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Clostridium difficile Infection and Treatment in the Pediatric Inflammatory Bowel Disease Population

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Abstract

Objective—Recent changes in the epidemiology of *C. difficile* infection include an increase in the incidence of *C. difficile*-associated disease (CDAD), and the identification of patients with inflammatory bowel disease (IBD) as a group-at-risk. In addition, effectiveness of antimicrobial therapies has been questioned. Our aim was to estimate the incidence of CDAD in a pediatric IBD population, and review treatment efficacy.

Methods—We identified patients aged ≤18 years from our center's IBD database who tested positive for *C. difficile* toxin A and/or B between 8/1/07 and 12/31/08. Demographic information and treatment details were recorded. Chi-square and Fisher's exact test were used to compare categorical variables and student's t-test was used for continuous variables.

Results—From 372 pediatric IBD patients, we identified 29 patients who experienced a total of 40 cases of CDAD. The annualized incidence rate of CDAD was 7.2%. Initial treatment was successful in 17 cases (43%). Eventual success was documented with metronidazole in 15 cases (41%), with vancomycin in 16 cases (43%), and with other agents or a combination of agents in 6 cases (16%). Age, sex, and IBD type were not associated with initial treatment outcome or recurrence. The choice of initial antimicrobial treatment was not associated with treatment outcome. The type of IBD therapy medication was not associated with likelihood of CDAD recurrence although use of anti-inflammatory therapy was positively associated with initial antimicrobial treatment success.

Conclusions—CDAD occurred frequently in our cohort of pediatric IBD patients. Antimicrobial treatment success was achieved equally with either metronidazole or vancomycin. Initial treatment failed more than half the time, regardless of medication choice. Apparent lack of antimicrobial efficacy in resolving symptoms may reflect resistant *C. difficile* infection or increased IBD severity in a subset of patients who are *C. difficile* carriers. Awareness of the potential for a high incidence of CDAD and frequent failure rate of initial therapy is important in the management of children with IBD.

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Keywords

Clostridium difficile; inflammatory bowel disease; metronidazole; vancomycin

INTRODUCTION

Over the past decade the incidence of *Clostridium difficile* infection and associated disease (CDAD) has increased (1). *C. difficile* is an anaerobic, gram positive spore-forming bacillus responsible for a spectrum of disease. Morbidity from infection ranges from diarrhea to life-threatening pseudomembraneous colitis. While *C. difficile* colonizes the colon it is not invasive and tissue injury and inflammation is mediated by exotoxins (toxin A and toxin B) generated by the bacteria. A number of CDAD outbreaks since 2003 have been associated with the emergence of a more virulent strain that exhibits increased production of toxin A and/or B, as well as a third binary toxin (2).

While therapeutic use of anti-toxin antibodies appears promising (3), usual treatment involves use of vancomycin or metronidazole, although failure of both antibiotics has been reported. As well as failure to treat the infection, recurrence of CDAD in patients treated with medications is common. Kelly and Lamont (1) have recently reviewed data from several studies that took place before and after the year 2000 and demonstrated a decrease in the effectiveness of metronidazole to treat CDAD in the general population. While the frequency of treatment failure with vancomycin remained relatively unchanged (3.5% vs. 2.8 %), the frequency of failure with metronidazole increased markedly (2.5 %. vs. 18.2%). Recurrence of CDAD was similar after either metronidazole or vancomycin therapy (28.6 % vs. 19.9%)

Risk factors associated with CDAD include recent antibiotic therapy, prolonged hospitalization, advanced age, and immunosuppression (2). A mainstay of treatment for inflammatory bowel disease (IBD) is immunosuppressive therapy, and effective management can require long or frequent hospitalizations to manage problems associated with IBD. Recent studies have shown both an increased incidence and increased morbidity of CDAD in the adult IBD population compared with adults without IBD as well as increased frequency of carrier status (4–7). There is reason to believe that there is increased risk for CDAD among children with IBD, although this contention is supported by a single study at a pediatric IBD center in Italy (8).

Our aim was to estimate the incidence of CDAD in a pediatric IBD population in the United States, and to review anti-microbial treatment efficacy.

MATERIALS AND METHODS

We queried the database of IBD patients at Cincinnati Children’s Hospital Medical Center to identify subject with IBD aged ≤18 years who tested positive for *C. difficile* toxin A and/or B between August 1, 2007 and December 31, 2008. Patients testing positive for *C. difficile* toxin A and/or B in the eight weeks prior to their initial IBD diagnosis were also included. All stool specimens were analyzed for the detection of *C. difficile* toxins by ImmunoCard Toxins A & B (Meridian Bioscience, Cincinnati, Ohio) according to the manufacturer's instructions. This qualitative, horizontal-flow enzyme immunoassay has a sensitivity of 83% ± 6.7% and a specificity of 95% ± 1.6% for *C. difficile* infection screening. After identification of study patients, a data dictionary of key concepts was constructed and a medical chart review on each patient was performed using a standardized case report form. Patient demographics, symptoms at the time of the positive test, treatments, hospitalizations,

recurrence of *C. difficile* infection, and date of infection relative to IBD diagnosis were extracted. Disease activity (quiescent, mild, moderate, severe) prior to the patient's positive *C. difficile* test was also extracted from the medical charts. Whenever possible, data were cross checked through review of electronic records. Spot checks of data extractions were performed by a second reviewer.

A functional definition was used to confirm that study patients exhibited symptoms indicative of CDAD: a self-reported or family-reported increase in the frequency of loose stool above baseline, often accompanied by blood in the stool, abdominal pain, or fever (Table 1). All patients with a positive test received antibiotic therapy and improved clinically. For each occurrence of *C. difficile* infection, we defined treatment success as documented resolution of symptoms or *C. difficile* toxin test negativity after treatment. In cases where an initial antimicrobial drug was not tolerated or did not provide symptom relief and was changed, and the next drug proved successful, it was coded as the success drug. In one case the initial treatment drug was not identified. Recurrence was defined as a second confirmed *C. difficile* infection occurring after a treatment success for the prior infection. Hospital acquisition was surmised if the positive *C. difficile* test occurred from two days to six weeks after hospital admission. This study was performed with the approval of the local institutional review board.

Data Analysis

If no data on a particular variable was found in the medical chart review of a study patient, then the patient was excluded from that analysis. This type of censoring occurred for no more than 1–4 study patients for any given analysis. All other study subjects were included as evaluable. Chi-square and Fisher's exact test were used to compare categorical variables between groups, and student's t-test was used to compare continuous variables between groups. All analyses were conducted using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

From our center's IBD database of 372 pediatric patients we identified 29 patients (7.8%, CI_{95} 5.5–11.0%) with a positive *C. difficile* stool test between August 2007 to December 2008. All exhibited symptoms consistent with CDAD at the time of testing (Table 1) and showed clinical improvement after antimicrobial treatment. A single recurrence episode was documented in 11 (38%) of these patients, for a total of 40 cases. This represents an annualized incidence of 7.2%. In 5 of the 29 patients (17%), CDAD occurred from 2–8 weeks before diagnosis of IBD was established. In 6 patients IBD diagnosis was followed by occurrence of CDAD within 8 weeks, while in the remainder, duration of IBD varied from 4 months to over 10 years prior to the occurrence of CDAD. For those patients followed for a minimum of 6 months prior to the occurrence of CDAD, 66 % were considered to have either mild disease activity or be in remission (compared to 88.7% with similar disease activity in the IBD database).

There were no differences in age, sex, or type of IBD between patients with CDAD and patients without an occurrence of CDAD in the study time frame (Table 2). Furthermore these parameters were not associated with recurrence of CDAD (data not shown). The majority of CDAD was community acquired as only 6/39 evaluable cases (15%) occurred during or in the 6 week period immediately following hospitalization. Prior antimicrobial exposure, a known risk factor for CDAD, was documented in half of the 40 episodes. These included 2 patients who contracted *C. difficile* while prescribed metronidazole for non-diarrheal IBD symptoms.

Initial antimicrobial therapy was successful in 43% of evaluable cases (17/39). Metronidazole was the inital treatment in the majority of cases (27/38 evaluable cases), followed by vancomycin (9/38) and nitazoxanide (2/38). Age, sex, type of IBD and the choice of initial antibiotic were not associated with initial treatment outcome (Table 3). Up to five treatment changes were needed to achieve treatment success. Final success was achieved in equal numbers when either metronidazole (41%, 15/37 evaluable cases) or vancomycin (43%, 16/37) was the final treatment drug. Nitazoxanide or a combination of vancomycin with metronidazole, nitazoxanide, intravenous IgG, or rifaxamin were also used in 6/37 cases (16 %).

Prior use of antibiotics, protein pump inhibitors (PPIs), probiotics, steroids, immune modulators, or biological treatments did not affect initial treatment success (Table 4). The use of anti-inflammatory medications (aminosalicylates) was associated with initial treatment success; 62% of patients taking anti-inflammatory medications prior to infection had initial CDAD treatment success ($P = 0.02$). No association was observed between type of IBD medication and CDAD recurrence (data not shown).

DISCUSSION

A number of retrospective studies have examined the incidence of CDAD in adult patients with IBD (summarized in Table 5). While different parameters have been measured in each study, it is clear that adults with IBD have between two and three times higher incidence of CDAD than the adults without IBD. In the general pediatric population, one multi-center study (9) found the incidence of CDAD in children to be comparable to that of non-IBD adults. Using these historical data for context, the incidence of CDAD in pediatric patients with IBD in our retrospective study (7.2 %) exceeds the incidence in children without IBD by 18- to 100-fold (9,10) and adults with IBD by 1.5-fold (4). Our center is thought to care for the vast majority of pediatric patients with IBD in our area, so it is likely that we were able to identify all or nearly all of the episodes of CDAD through our retrospective database review. Thus our data give an approximate incidence based on a large and stable population of children with IBD, and is consistent with Pascarella et al. in Italy (8) who showed a 24.7% incidence of CDAD in children with IBD admitted to the hospital for diarrhea and abdominal pain.

While two adult studies have documented increased incidence of CDAD in patients with ulcerative colitis (UC) compared to those with Crohn's Disease (CD) (5,6) we did not see a similar association. It is not known if this represents a real difference between pediatric and adult UC or if this is an artifact of the composition of our population which is typical of the distribution of CD in children (3:1, CD:UC). Issa and coworkers (4) also found that the incidence of CDAD in adult IBD patients (higher in patients with CD) matched the distribution of their IBD Center population. Furthermore, Pascarella and coworkers showed that specific IBD type was also not associated with CDAD incidence in pediatric patients (8).

An important aspect of the changing epidemiology of CDAD is the increase in community-acquired cases (2,10). This is particularly true for IBD patients. Similar to both adult and pediatric IBD patients (4,5,8), the majority of CDAD in our pediatric patient population was community acquired. The increased number of community acquired infections among those with IBD has important surveillance implications and dictates even non-hospitalized patients are at risk for CDAD.

Symptoms of diarrhea and abdominal pain are common to both infectious colitis and to progression of IBD, and may signal a need for more aggressive IBD therapy rather than

antimicrobial treatment. It is known that there is a relatively high rate of carriage of *C. difficile* in IBD patients. In a prospective study, *C. difficile* was detected in stool cultures from 8% of IBD patients (in remission) compared to 1 % of healthy controls, none of whom experienced clinical symptoms during a 6-month follow-up (7). Our use of retrospective data precludes knowledge of carrier status, and it is a possibility that *C. difficile* positive patients in our study who underwent multiple rounds of antimicrobial treatment prior to symptom resolution were indeed carriers whose symptoms were due rather to IBD exacerbation. Notably, Issa and coworkers (4) also reported initial anti-microbial treatment failure in 58% of adult patients with IBD, much higher than reported in the general population (1). The role of *C. difficile* carriage in subsequent CDAD or in relapse in IBD patients is an important issue and remains to be elucidated.

The benefit of screening for *C. difficile* toxin in IBD patients with apparent relapse is therefore controversial. However, in 2 recent studies of adult IBD patients during a relapse, from 5.5% – 19% of stool samples were found to be *C. difficile* toxin positive, and these patients improved clinically after antimicrobial treatment (11,12). Likewise, in another study, 25% of pediatric IBD patients admitted to the hospital had *C. difficile* positive stool samples (8). In the absence of a comprehensive prospective study, we would recommend *C. difficile* toxin stool screening in all children with IBD experiencing an increase in disease symptoms in order to begin antimicrobial intervention in a timely fashion, with the caveat that failure may signal worsening of the underlying IBD.

Studies in adults with IBD have found either an increased risk of CDAD (4) or a worse outcome in patients (13) on immunomodulator treatments. In addition, PPI use has been found to be independently associated with CDAD risk (2). While our study design did not allow us to look directly at these questions, we did examine risk in the context of recurrence and did not find any association in our pediatric population. Pascarella et al. did not find a correlation between CDAD and IBD therapy or PPI use in pediatric patients as well (8).

Of note, we found that use of a common IBD anti-inflammatory medication (aminosalicylates) was associated with an improved response to treatment in patients with CDAD using these medications compared with patients not using these medications (P= 0.02). The biological basis of this finding is not known. The inflammatory effects of toxins A and/or B are required for at least part of the pathogenicity of *C. difficile* and it may be that the reduction in pro-inflammatory cytokines mediated by aminosalicyates (14) may aid in symptom resolution in certain individuals.

Limitations of our study include the use of retrospective data from a single-center tertiary care center, the absence of a control group, and the potential for type II errors due to sample size. However, our work does confirm the changing epidemiology of *C. difficile* infection in a pediatric IBD population, including an increased incidence of CDAD acquired in the community and greatly reduced effectiveness of both metronidazole and vancomycin.

More must be understood about the unique epidemiology of CDAD in the IBD population, including the role of mucosal/immunological factors, before treatment strategies can be improved to yield better outcomes. To further our current understanding, prospective studies must be performed that include identification of *C. difficile* carrier status, consistent definitions of treatment success and recurrence, and exploration of alternative therapies such as the use of probiotics, toxin binders, new antimicrobials and monoclonal antibody therapy.

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TABLE 1

Symptoms in Study Group*

	N	%
Increased diarrhea	33	89%
Blood in stool	22	53%
Abdominal pain	28	56%
Fever	5	14%

*Symptoms exhibited prior to testing for Toxin A/B in 36 evaluable cases

TABLE 2

Characteristics of IBD Database Patients

	Reference Group* (N = 346)		Toxin A/B Positive (N = 29)			
	Mean	**SD**	**Mean**	**SD**	**P value**	**CI_{95}**
Age (years)	14.4	3.8	13.1	4.5	0.12	(−0.31 – 2.81)
	N	%	N	%	P value	
Sex						
Male	169	49	16	55	0.51	
Female	177	51	13	45		
IBD Type						
UC	81	23	5	17		
CD	225	65	19	65	0.46	
IC	40	12	5	17		

*Reference group consists of patients in our center's IBD database who did not test positive for Toxin A/B during the study period.

IBD = inflammatory bowel disease; SD = standard deviation; CI_{95} = 95% confidence interval; UC = Ulcerative colitis; CD = Crohn's disease; IC = Indeterminate colitis

TABLE 3

Predictors of Initial Treatment Outcome

	Success (N=17)		Failure (N=22)			
	Mean	**SD**	**Mean**	**SD**	**P value**	**CI_{95}**
Age (years)	12.1	(4.6)	11.7	(4.6)	0.80	(−2.64 – 3.40)
	N	%	N	%	P value	
Sex						
Male	9	53	10	45	0.75	
Female	8	47	12	55		
IBD Type						
UC	5	30	2	9		
CD	9	53	15	68	0.69	
IC	3	17	5	23		
Medication						
Metronidazole	12	80	15	71	0.71	
Vancomycin	3	20	6	29		

SD = standard deviation; CI_{95} = 95% confidence interval; IBD = inflammatory bowel disease; UC = Ulcerative colitis; CD = Crohn's disease; IC = Indeterminate colitis

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TABLE 4

Association of Prior Medication with Initial Treatment Success

		Initial Treatment Success				
Medication class		**Failure**		**Success**		**P value**
		N	**%**	**N**	**%**	
Antibiotic	No	12	55	7	41	0.52
	Yes	10	45	10	59	
PPI	No	10	45	9	53	0.75
	Yes	12	55	8	47	
Probiotic	No	17	77	15	88	0.44
	Yes	5	23	2	12	
Anti-inflammatory	No	14	64	4	24	0.02
	Yes	8	36	13	76	
Steroid	No	13	59	10	59	1.00
	Yes	9	41	7	41	
Immune modulator	No	13	59	12	71	0.46
	Yes	9	41	5	29	
MTX	No	20	91	17	100	0.50
	Yes	2	9	0	0	
6MP	No	17	77	13	76	1.00
	Yes	5	23	4	24	
AZT	No	20	91	16	94	1.00
	Yes	2	9	1	6	
Biological	No	17	77	14	82	1.00
	Yes	5	23	3	18	
Remicade	No	17	77	15	88	0.44
	Yes	5	23	2	12	
Humira	No	22	100	16	94	0.44

Medication class	Initial Treatment Success				P value
	Failure		Success		
	N	%	N	%	
Yes	0	0	1	6	

PPI = proton pump inhibitor; MTX = methotrexate; 6MP = 6-mercaptopurine; AZT = azidothymidine

TABLE 5

Prevalence of CDAD

Reference	Study Type	Study Population	Incidence
Pascarella *et al.* (8)	Retrospective case-control	Children	8.9%
		Children with IBD	24.7 %
Kim *et al.* (9)	Retrospective multi-center	Children	4.0 per 1000 admissions
Nguyen *et al.* (6)	Retrospective multi-center	Adult	4.5 per 1000 discharges
		Adult with CD Adult with UC	10.9 per 1000 discharges 37.3 per 1000 discharges
Benson *et al.* (10)	Retrospective single center	Children	0.68 cases per 1000 patient-days
Rodemann *et al.* (5)	Retrospective single center	Adult	12.3 per 1000 admissions
		Adult with CD Adult with UC	15.9 per 1000 admissions 39.4 per 1000 admissions
Issa *et al.* (4)	Retrospective single center	Adult with IBD	4.6%

CDAD = *C. difficile*-associated disease; IBD = inflammatory bowel disease; CD = Crohn's disease; UC = Ulcerative colitis