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***Clostridium difficile* Infection: A Rarity in Patients Receiving Chronic Antibiotic Treatment for Crohn's Disease**

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Abstract

Background—Prolonged antibiotic use is limited by several adverse effects, one of which is *Clostridium difficile* infection (CDI). The aim of this study was to determine the incidence of CDI in patients receiving chronic antibiotic treatment for Crohn's disease (CD).

Methods—We conducted a retrospective review of 100 patients with CD for which 6 months of outpatient antibiotic therapy was prescribed. Data were collected regarding demographics, CD phenotype, treatment history, and CDI. The incidence of CDI in our patient population was calculated and compared with historical controls.

Results—100 patients were studied—60% of men, mean age 23.9 years at CD diagnosis. Eighty-two percent had disease involving the ileum, and 33% had disease involving the colon. The mean duration of antibiotic therapy was 39.6 months (range, 6–217 months). The most commonly prescribed classes of antibiotics were fluoroquinolones (84%), penicillins (57%), and cephalosporins (32%). Forty-nine percent of patients were treated with concomitant thiopurines, 45% with budesonide, and 41% with biologics. The overall incidence of CDI was 2%. This incidence of CDI was lower than previously reported for non-CD patients receiving chronic antibiotics for continuous-flow left ventricular assist device infections (12.5%) and orthopedic prosthesis infections (22.2%).

Conclusions—The incidence of CDI is rare in patients receiving chronic antibiotic treatment for CD, and it seems significantly lower than for non-CD populations reported in the literature.

Keywords

Clostridium difficile infection; Crohn's disease; chronic antibiotic

Dysbiosis refers to an alteration in the bacterial composition of the bowel. Dysbiosis is considered to play a significant role in the pathogenesis of numerous conditions affecting human health, including Crohn's disease (CD). A rapidly increasing body of literature has shown that patients with CD have reduced microbiome diversity and shifts in the concentrations of both protective and invasive bacterial species.^{1–13} A recent systematic review of 72 abstracts showed that the relative abundance of Bacteroidetes and Enterobacteriaceae (specifically *Escherichia coli*) are increased in CD, whereas Firmicutes

and *Faecalibacterium prausnitzii* are found at lower abundance.¹⁴ Evidence suggests that dysbiosis may play an important role in initiating and maintaining the chronic inflammation that characterizes CD.

Given the impact of the microbiome, CD commonly affects areas of the gastrointestinal tract with high bacterial concentrations, such as the terminal ileum and colon. Antibiotic therapy is thought to favorably alter the microbiome in patients with CD and reduce bacterial invasion into gut tissue.^{15–18} Although studies in animals have shown antibiotics to be effective in acute and chronic colitis and ileitis,¹⁹ the role of antibiotics in the treatment of active CD in humans is unclear. Current guidelines only recommend the use of antibiotics in perianal disease, bacterial overgrowth, and infectious complications of CD.²⁰ A recent meta-analysis including 16 randomized control trials in varied CD populations showed that antibiotics may be effective in inducing remission and preventing relapse.²¹ Therefore, some patients are prescribed chronic antibiotics as a component of their CD treatment.

The prolonged use of antibiotics for any medical condition raises the concern for *Clostridium difficile* infection (CDI). Two studies following patients with left ventricular assist device infections and infected orthopedic prostheses who required varied antibiotic regimens for an average duration of 15.2 and 48.9 months, respectively. The rates of CDI in these 2 studies were reported at 12.5% and 22.2%.^{22,23}

The incidence of CDI is of particular concern in patients with inflammatory bowel disease (IBD). Not only is there an increased incidence of CDI in this population, CDI often induces disease relapse and is associated with higher rates of colectomy.²⁴ In the largest existing cohort study following more than 350,000 patients with IBD over 10 years in the United States, CDI was diagnosed in 2.8% of patients with ulcerative colitis and 1.0% of patients with CD.²⁵ In another study evaluating the incidence of CDI in patients hospitalized between 1998 and 2004, the incidence of CDI in hospitalized patients with ulcerative colitis and CD was 3.73% and 1.09%, respectively, whereas the incidence in the general population was only 0.45%.²⁶ Further studies have shown that the overall incidence of CDI in patients with IBD has increased significantly over the last 2 decades.^{27–30} Potential risk factors that have been identified for CDI in patients with IBD include IBD subtype, older age, steroid use, severity of disease, extent of disease, and recent antibiotic therapy.^{27,31,32}

Although some retrospective studies have shown that CDI incidence in patients with IBD may be associated with previous antibiotic use,²⁷ to date there has not been any study specifically evaluating the incidence of CDI in patients receiving chronic antibiotic therapy. In this study, we aim to determine the incidence of CDI in patients with CD being treated with chronic antibiotics. The secondary aim of this study was to describe the specific clinical characteristics of patients with CD who develop CDI with chronic antibiotic treatment.

MATERIALS AND METHODS

Data Collection

We conducted a retrospective chart review of the outpatient records of 100 patients who met the study inclusion and exclusion criteria (described in “Study Subjects”). During the chart

review, the following information for each patient was collected: basic demographics and smoking status; details regarding CD (duration, extent, surgical history); details regarding nonantibiotic treatment for CD (use of steroids, immunomodulator therapy, biological therapy, other therapy); details regarding antibiotic treatment for CD (type and duration of antibiotics); and details regarding CDI. Incidence of CDI was measured during the period of antibiotic therapy until either the first office visit after therapy was stopped or the end of the study period (in the cases of continued therapy). All data were collected over a 3-month period and entered into a secure, deidentified database. The study design was approved by the Columbia University Institutional Review Board.

Study Subjects

The study population consisted of patients seen in a large practice within the Columbia University Division of Digestive and Liver Diseases that specializes in the management of IBD. Patient charts were pulled in alphabetical order from the filed practice records (dating from January 1992 to January 2015). All subjects included in the study had documented CD for which they were prescribed continuous outpatient antibiotic therapy for 6 months. Excluded from the study were patients with incomplete or limited records (fewer than 3 office visits during the study period) and those who received metronidazole and/or vancomycin (accepted treatments for CDI) as part of their continuous chronic antibiotic therapy.

Endpoints and Statistical Analysis

Our primary endpoint was the incidence of CDI in patients with CD treated with chronic antibiotics. Descriptive statistics were used to characterize the study population and compare the CDI incidence between the current study population and historical controls reported in previously published studies.

RESULTS

Patient Characteristics

Patient characteristics, including details regarding the diagnosis of CD, are shown in Table 1. Of the 100 study patients, 60 were men, with a mean age of CD diagnosis of 23.9 years (range, 6–60 years). A majority of patients had ileal involvement, including 53 with isolated ileal disease. Thirty-three patients had disease involving the colon, and a total of 18 patients had perianal CD. Only 27 of our study patients had required surgery for the management of their CD: 19 with some degree of bowel resection (10 with only ileal resection) and 8 with surgery for the management CD-related strictures, fistulas, and abscesses. During the study period, 19 patients were hospitalized for CD-related complications. At the time of chronic antibiotic initiation, only 1 patient was actively smoking and 6 others had been previous smokers.

Characteristics of Chronic Antibiotic Treatment

Details regarding the chronic antibiotic regimens used in our study population are shown in Table 2. Chronic antibiotic therapy was started at a mean age of 39.8 years (range, 13.8–72.8 years)—corresponding to a mean disease duration of 10.1 years (range, 0–48.1 years). The

mean duration of antibiotic treatment was 39.6 months (range, 6–217 months), and the mean number of cumulative antibiotics given to each patient as part of their chronic treatment regimen was 3.2 (range, 1–14).

The most common class of antibiotics that was prescribed was fluoroquinolones—taken by 84% of patients at some point during their treatment. The most commonly administered fluoroquinolone antibiotic was ciprofloxacin. Table 2 summarizes these findings and provides the mean duration of treatment with each class of antibiotics.

Characteristics of Concomitant Medical Treatments

The most frequently prescribed concomitant medications were thiopurines—in 49% of patients. Forty-five of patients were treated with budesonide; 41% with biological agents; 3% with methotrexate; and 6% with other agents. Table 3 shows details regarding the concomitant therapies.

Incidence of CDI

For patients who finished antibiotic therapy during the study period ($n = 74$), the mean follow-up for incident CDI was 12 months postexposure (range, 3–20 months). Only 2 patients in our study population of 100 were diagnosed with CDI during the period in which they were receiving chronic antibiotic therapy. Given that a total of 3961 months of antibiotic therapy were prescribed to our study population, this equates to 1 incident case of CDI per 165 patient-years of antibiotic therapy.

The 2 patients diagnosed with CDI shared very few clinical characteristics. Patient 1 was a boy diagnosed with Crohn's ileitis at the age of 15 years. He was a nonsmoker and had undergone a fistulotomy shortly after diagnosis. Antibiotic therapy was started 30.1 years after CD diagnosis, and it was continued for 45 months before the detection of CDI (ciprofloxacin for 37 months and augmentin for 8 months). The patient received concomitant 6-mercaptopurine and adalimumab during his antibiotic course. Of note, he had been hospitalized 2 months before the diagnosis of CDI (at which time a stool *C. difficile* test was negative).

Patient 2 was a woman diagnosed at the age of 21 years with Crohn's ileocolitis with perianal involvement. She was also a nonsmoker and had a history of ileal resection. Antibiotic therapy was started 12.4 years after the diagnosis of CD, and it was continued for 6 months before the diagnosis of CDI (ciprofloxacin only). The patient was prescribed concomitant budesonide and 6-mercaptopurine during her antibiotic course, and she had also received stem cell infusions as part of an experimental protocol in 2 months before CDI diagnosis.

DISCUSSION

The most important risk factor for the development of CDI in the general population is previous antibiotic use.³³ An undisrupted microbiome is necessary for protection against pathogen colonization, and the mechanism by which antibiotic use leads to an increased risk of CDI is alteration of normal intestinal flora. A decrease in the diversity of the gut

microbiome is detected within days of antibiotic use.³⁴ The new community of bacteria that is established in the weeks after antibiotic cessation is different from that before antibiotic administration.^{35,36} Although studies have shown an association between previous short-term antibiotic use and incident CDI in the general IBD population,²⁷ this study is the first that examines a unique population of patients with CD who are treated with prolonged antibiotic therapy.

Despite the continuous, long-term use of antibiotics in our study subjects, we found a low rate of CDI (2%). Compared with populations in 2 previous studies receiving similar chronic antibiotics for non-CD conditions, our patients had significantly lower rates of CDI. The first study, by Jennings et al,²² reported the clinical outcomes associated with 6 weeks of chronic antimicrobial suppression therapy in 16 patients with continuous-flow left ventricular assist devices. The mean duration of therapy was 15.2 months (range, 2.9–44.5 months). Two patients (12.5%) were diagnosed with CDI during their antibiotic therapy, equaling 1 incident case of CDI per 10.1 patient-years of antibiotic therapy. Compared with our population with CD, the subjects in this study had a higher overall incidence of CDI (12.5 versus 2%), and they had fewer years of therapy leading to each incident case of CDI (10.1 versus 165). The second study, by Segreti et al,²³ reported the clinical outcomes associated with prolonged antibiotic therapy in 18 patients with infected orthopedic prostheses. The mean duration of therapy was 48.9 months (range, 4–103 months). Four patients (22.2%) were diagnosed with CDI during antibiotic therapy, equaling 1 incident case of CDI per 18.3 patient-years of antibiotic therapy. Again, compared with our population with CD, the subjects in this study had higher overall incidence of CDI (22.2 versus 2%), and they had fewer years of therapy leading to each incident case of CDI (18.3 versus 165).

Our findings seem to indicate that antibiotics may not play as significant a role in CDI development in patients with CD as it does in the general population, consistent with some past studies. A retrospective analysis of inpatient CDI at a tertiary referral center showed that antibiotic use was reported in 69% of non-IBD patients in 3 months before CDI diagnosis, whereas it was reported in only 40% of patients with IBD.³⁷ Furthermore, one of the few prospective studies assessing the link between IBD and CDI found a very low overall prevalence of CDI in symptomatic patients (3.6%), with multivariable analysis showing no association between CDI and antibiotic use.³⁸

What our results and those of the previously cited studies suggest is that factors other than antibiotic use might play a more important role in the development of CDI among patients with CD. Proposed risk factors for CDI in this patient population include altered nutritional and immunological states, repeated hospitalization, genetic predisposition, and the frequent and recurrent use of immunomodulating drugs.³⁹ One important risk factor for CDI that our results support is disease extent and phenotype. In previous studies that have reported higher rates of CDI than ours, up to 91% of patients with IBD who developed CDI (including a majority of whom had CD) had colonic disease involvement.²⁷ Only a minority of our patients (33%), however, had colonic CD. It is likely that the predominantly ileal phenotype of our patients influenced the low incidence of CDI.

A possible protective element against CDI may be the unique microbiome in patients with CD, and specifically ileal CD.⁴⁰ Given that antibiotics predispose to CDI based on alterations of the microbiome, we hypothesize that the low incidence of CDI seen in our study despite prolonged antibiotic therapy is a result of the distinctive microbiome of our patients. A recent study suggested that secondary bile acid synthesis by specific intestinal bacteria may correlate with resistance to CDI.⁴¹ Altered bile acid metabolism has long been recognized in ileal CD,^{42,43} and it is possible that the interplay between our patients' CD phenotype and antibiotic administration may have modified the susceptibility to CDI. Similarly, studies have illustrated that patients with ileal CD who carry the NOD2/CARD15 mutation have altered mucosal innate immunity because of changes in intestinal secretion of antimicrobial peptides and defensins.⁴³ Given that the damage and inflammation mediated by CDI is dependent on host epithelial-derived immune response,⁴⁴ we propose that alterations in the microbiome of our CD population both preceding and resulting from chronic antibiotic therapy may have impacted the incidence of CDI.

The major strength of our study is the patient population. Each of our patients was confirmed to have been receiving at least 6 continuous months of antibiotic therapy for CD. Moreover, any patient receiving metronidazole and/or vancomycin (the first-line treatments for CDI) was excluded. The antibiotics most commonly prescribed to our patients are the same that have been associated with an increased risk of CDI in the general population.³³ Despite this, our incidence of CDI was very low, likely highlighting the fact that a protective factor was at play.

There are limitations of our study. First, as with any retrospective analysis, the quality of the data that were reviewed may have been limited or incomplete. Even for those patients with documented antibiotic therapy, it is possible that therapy was temporarily interrupted during the interval between office visits. Second, this study only evaluated the outpatient records of our patients. It is important to point out, though, that few patients were hospitalized during the period in which they were included in the study. Third, the manner in which antibiotic therapy was administered was not uniform, with different regimens being prescribed. Fourth, the decision to test patients for CDI was driven by clinical suspicion, rather than a standardized protocol. Although it is routine in our practice to test for CDI when there is a change in a patient's clinical course, negative results are not uniformly reported in the paper chart. Thus, it could not be precisely determined how many of patients were tested for CDI during the study period. We are confident, however, that all positive test results were captured in the chart, as any abnormal labs and changes in therapy are meticulously recorded. Finally, the descriptive nature of this study was primarily intended to be hypothesis-generating, and therefore, causal relationships between antibiotic exposure and outcome cannot be confirmed. Furthermore, the comparison of our patients with reports of other populations receiving chronic antibiotics is limited by the fact that we did not have access to the full details of those historical controls. Nonetheless, the antibiotic types used by our population and those reported in the literature were similar, and we hope our comparison offers some insight into the unique nature of chronic antibiotic therapy for CD.

In conclusion, this study shows that the incidence of CDI is rare in patients receiving chronic antibiotic treatment for CD. This was true, despite the prolonged use of a wide range of

antimicrobial agents for varied disease duration, extent, and concomitant medical therapy. Furthermore, the incidence of CDI seems to be lower in our study population than in other populations that received chronic antibiotic therapy for non-CD conditions. We hypothesize that the altered gut microbiome in CD may offer a degree of protection from CDI. We hope that studies such as ours will lead to future research that specifically analyzes changes in the CD microbiome that result from various chronic therapies, including prolonged antibiotic use.

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TABLE 1

Characteristics of Study Patients at the Time of Chronic Antibiotic Initiation

Patient Characteristics	Overall Study Population (n = 100)
Male gender, %	60
Age at CD diagnosis, yr ^a	23.86 (6–60)
CD extent, %	
Stomach and small bowel	1
Jejunoleitis	4
Ileitis	53
Ileocolitis with perianal disease	9
Ileocolitis without perianal disease	15
Colitis	9
Perianal disease	9
History of CD-related surgery, %	
Stricturoplasty	1
Fistula surgery	3
Incision and drainage of perianal abscess	4
Ileal resection	10
Ileocolic resection	4
Colon resection	3
Total proctocolectomy with pouch	2
Hospitalization during study period, %	19
Smoking status, %	
Former smoker	6
Active smoker	1

^aValues shown as mean (range).

TABLE 2

Characteristics of Chronic Antibiotic Treatment

Treatment Characteristics	Overall Study Population (n =100)
Age at which antibiotics were started, yr ^a	33.79 (13.88–72.84)
Duration of disease at which antibiotics were started, yr ^a	10.09 (0–48.10)
Duration of antibiotic treatment, mo ^a	39.61 (6–217)
Number of antibiotics in the treatment regimen ^a	3.18 (1–14)
Fluoroquinolone treatment, ^b %	84
Duration of treatment, mo ^a	25.63 (1–201)
Penicillin treatment, ^c %	57
Duration of treatment, mo ^a	17.98 (1–84)
Cephalosporin treatment, ^d %	32
Duration of treatment, mo ^a	16.41 (1–68)
Bactrim treatment, %	10
Duration of treatment, mo ^a	13.70 (3–31)
Rifaximin treatment, %	8
Duration of treatment, mo ^a	12.63 (1–36)
Other antibiotics, ^e %	8
Duration of treatment, mo ^a	2.50 (1–6)

^aValues shown as mean (range).

^bAntibiotic regimen including ciprofloxacin, levofloxacin, moxifloxacin, and/or gatifloxacin.

^cAntibiotic regimen including augmentin and/or ampicillin.

^dAntibiotic regimen including cephalexin.

^eAntibiotic regimen including clindamycin, vibramycin, clarithromycin, tinidazole, and/or linezolid.

TABLE 3

Frequency of Concomitant Therapy During Antibiotic Treatment

Therapy	Overall Study Population (n = 100)
Budesonide, %	45
Thiopurine, %	
6-mercaptopurine	36
Azathioprine	13
Methotrexate, %	3
Biologic, %	
Infliximab	30
Adalimumab	9
Certolizumab	2
Thiopurine and biologic, %	24
Other, ^a %	6

^aOne patient use natalizumab; 1 patient use tekinumab; 4 patients receiving stem cell therapy.