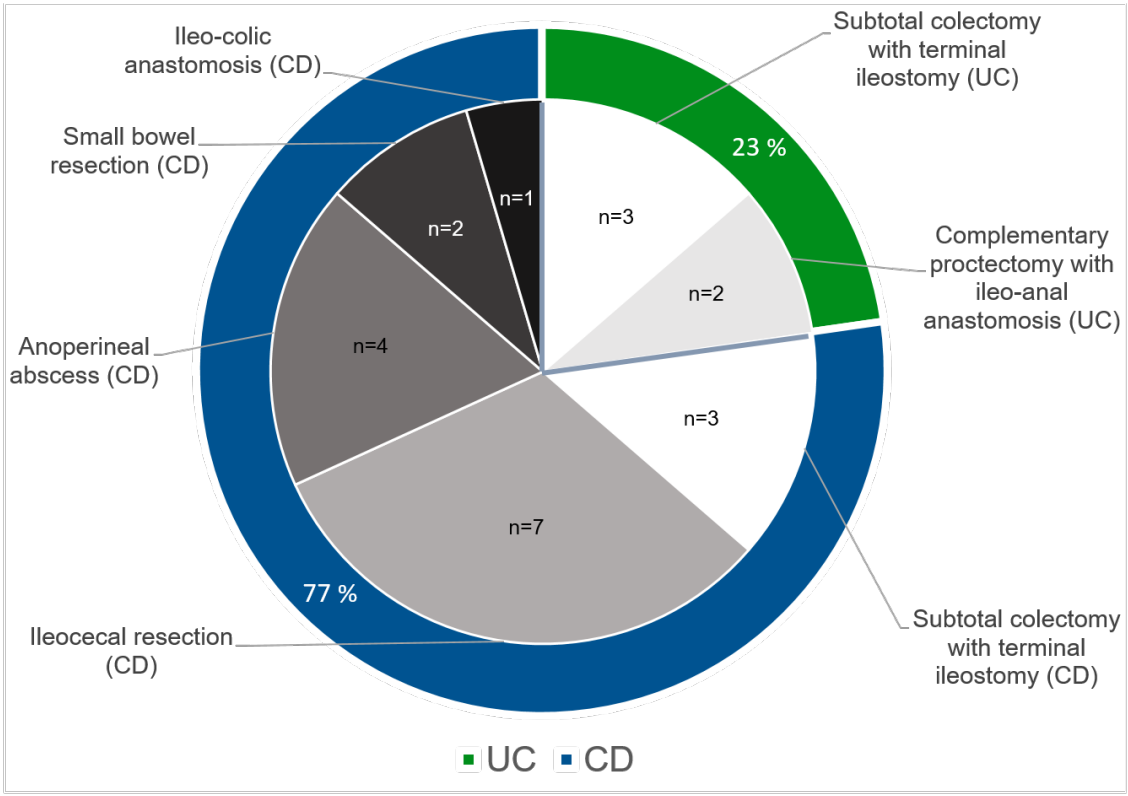

Figure 5: Surgeries performed during the year after CDI

The results of univariate and multivariate analysis to identify independent risk factors of poor IBD outcomes during the year after CDI are shown in Table 4. The three patients who underwent surgery during CDI were excluded from the final analysis, because at least one pejorative outcome was already achieved.

For the risk of hospitalization, biologic treatment was significantly associated with IBD related hospitalization during the year after CDI on univariate analysis (OR=2.68, 95%CI: 0.78-6.64; p=0.0261), but not on multivariate analysis. Recurrence of CDI was significantly associated with IBD related hospitalization during the year after CDI on univariate (OR=14.5, 95%CI: 1.47-143.74; p=0.0024) and multivariate analysis (OR=28.06, 95%CI: 2.75-286.26; p=0.005).

Concerning the risk of IBD treatment modification, age at diagnosis of CDI was significantly associated with IBD treatment modification during the year after CDI on

univariate (OR=0.33, 95%CI: 0.14-0.78; p=0.0082) and multivariate analysis (OR=0.32, 95%CI: 0.13-1.05; p=0.010).

For the risk of surgery, recent antibiotics use was significantly associated to an increased risk of surgery during the year after CDI (OR=4.15, 95%CI: 1.26-13.61; p=0.019) on multivariate analysis. On the primary statistical analysis, the relation between use of at least two lines of antibiotics and surgery during the year after CDI was so strong that Chi2 test was inadequate. A second statistical analysis with a Fisher test revealed a significant association between use of at least two lines of antibiotics and a decreased risk of surgery during the year after CDI on univariate analysis (OR=0.08, 95%CI: 0.004-1.46; p=0.0188).

Concerning the risk of occurrence of at least one pejorative outcome (hospitalization, IBD treatment modification and/or surgery), age at diagnosis of CDI was associated with a decreased risk to their occurrence on univariate (OR=0.27, 95%CI: 0.11-0.69; p=0.0033) and multivariate analysis (OR=0.27, 95%CI: 0.10-0.71; p=0.008).

Table 4: Univariate and multivariate logistic regression analysis of factors predicting hospitalizations, surgery or IBD treatment modification during the year following CDI

	Hospitalization				IBD treatment modification				Surgery				One of the three outcomes			
Factors predicting IBD outcomes after CDI	Univariate odds ratio (95% CI)	p value	Multivariate odds ratio (95% CI)	p value	Univariate odds ratio (95% CI)	p value	Multivariate odds ratio (95% CI)	p value	Univariate odds ratio (95% CI)	p value	Multivariate odds ratio (95% CI)	p value	Univariate odds ratio (95% CI)	p value	Multivariate odds ratio (95% CI)	p value
Female gender	1.76 (0.74-4.22)	0.19	1.53 (0.57-4.09)	0.39	1.52 (0.67-3.44)	0.31			0.62 (0.23-1.64)	0.33			1.00 (0.43-2.29)	1.00		
Tobacco	0.62 (0.18-2.12)	0.44			1.17 (0.39-3.42)	0.79			0.74 (0.19-2.90)	0.67			1.00 (0.32-3.04)	1.00		
IBD subtype (UC vs CD)	0.67 (0.28-1.63)	0.38			0.67 (0.29-1.54)	0.34			0.35 (0.11-1.07)	0.0528	0.88 (0.22-3.56)	0.86	0.93 (0.40-2.17)	0.87		
IBD disease duration > 4,8 years	1.45 (0.61-3.44)	0.39			0.66 (0.29-1.48)	0.31			2.06 (0.76-5.58)	0.15	2.37 (0.69-8.18)	0.17	0.83 (0.36-1.92)	0.67		
Surgery before CDI	1.60 (0.57-4.55)	0.37			0.79 (0.28-2.18)	0.64			1.76 (0.57-5.42)	0.32			1.04 (0.36-2.94)	0.94		
Previous IS or biologics	2.43 (0.85-6.92)	0.09	3.15 (0.69-14.2)	0.14	1.69 (0.68-4.15)	0.25			5.74 (1.17-28.09)	0.0145	5.75 (0.89-36.93)	0.065	1.55 (0.63-3.81)	0.33		
Age at diagnosis of CDI ⩾ 34,6 years old	1.2 (0.51-2.83)	0.66			**0.33 (0.14-0.78)**	**0.0082**	**0.32 (0.13-0.76)**	**0.010**	0.38 (0.13-1.05)	0.0533	0.33 (0.09-1.15)	0.082	**0.27 (0.11-0.69)**	**0.0033**	**0.27 (0.10-0.71)**	**0.008**
Community acquisition of CDI	0.88 (0.27-2.92)	0.84			1.21 (0.38-3.82)	0.75			1.11 (0.26-4.41)	0.89			0.91 (0.28-2.99)	0.88		
Recent antibiotherapy	0.77 (0.32-1.85)				0.74 (0.32-1.68)	0.47			2.51 (0.92-6.81)	0.06	**4.15 (1.26-13.61)**	**0.019**	1.00 (0.43-2.32)	1.00		
Severe and/or complicated CDI	2.13 (0.88-5.16)		2.25 (0.83-6.08)	0.11	0.98 (0.44-2.21)	0.97			1.18 (0.45-3.07)	0.74			0.81 (0.36-1.88)	0.63		
One line of antibiotics for CDI	1.18 (0.28-4.97)				1.37 (0.36-5.23)	0.65			0.66 (0.15-2.84)	0.58			1.77 (0.44-6.69)	0.39		

⩾ 2 lines of antibiotics for CDI	0.45 (0.11-1.75)	0.24			0.35 (0.10-1.24)	0.09	0.34 (0.09-1.23)	0.100	**0,08 * (0,004-1,46)**	**0.0188***			0.33 (0.10-1.06)	0.0513	0.26 (0.06-1.04)	0.057
Steroids at time of CDI	1.08 (0.41-2.81)	0.87			1.46 (0.59-3.65)	0.41			1.01 (0.35-2.97)	0.98			1.91 (0.70-5.23)	0.19		
IS at time of CDI	0.82 (0.28-2.41)	0.72			1.51 (0.55-4.09)	0.42			0.53 (0.14-2.03)	0.35			1.52 (0.52-4.43)	0.44		
Biologics at time of CDI	**2.68 (1.08-6.64)**	**0.0261**	2.32 (0.78-9.90)	0.13	2.53 (1.05-6.06)	0.03	2.32 (0.95-5.67)	0.065	1.96 (0.74-5.21)	0.17	1.20 (0.32-4.46)	0.78	1.98 (0.80-4.91)	0.13	2.10 (0.77-5.72)	0.14
ICU admission	2.06 (0.27-15.64)	0.47			0.36 (0.03-3.70)	0.37			3.6 (0.46-27.99)	0.19	2.95 (0.24-36.45)	0.39	0.59 (0.08-4.41)	0.59		
Recurrence	**14.5 (1.47-143.74)**	**0.0024**	**28.06 (2.75-286.26)**	**0.005**	1.56 (0.33-7.46)	0.57			1.38 (0.25-7.74)	0.71			3.88 (0.43-34.7)	0.19	5.20 (0.51-52.3)	0.161

* A different statistical analysis with Fisher test was performed

DISCUSSION

This multicentric cohort reports the real-life experience of IBD patients with concomitant CDI, in a multicenter cohort, with a follow-up of one year after CDI. Notably almost half of CDI were severe, 3/4 of the patients were hospitalized for CDI, three patients underwent surgery at time of CDI, and two died. Almost 3/4 of the patients needed only one line of antibiotics, but 15% of them required two or three lines. The use of at least two lines of antibiotics was associated to a decreased risk of surgery during the year after CDI. Moreover, CDI seems to have a significant impact on IBD course during the year after CDI episode: 1/3 of these 96 IBD patients were hospitalized during the year after CDI, 1/4 underwent a surgery, and half of them underwent a modification of their IBD treatment.

Single center and multicenter studies have consistently demonstrated the significant impact of CDI on patients with IBD (11). Compared with non-IBD controls, patients with concomitant IBD and CDI have 4-fold greater mortality and are 6 times more likely to require surgery (5). They also had longer hospital stays and excess hospitalization charges (5). Nevertheless, long-term IBD outcomes have been poorly reported. There are only few reports assessing if CDI has an impact on the course of IBD beyond the acute CDI episode. Two studies reported a higher rate of UC-related emergency room visits or hospitalizations, and higher colectomy rates than with the UC alone in the year following the initial episode of CDI (20,21). A retrospective study reported a nearly 6-fold excess mortality at 30 days and 365 days after the initial hospitalization for CDI (22). Another retrospective study identified a mean increase in 0.89 hospitalizations per patient in the year after CDI with more than half the patients

requiring escalation of their IBD therapy: 1/4 of the cohort required initiation or escalation of biologic therapy (23). To our knowledge, there is no study assessing the impact of CDI on IBD course at mid-term. We here report a large cohort study including 96 CDI episodes in 86 IBD patients, with a constant and homogeneous follow-up period of one year after CDI. Our results highlight that CDI has a major impact on IBD course during the year following CDI. We showed that almost 50% of the patients had an IBD treatment modification during the year after CDI; in the literature only 10% to 15% of IBD patients (without CDI) have to change their treatment every year (24). More than 30% of the patients have been hospitalized during the year after CDI, compared to 20% per year of IBD patients in Western Europe (25). Finally, 25% of the patients had a surgery during the year after CDI episode, versus 8% per year in CD patients without CDI (26). These results underline that CDI may have a significant and pejorative impact on the course of IBD within the months after CDI. Along this, IBD patients should be closely monitored, with careful clinical and biological evaluations, including C-reactive protein and fecal calprotectin, and maybe endoscopic and iconographic evaluations, during the first months after CDI episode, in order to eventually intensify their treatment to maintain deep remission, and prevent the occurrence of IBD complications.

Most of the clinical trials investigating CDI medications have excluded IBD patients. There are no prospective trials comparing antibiotics regimens among IBD patients with CDI, thus evidences from the non-IBD population are used to guide management. Prior literature in non-IBD patients has suggested that there is no difference in cure between vancomycin and metronidazole for mild disease (27), that fidaxomicin is non-inferior to vancomycin in CDI cure, and offers a lower recurrence rate (28,29). New recommendations have been recently published in March 2020 for

non-IBD patients: the new guidelines no longer recommend metronidazole as first-line therapy (13). For both mild and severe CDI, either vancomycin or fidaxomicin are preferred (13). On our multivariate analysis, the use of two lines or more of antibiotics was protective of poor IBD outcomes during the year following CDI. Regarding to the details of antibiotics regimen used in our cohort (Figure 1), more of 30% of the patients had received metronidazole as a first line of antibiotics, whereas all the patients had received vancomycin or fidaxomicin in second or third line of antibiotics, suggesting that vancomycin or fidaxomicin should be considered as first-line therapy for CDI in IBD patients. Many experts have argued for the use of vancomycin first-line in the IBD population, though no prospective data demonstrating its benefit over metronidazole exist in this specific IBD population (18,30). Furthermore, an American Gastroenterological Association expert review recommended in 2017 that IBD should be considered another severity marker of CDI and that vancomycin or fidaxomicin be considered first-line therapy for CDI in IBD patients (31).

There are several limitations to the present study, mainly due to its retrospective design and the size of the cohort. However, it is important to note that the data were prospectively collected from three referral centers in IBD. We used a definition of CDI severity although it was not validated for CDI in IBD. In our study, severity of CDI was not associated with any IBD outcomes neither on univariate or multivariate analysis, suggesting that CDI severity definition is inadequate for CDI in IBD. Biological parameters included in this definition such a hypoalbuminemia could have been attributable to the activity of IBD rather than to CDI, and underlying IBD itself should be considered as another severity marker of CDI.

Further prospective data are needed to help to clarify the therapeutic management of CDI and its impact on the course of IBD. There are several areas of knowledge deficit in the management of CDI among patients with IBD. Prospective studies adjusted for severity of underlying IBD and CDI are essential to evaluate the appropriate CDI treatment algorithm in IBD population.

CONCLUSION

In conclusion, this retrospective real-life multicentric study reports a major impact of CDI in IBD course during the year following, with high rates of IBD related hospitalizations, IBD treatment modification and surgery. IBD should be considered as a severity marker of CDI, and vancomycin or fidaxomicin should be considered as first-line therapy for CDI in IBD population. After a CDI episode, IBD patients should be closely monitored with careful clinical and biological surveillance, in order to avoid poor outcomes such as surgery.

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AUTEUR : PRUIT Manon
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Titre de la thèse : La survenue d'une infection à *Clostridioides difficile* est associée à une aggravation des maladies inflammatoires chroniques intestinales à court et à moyen terme

Thèse - Médecine - Lille 2020
Cadre de classement : Gastro-entérologie
DES + spécialité : Gastro-entérologie et hépatologie
Mots-clés : Maladies inflammatoires chroniques intestinales, *Clostridioides difficile*

Introduction : Les patients atteints de maladies inflammatoires chroniques intestinales (MICI) sont plus à risque de développer une infection à *Clostridioides difficile* (ICD), associée à un plus haut risque de mortalité et de chirurgie en comparaison aux patients atteints de MICI seule. Peu d'études ont évalué la prise en charge des ICD chez les patients MICI et leur impact sur le devenir de la MICI à court et moyen terme. Les objectifs de cette étude étaient *(1)* d'évaluer la sévérité, la prise en charge et les conséquences de l'ICD dans une large cohorte de patients MICI, et *(2)* d'évaluer l'impact de l'ICD sur la MICI à court et moyen terme.

Matériel et méthodes : Nous avons mené une étude observationnelle rétrospective et multicentrique incluant consécutivement tous les patients MICI présentant de manière concomitante une ICD, de janvier 2010 à décembre 2018. Chaque patient était suivi un an après l'épisode d'ICD. Les critères de jugement étaient la survenue d'une hospitalisation, d'une modification du traitement de fond de la MICI et/ou d'une chirurgie dans l'année suivant l'ICD.

Résultats : Quatre-vingt-seize échantillons de selles étaient positifs pour le *Clostridioides difficile* chez 86 patients MICI. Quarante-cinq (47%) ICD étaient sévères, 75 (78%) patients étaient hospitalisés pour l'ICD, dont 4 (4%) en unité de soins intensifs. Soixante-dix (70%) patients n'ont reçu qu'une ligne d'antibiotique, 13 (14%) en ont reçu deux ou trois. Trois (3%) patients ont été opérés pendant l'ICD, 2 (2%) sont décédés. Pendant l'année suivant l'ICD, 32 (33%) patients ont été hospitalisés, 45 (47%) ont eu une modification de traitement de fond de la MICI, et 22 (23%) ont subi une chirurgie. En analyse multivariée, le recours à au moins deux lignes d'antibiotiques, contenant systématiquement de la vancomycine ou de la fidaxomicine, était protecteur de la survenue d'un ou plusieurs évènements péjoratifs associés à la MICI dans l'année suivant la MICI.

Conclusion : Cette étude de vraie vie montre l'impact majeur de l'ICD sur la MICI dans l'année suivant l'ICD, avec des taux d'hospitalisation, de modification de traitement de fond de la MICI et de chirurgie élevés. La MICI devrait être considérée comme un marqueur de sévérité d'ICD, et la vancomycine ou la fidaxomicine devraient être utilisés en première ligne d'antibiothérapie chez ces patients. Après une ICD, ces patients devraient être rigoureusement suivis afin de prévenir la survenue d'une complication liée à la MICI.

Composition du Jury :

Président :	**Monsieur le Professeur Pierre DESREUMAUX**
Assesseurs :	**Monsieur le Professeur Sébastien DHARANCY** **Madame le Docteur Marie TITECAT** **Madame le Docteur Vanessa BONDJEMAH**
Directeur de thèse :	**Monsieur le Professeur Benjamin PARIENTE**