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Low Risk of *Clostridium difficile* Infections in Hospitalized Patients with Inflammatory Bowel Disease in a German Tertiary Referral Center

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Key Words

Clostridium difficile infection • Inflammatory bowel disease • Crohn's disease • Ulcerative colitis • Immunosuppressive therapy

Abstract

Introduction: Many reports, mainly from the US and Canada but also a recent report from a center in Europe, have documented the increasing impact of *Clostridium difficile* infections in patients with inflammatory bowel disease (IBD) during the last years. To determine the prevalence of *C. difficile* infections in hospitalized IBD patients in a tertiary referral center in Germany, we conducted this retrospective analysis.

Methods: Data of all IBD in-patients treated due to an acute flare of their IBD at the Department of Internal Medicine I of the University of Regensburg between January 1, 2001, and June 30, 2008, were analyzed. In patients with a concomitant diagnosis of *C. difficile* infection, further variables such as IBD-related treatment at the time of infection or outcome were examined. **Results:** In total, 995 in-patients with IBD were treated in this hospital [638 patients with Crohn's disease (CD), 357 with ulcerative colitis (UC)] during the study period. Of these, 279 patients with CD and 242 patients with UC were admitted with an acute flare and suffering from diarrhea and abdominal pain. Only 10 of those were diagnosed

as having a concomitant infection with *C. difficile*. Six patients were female and the median age was 49 years (range: 15–80). Six patients with *C. difficile* infections suffered from UC and 4 patients from CD, all with previous colonic involvement. Eight patients used immunosuppressive therapies; only 2 patients were treated with antibiotics before infection. **Conclusion:** In contrast to recent reports from other countries, only a low percentage of hospitalized patients with acute flares of their IBD were identified as having an underlying *C. difficile* infection in this German tertiary referral center. However, in IBD patients with an acute flare, a concomitant *C. difficile* infection should be excluded, especially in patients with immunosuppressive treatment and colonic involvement of their disease. Further research is needed to evaluate if regions with different risks of *C. difficile* infections exist and to find out more about potential reasons for this observation.

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Introduction

A large number of reports from many different regions have documented the rising incidence of *Clostridium difficile* infections during the last decade [1, 2]. Elderly patients are particularly susceptible to infections; addi-

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tionally, factors like recent use of antibiotics and immunosuppressive drugs and systemic comorbidities are suggested to increase the risk of *C. difficile* infection [2].

After regional outbreaks of *C. difficile* in the US, Canada and subsequently in parts of Europe, a hypervirulent epidemic strain of *C. difficile* (North American pulsed-field type 1, PCR ribotype 027) resistant to fluoroquinolone attracted a great deal of attention [3–5].

As patients with inflammatory bowel disease (IBD) – comprising Crohn's disease (CD) and ulcerative colitis (UC) – frequently present with diarrhea and abdominal pain, differentiation between an acute flare and enteric infection seems to be necessary in this setting. This is even more so since several studies, mainly from the US and Canada, have documented a dramatic rise of *C. difficile* infections in patients with IBD, both in studies from tertiary referral centers and in national surveys [6–10]. More recently, an increasing incidence in IBD patients has also been identified in Greece [11] and Belgium [12], as well as a high prevalence of *C. difficile* infection in Italian pediatric IBD patients [13].

However, data on the impact of *C. difficile* infections in adult IBD patients from other centers in Europe are missing. Therefore, the purpose of this retrospective study was to assess the prevalence of *C. difficile* infections in patients with IBD in a tertiary center in Germany.

Study Cohort

All in-patients treated for an acute flare of their IBD at the Department of Internal Medicine I of the University of Regensburg between January 1, 2001, and June 30, 2008, were included in this retrospective analysis. Every single admission of a patient was evaluated separately if the patient was admitted to our department more than once. Patients hospitalized only due to disease complications (e.g. fistulas or extraintestinal manifestations), but not suffering from diarrhea, were excluded from this study.

The University of Regensburg is a tertiary referral center which treated 29,162 in-patients in 2007, 3,690 of whom were treated at the Department of Internal Medicine I. IBD patients are referred to this institution from primary care physicians as well as from secondary and primary centers.

The diagnosis of CD, UC or indeterminate colitis was based on endoscopic, histological and radiological findings.

For all patients included in the study, computer-based discharge registries were searched using text searches for '*Clostridium difficile*', '*C. difficile*' or '*C. diff.*' to identify patients with this concomitant diagnosis. Patient records were checked to identify every patient which was tested for *C. difficile* infection during the relevant hospitalization. The diagnosis of *C. difficile* infection was made by stool toxin analysis (ELISA stool toxin A and B) and/or histological evidence with classic pseudomembrane formations.

In patients with a concomitant diagnosis of *C. difficile* infection, further demographic data such as age, time since first diagnosis of IBD, clinical symptoms, IBD-related treatment at time of infection, nosocomial infection, season at time of infection, treatment for *C. difficile* infection and outcome were collected.

Statistical analyses were performed using SPSS software (16.0, Chicago, Ill., USA).

Results

Basic Characteristics

During the study period between January 1, 2001, and June 30, 2008, 995 in-patients with IBD were treated in this hospital (638 patients with CD, 357 with UC). In 279 patients with CD and 242 patients with UC, an acute flare with typical symptoms of diarrhea and abdominal pain was the reason for hospital admission. Other reasons for admission were fistulas or extraintestinal manifestations. Patients treated due to disease complications were not included in this analysis.

In all IBD patients with an acute flare, 438 stool tests on pathogenic intestinal bacteria were performed (82.5%). 248 patients were tested particularly with regard to *C. difficile* by stool toxin analysis (47.6% of all patients), with 120 patients diagnosed as having CD, and 128 patients diagnosed with UC. The number of tests per year in IBD patients with a flare of their disease is presented in table 1.

In total, 3,267 samples from all the patients treated at the Department of Internal Medicine I – including non-IBD patients – were tested for *C. difficile* during the study period at the Institute for Microbiology and Hygiene. In this entire population, an increase of *C. difficile* infections was observed, peaking in 2005 with positive test results in 12.7% of the patients. Between 2001 and 2004, 93 of 1,661 tests on *C. difficile* infections were positive, and between 2005 and 2008, 166 of 1,606 tests showed positive results ($p < 0.0001$, Fisher's exact test).

IBD Patients with *C. difficile* Infection

Only 10 of all the IBD patients with symptoms of an acute flare with diarrhea were diagnosed as having a concomitant infection with *C. difficile* (3.9% of all tested IBD patients). In 9 of the 10 patients, the diagnosis of *C. difficile* infection was confirmed by stool toxin analysis; in 1 patient the diagnosis was made endoscopically and histologically despite negative stool toxin analysis.

Of the 10 patients, 6 were female and the median age was 49 years (range: 15–80). Six patients with *C. difficile* infections had UC (2.7% of all tested patients with UC). Of the remaining 4 CD patients (4% of all tested patients

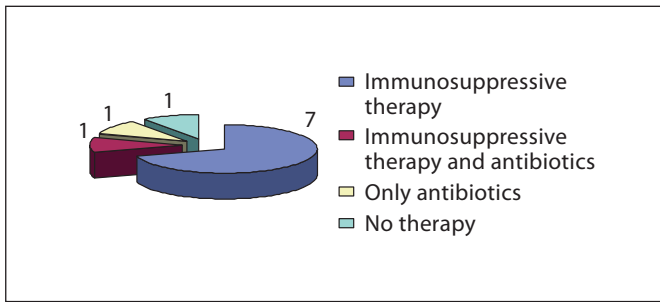


Fig. 1. Therapy at time of infection.

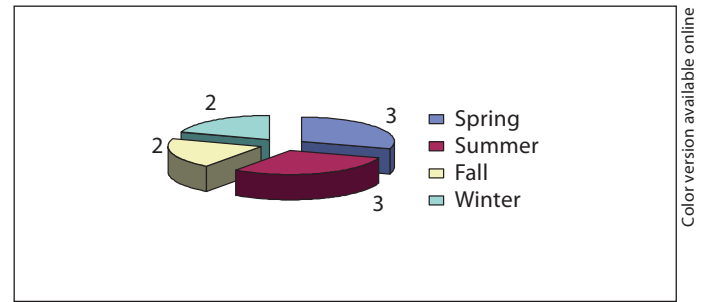


Fig. 2. Season at time of infection.

with CD), 1 patient showed a superinfection with *C. difficile* at the time of first diagnosis of IBD. In 2 patients, both of whom had UC, the time of first diagnosis of IBD was less than 1 year before infection with *C. difficile*. In addition, patients with a history of IBD stretching back more than 10 years were affected. Interestingly, in all patients with CD, involvement of the colon was documented (table 2).

Medication at Time of Infection

Eight patients with concomitant *C. difficile* infection had immunosuppressive therapies such as corticosteroids (6 patients) or azathioprine (2 patients) at the time of infection. Only 2 patients were treated with antibiotics before *C. difficile* infection was diagnosed, and one of these patients was simultaneously treated with azathioprine (fig. 1). No patient was on anti-TNF therapy. There was no seasonal variation of *C. difficile* infections (fig. 2).

One infection was found each during the years 2001–2004 and 2006–2007 and 2 infections each during 2005 and 2008. Comparing the first 4 years (2001–2004) to the next 3.5 years (2005–2008) of the observation period, no statistically significant difference between the two periods was seen ($p = 0.21$, Fisher's exact test).

Outcome

All patients were successfully treated with metronidazole, except for the patient with concomitant *C. difficile* infection at the time of first diagnosis of CD. In this patient, a total proctocolectomy became necessary due to toxic megacolon. All other patients showed remission of symptoms during antibiotic therapy. Additionally, in 7 patients, stool toxin was negative after withdrawal of metronidazole. None of the patients revealed a recurrence of episodes of *C. difficile* infections after primary treatment.

Table 1. Tested patients with flare-ups per year

Year	Number of flare-ups	Number of tests on <i>C. difficile</i>	Patients with flare tested, %
2001	96	43	44.8
2002	66	34	51.5
2003	79	31	39.2
2004	73	28	38.4
2005	66	26	39.4
2006	53	27	50.9
2007	59	36	61.0
2008 (until June 30)	29	23	79.3

Discussion

In this retrospective observational study over a 7-year period, we found only a few hospitalized patients with IBD and concomitant *C. difficile* infection in this tertiary referral center. These results are even more interesting since the incidence of *C. difficile* infections in the total patient population in this department showed a significant increase during the study period, which is similar to results from other centers. Our observation with regard to IBD patients therefore stands in contrast to several reports, mainly from North America.

An alarming rise in the incidence and prevalence of *C. difficile* infections in IBD patients has been described both in studies from single tertiary specialty centers and reports using nationwide databases [6–10]. Worse outcomes and higher mortality were also seen in patients with *C. difficile* infections and underlying IBD with a rising case fatality during the later years [7, 9]. In our series, we could not find an increase of *C. difficile* infections in our patients during the observation time in spite of rising awareness of possible infections in the later years. This is

Table 2. Characteristics of all patients with *C. difficile* infection and IBD

Gender	Kind of IBD	Age years	Developed <i>C. difficile</i> during hospital stay ¹	Symptoms	Therapy	Time since first diagnosis of IBD	Colonic involvement
Female	UC (pancolitis)	51.0	no	watery diarrhea	metronidazole	<1 year	yes
Male	CD	47.0	yes	toxic megacolon	surgery	at first diagnosis	yes
Female	UC (left-sided)	30.0	no	watery diarrhea, abdominal pain	metronidazole	>10 years	yes
Female	UC (pancolitis)	15.0	no	watery diarrhea	metronidazole	<1 year	yes
Male	UC (pancolitis)	52.0	yes	fever	metronidazole	>10 years	yes
Female	CD	47.0	no	watery diarrhea	metronidazole	>10 years	yes
Male	UC (proctitis)	60.0	no	watery diarrhea	metronidazole	1–3 years	yes
Female	UC (pancolitis)	80.0	yes	watery diarrhea	metronidazole	5–10 years	yes
Female	CD	72.0	no	watery diarrhea, abdominal pain, fever	metronidazole	3–5 years	yes
Male	CD	28.0	no	watery diarrhea, abdominal pain	metronidazole	>10 years	yes

¹ Defined as primary negative test result with a subsequent positive result during the hospital stay.

Table 3. Summary of the existing literature

First author	Patient population	Testing methods	Incidence or prevalence of <i>C. difficile</i> infection	Trends of <i>C. difficile</i> infections
Rodemann [6]	IBD vs. non-IBD	stool toxin analysis	doubled in CD, tripled in UC	increasing
Ananthkrishnan [7]	IBD vs. non-IBD	n.a.	n.a.	increasing, IBD associated with worse outcome
Nguyen [8]	IBD vs. non-IBD	n.a.	doubled in UC	increasing, IBD associated with higher mortality in UC
Ricciardi [9]	IBD vs. non-IBD, national survey	n.a.	rising in UC and CD with colonic involvement	UC with increasing case fatality
Issa [10]	IBD, referral center	stool toxin analysis	doubled in IBD	use of immunosuppressive drugs and colonic involvement as risk factors
Bossuyt [12]	IBD vs. non-IBD	stool toxin analysis	3.75-fold increase	use of immunosuppressive drugs not influencing the risk
Pascarella [13]	pediatric IBD vs. non-IBD, single-center	stool toxin analysis	higher prevalence in IBD vs. non-IBD	
Mylonaki [15]	IBD, acute flare	stool toxin analysis	5.5% over 5-year period	
Ott (this study)	IBD, acute flare	stool toxin analysis, flexible sigmoidoscopy	3.9% over 7.5-year period	

n.a. = Not applicable.

confirmed by our data showing an increasing percentage of IBD patients with flare being tested, especially since 2006. In addition, we could not find a seasonal variation of *C. difficile* infection, although it has been described in previous studies with a lower risk of infection in summer months [8, 14]. A summary of the existing literature on *C. difficile* infections in IBD patients is given in table 3.

Mylonaki et al. [15] found 5.5% of the relapses in IBD patients to be associated with *C. difficile* infections in their case series from Great Britain, which is comparable to the results obtained in our retrospective study (3.9% of all tested IBD patients with diarrhea). In contrast to their study, where 60% of the patients with an acute flare were tested for *C. difficile* toxin, we tested for *C. difficile* infection in only 48% of the patients with a diarrheal flare. Not testing all the patients with diarrhea has to be considered the main limitation of our study, despite the increasing numbers of patients with acute flares being tested during the later years.

In this context, possible underdiagnosing of *C. difficile* infection might be caused by the application of antibiotic therapy without prior testing. In our series, a total number of 92 of 521 flares (17.6%) were treated with antibiotic therapy, although no test on *C. difficile* was performed.

Another limitation was the toxin-based ELISA used for testing in our study, which is known to be less sensitive (70–90%) than cytotoxicity tests. Repeated testing has been shown to increase the diagnostic yield to up to 92–95% [1, 16]. Nevertheless, there are some controversies on repeated testing for *C. difficile* infection. In their study, Nemat et al. [17] showed a low value of repeated tests, and repeated testing has been suggested to result in false-positive tests [18]. Therefore, a clear guideline recommending the optimal number of tests still does not exist. At our department, initially one test is performed in IBD patients with diarrhea. If the patient does not respond to anti-inflammatory treatment, a second stool test is ordered as well as endoscopic investigations, which led to the diagnosis in one of our patients despite negative stool toxin analysis.

The varying incidence of *C. difficile* infections in different countries might partly be explained by differences of the examined patient populations. For example, different strategies in the treatment of patients with IBD, e.g. the frequent use of anti-TNF therapies in several countries, might play a role. A previous report identified immunosuppressive therapies as an important predisposing factor for *C. difficile* infections [19]. This is supported by our results as 80% of our positive patients received immunosuppressive therapy prior to the diagnosis of *C.*

difficile infection. Surprisingly, prior use of antibiotics, which is known as the main cause for *C. difficile* infection in the general population was only found in 2 patients [2]. Although *C. difficile* infections may not be limited to the colon [1, 20], in all of our patients with CD, colonic involvement was seen. Therefore, one may speculate that in addition to UC patients, CD patients with colonic involvement are at a higher risk for *C. difficile* infection. This observation is consistent with results of earlier studies identifying colonic disease as a risk factor for *C. difficile* infection [8, 9].

Conclusion

In this German tertiary referral center only a low percentage of hospitalized patients with IBD were found to have a concomitant *C. difficile* infection. Therefore, in contrast to reports from North America and Belgium, IBD patients hospitalized due to an acute flare have only a moderate risk for *C. difficile* infection in our region. This observation suggests the possibility that low- and high-risk areas for *C. difficile* infections might exist. As this is the first study showing possible geographic variation, further research on underlying reasons is needed.

Nevertheless, in clinical practice in all IBD patients with an acute diarrheal flare, a superinfection with *C. difficile* should be excluded. This is of special importance in patients with immunosuppressive treatment and colonic involvement to prevent medical malpractice using detrimental immunosuppressive therapies in *C. difficile*-infected IBD patients, shorten the time of hospitalization and improve patient outcome.

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