Enteric Infections In Hospitalized Pediatric Inflammatory Bowel Disease Patients With Relapse

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Citation

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Abstract

BACKGROUND & AIMS: Enteric infections can mimic or induce Inflammatory Bowel disease (IBD) flares. Our aim was to assess the incidence and long-term impact of enteric infections in pediatric IBD patients.
METHODS: Medical records of patients admitted with IBD flares between 2003 and 2010 were reviewed. Short (4 weeks) and long-term (1 year) outcomes following index admission were evaluated.
RESULTS: 92 IBD flares requiring hospitalization in 59 patients were evaluated. Enteric infections contributed to 24% of all flares (22 episodes, 14 patients with ulcerative colitis and 8 with Crohn's disease). Clostridium difficile infection (CDI) was predominant (12/22, 54%). Cryptosporidium (n=4), Salmonella (n=4), Shigella (n=1) and Coronavirus (n=1) were also isolated. Patients with CDI, had increased re-hospitalizations (p=0.03) and treatment escalation (p=0.01) within one year compared to non-CDI patients.
CONCLUSIONS: Enteric infections are common, contributing to approximately 1 in 4 IBD flares. CDI is associated with increased disease severity in children.

INTRODUCTION

Inflammatory bowel disease (IBD) which includes Crohn's disease (CD) and ulcerative colitis (UC) is a chronic relapsing immunologically mediated disorder. The determinants of IBD relapse continue to be of great clinical interest. Several plausible triggers for relapse have been proposed including use of antibiotics, non-steroidal anti-inflammatory drugs, acute stress, and smoking; however, none of these variables have been definitely proven. (1) Over the last decade, several studies have suggested the role of intestinal infections in the pathogenesis and relapse of IBD. (2, 3) Antibiotics have been effectively used in clinical practice for the treatment of both CD and UC, especially for pouchitis and perianal disease, which suggests a possible role of enteropathogenic organisms in the clinical relapse of IBD. Furthermore, the treatment for IBD is essentially immunosuppression, which can lead to increased susceptibility to opportunistic infections.

Infections with a wide range of enteric microorganisms have been associated with IBD relapses with the reported incidence in adult IBD patients between 9-20%. (4-7) Given the high incidence of enteric infections, particularly Clostridium difficile (C. difficile) and lack of reliable predictors to differentiate enteric infection from a true disease relapse several studies recommend examination of stools in IBD patients presenting with diarrheal relapse. (4) As infections are more common in pediatric population in general, it is believable that the overall incidence of infection-associated relapses is higher among children with IBD than their adult counterparts. However, only a few studies have investigated the incidence of infection with flares in pediatric patients, and these studies were largely restricted to Clostridium difficile infection (CDI). (8, 9)

As children with IBD may have more aggressive or complicated clinical course than adults, proper identification of the cause of relapse becomes pivotal in the optimal management of that patient's disease. Also, microbiological diagnosis of infection early in relapse may reduce unnecessary use of steroids and/or exposure to other immunosuppressive medications. Earlier studies have demonstrated that C. difficile is associated with increased morbidity in children with IBD but the effect of enteric infections other than CDI on the severity of IBD has not

been studied in this patient population.

To address these questions, we performed a retrospective chart review of pediatric patients with IBD at The Children's of Alabama. The aims of our study were to determine the incidence of enteric infections in hospitalized pediatric IBD patients and also to evaluate the impact of such infections on their clinical outcome.

MATERIALS AND METHODS

Medical records of all IBD patients under the age of 18 years who were followed at Children's of Alabama between 2003 and 2010 were retrospectively reviewed. We identified patients who were admitted with diarrhea and acute exacerbation of IBD and included those patients who had stool studies performed at admission. Patients who were not followed-up in our hospital, patients who were admitted with disease related complications but not suffering from diarrhea, and patients for whom we could not obtain medical records were excluded. In our hospital, the clinical and the laboratory data of all patients were entered in to a common electronic medical record system. We therefore reviewed and collected individual patient demographic, clinical and laboratory data for each hospitalization and subsequent clinic visit after discharge. Disease activity was measured by using most recent colonoscopy, laboratory values, and symptoms reported by individual patient during most recent outpatient visit prior to index hospitalization.

Routine stool studies performed at our center during relapses include stool for culture, microscopy for ova and parasites, C. difficile toxin, Giardia and Cryptosporidium. C. difficile was tested by using Immunoassay for toxins A&B. Cryptosporidium and Giardia were tested by using rapid immunoassay technique using ImmunoCard STAT! ® (Meridian Bioscience, Inc, Cincinnati, OH).

To evaluate the short-term and long-term clinical outcomes, we compared patients with positive stool studies with a control group of IBD patients who were admitted with flare, but had negative stool studies and had no prior history of CDI. Short-term outcomes measured were re-hospitalization and need for colectomy at 4 weeks following index admission. Long-term outcomes included the need for escalation of therapy, number of IBD related hospitalizations, and colectomy rate at one year following index hospitalization. To identify the impact of specific pathogen, we also compared patients with CDI and non-CDI.

A relapse was defined as an increase in number of stools from individual patient's baseline. In those patients with positive stool studies treated with antimicrobials, we defined treatment success as documented resolution of clinical symptoms or negative stool studies after treatment. Treatment failure was defined as persistence of clinical symptoms and/or positive stool test while on treatment. Escalation of medical therapy was defined as addition of immunomodulator therapy or biologic therapy to anti-inflammatory treatment, increase in the dose of immunomodulator or biologic medicines, or addition of biologic therapy to immunomodulator treatment.

Statistical analysis:
Categorical variables were summarized by frequencies while continuous variables were summarized by using mean, median and standard deviation. Chi-square analysis and Fisher exact tests were used to compare categorical variables and Student's t-test and Wilcoxon Rank Sum test were used to compare continuous variables between groups.
The study was approved by University of Alabama at Birmingham institutional review board with waiver of informed consent

RESULTS

We identified 59 eligible patients who experienced a total of 92 flares requiring hospitalization. Enteric infections were found in 22 (24%) relapses in 22 (14 UC and 8 CD) patients. The control group comprised of 37 patients (16 UC and 21 CD). The baseline characteristics between the two groups are illustrated in Table 1. C. difficile was the most common organism isolated (12/24, 50%), comprising 13% of all hospitalizations. We also observed 12 non-CDI including Cryptosporidium (n=4), Salmonella (n=4), Shigella (n=1), and Coronavirus (n=1).

Maintenance therapy for IBD was continued in all patients with enteric infection. Forty-six percent of the patients with infection (11/24) were also initiated on steroid therapy at admission; however, treatment was discontinued in six patients once a pathogen was identified in stools. Five patients (22.7%; 4 with CDI and 1 with non-CDI) received a course of steroids with a taper over 6 weeks.

To evaluate the impact of infections on the disease course, we compared the patients with positive stool studies and the control group (Table 1).

Table 1

Demographic and clinical characteristics of patients by infectious status

	With infection (N=22)	Without infection (N=37)	p-value
Age (years), mean (SD)	10.9 (2.5)	12.8 (3.2)	0.02
Sex (female), n (%)	12 (54.5)	22 (59.5)	0.71
Race, n (%)			
Caucasian	15 (68.2)	28 (75.7)	
African American	6 (27.3)	7 (18.9)	0.78
Other	1 (4.5)	2 (5.4)	
IBD type, n (%)			
UC	14 (63.6)	16 (43.2)	0.12
CD	8 (36.4)	21 (56.8)	
Disease location, n (%)			
Stomach/esophagus	0 (0.0%)	1 (2.7%)	
Small bowel only	2 (9.0%)	4 (10.8%)	
Small bowel + colon	6 (27.2%)	16 (43.2%)	
Pancolitis	11 (50.0%)	10 (27%)	
Left colon only	3 (13.6%)	6 (16.2%)	
Time from IBD diagnosis (months), median	10.5 (5.0-17.0)	18.0 (11.0-23.0)	0.01
Treatment prior to hospitalization, n (%)			
Corticosteroid	2 (9.1)	4 (10.8)	
Azathioprine	12 (54.5)	23 (63.2)	0.56
aTNF-α [a]	7 (31.8)	11 (29.7)	0.86
5-ASA [b]/Sulfasalazine	19 (86.4)	30 (81.1)	0.72
Length of hospital stay (days), median (IQR)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	0.85
Escalation of therapy within 4 weeks, n (%)	2 (9.1)	7 (18.9)	0.46
Escalation of therapy within one year, n (%)	9 (40.9)	14 (37.8)	0.81
No. of patients requiring surgery within 4 weeks, n (%)	0 (0.0)	0 (0.0)	–
No. of patients requiring surgery within one year, n (%)	3 (13.6)	3 (8.1)	0.66
No. of patients readmitted within 4 weeks, n (%)	2 (9.1)	5 (13.5)	0.70
No. of patients readmitted within one year, n (%)	8 (36.4)	11 (29.7)	0.59

[a] = anti-tumor necrosis factor alpha; [b] = 5-aminosalicylic acid

Short-term outcomes:
The mean length of hospital stay was identical in both groups and none of the patients required colectomy during this time frame. Two patients in the infection group (9%) and five patients in the control group (13%) were re-admitted within 4 weeks following index admission; however, this was not significant (p=0.7).

The two patients in the infection group requiring re-admission had pancolitis from UC, and both were on biologics at the time of acquiring infection. Among the patients in the non-infection group, three had CD involving small bowel and colon, and two were diagnosed with UC involving left side of the colon.

Long-term outcomes:
Eight patients in the infection group were re-admitted on 17 occasions compared to 11 patients in control group who required 14 admissions (p=0.5) due to IBD exacerbation in the year following index hospitalization. One patient in the infection group was readmitted twice in the same year for worsening of his underlying disease and he eventually required colectomy due to persistence of symptoms in spite of treatment with biologics. The need for escalation of therapy was identical in both groups. Nine patients in the infection group and 14 patients in the control group required a change in their baseline immunosuppressive therapy due to ongoing symptoms (p= 0.81) (Table 2).

Table 2

Need for escalation of therapy in patients with and without infection

	With infection (N=9)	Without infection (N=14)
Changed to Immunomodulators	1	1
Immunomodulator dose escalation	1	4
Changed to Biologics	4	4
Biologic dose escalation	3	5

When followed for one year, 13% of the patients in the infection group, all with CDI, eventually required colectomy; whereas 8% of the control group needed surgery (p=0.6). All patients who underwent colectomy had an underlying diagnosis of UC, which was refractory despite maximizing medical therapy with immunomodulators and biologics.

Impact of specific pathogen:
The clinical variables and outcomes of IBD patients with CDI and non-CDI are illustrated in Table 3. Patients with CDI tended to have more UC compared to non-CDI (p=0.07). While there were no differences in short-term outcomes, when these patients were followed for one year, patients in the CDI group required more frequent hospitalizations (58%vs 10%, p=0.03), increased need for treatment escalation (66.7%vs. 10%, p=0.01) and higher rates of colectomy (25% vs. 0.0%, p=0.2) in comparison to non-CDI group.

Table 3

Comparison of clinical characteristics between CDI and non-CDI patients

	CDI (N=12)	non-CDI (N=10)	p-value
IBD Type, n (%)			
UC	10 (83.3)	4 (40.0)	0.07
CD	2 (16.7)	6 (60.0)	
Disease activity, n (%)			
Mild	2 (16.7)	0 (0.0)	
Moderate-severe	6 (50.0)	2 (20.0)	0.11
Remission	4 (33.3)	8 (80.0)	
Recent antibiotic use, n (%)	0 (0.0)	2 (20.0)	0.19
Treatment prior to hospitalization, n (%)			
Corticosteroid	2 (16.7)	0 (0.0)	0.48
Azathioprine	7 (58.3)	5 (50.0)	>.99
aTNF-α[a]	4 (33.3)	3 (30.0)	>.99
5-ASA[b]/Sulfasalazine	11 (91.7)	8 (80.0)	0.57
Treatment during relapse, n (%)			
Antibiotics alone	8 (66.7)	8 (80.0)	
Antibiotics + steroids	4 (33.3)	1 (10.0)	0.32
Neither	0 (0.0)	1 (10.0)	
Outcome, n (%)			
Readmission within one year	7 (58.3)	1 (10.0)	0.03
Escalation of therapy within one year	8 (66.7)	1 (10.0)	0.01
Colectomy within one year	3 (25.0)	0 (0.0)	0.22

[a] = anti-tumor necrosis factor alpha; [b] = 5-aminosalicylic acid

When evaluated for potential risk factors for CDI, we found that 83% of infected patients had an underlying diagnosis of UC and 66% had active disease at presentation. There was no significant association of CDI with duration of disease or use of immunosuppressive medications. CDI was not observed in two patients who had a known history of prior antibiotic exposure before hospitalization.

All the patients with CDI were initially treated with metronidazole, which resulted in clinical improvement in nine patients. Three patients who failed to respond to Metronidazole were successfully treated with Vancomycin. One patient had a recurrence of C. difficile infection 5 months after index admission and she was effectively treated with a repeat course of metronidazole. Three of the four patients with Cryptosporidium were treated with Nitazoxanide resulting in early clinical improvement in two patients, while the third continued to have symptoms for 4 weeks after presentation despite targeted treatment. The one patient who did not receive treatment for Cryptosporidium had spontaneous resolution of symptoms 3 weeks after presentation. Two of the four patients with Salmonella were treated with antibiotics; however, there appeared to be no significant difference in duration or severity of symptoms in both treated and untreated patients. The one patient, who acquired Shigella infection, received a seven day course of Trimethoprim-Sulfamethoxazole with good response.

DISCUSSION

Enteric pathogens have been associated with disease flares and exacerbations of IBD. The data on hospitalized pediatric IBD patients with diarrheal flares are limited and restricted to CDI. Our study revealed that enteric infections were associated with 24% of all IBD relapses. Moreover, patients with CDI were more likely to have readmission and treatment escalation within one year following index admission.

The prevalence of enteric infections in our group (24%) was slightly higher than most of the adult studies reported (9-20%). (4-7) This increased prevalence may be due to the fact that enteric infections are common in children in general. The other possibility is that our patients were hospitalized for severe symptoms, which may have created a selection bias.

Although C. difficile has been shown to be associated with IBD flares, the long term impact of this pathogen on the natural course of IBD in children is still unclear. We identified significantly increased readmission rates and need for escalation of therapy in patients who acquired CDI. Our findings echo those of Kelsen et al (10) who also found similar increase in hospitalizations and escalation of therapy following CDI in children with IBD. While it is well known that CDI presents a greater risk for colectomy in the adult IBD population, our study also suggests that CDI may also increase the risk of colectomy in pediatric IBD patients. (11)

The association of CDI with IBD flare begs the questions: does the infection incite the flare or does the flare invite infection? While it is hard to blame a CDI occurring in the distant past for the worsening of disease a year following infection, it has been suggested that infections like C. difficile may alter the natural history of IBD. It is hypothesized that by triggering a patient's innate immune system, the organism may provoke activation of underlying disease, thus leading to increased hospitalizations and the need for escalation of medical treatment. This theory is confounded by the fact that the majority of our patients who acquired CDI had an active underlying disease possibly making these patients more susceptible to CDI. In two recent pediatric studies (8, 9), specific IBD type was not associated with increased risk for CDI. In our cohort of patients, 83% who acquired CDI also have UC, which is similar to several adult studies reported. (4, 12) Why colonic

IBD predisposes to CDI is still unanswered. Increased mucosal sensitivity to the C. difficile toxins in patients with colonic disease may subject these patients to a greater potential for enteric infections. Perhaps, the pre-existing mucosal inflammation permits low levels of toxin to produce infection (13).

While CDI is the most extensively studied organism, other enteropathogens like Cryptosporidium, Salmonella, Campylobacter jejuni, Cytomegalovirus (CMV) and parasites have also been reported to exacerbate IBD symptoms in adults. (14-20) We observed Cryptosporidium, Salmonella, Shigella and Coronavirus in association with IBD flares. In our cohort, specific antimicrobial therapy had no major impact on duration or severity of symptoms. All patients had eventual recovery to their baseline with no significant long-term complications, except in one patient with Coronavirus infection who required hospitalization and a change to biologic therapy at 3 months following index admission.

Although enteric pathogens are reported to be associated with IBD exacerbations, it is still unclear whether these organisms are in fact the cause of these acute flares. It is possible that these pathogens may be innocent bystanders due to probable colonization and have no direct relationship with IBD flares. (21) Due to retrospective nature, our data precludes the knowledge of carriage status and it is possible that some of the patients were indeed carriers. This possibility raises the question of the benefit of screening for enteropathogens, especially C. difficile in patients with suspected IBD flare; however, few recent studies in children have reported a high incidence of positive CDI in IBD patients and these patients improved clinically with antimicrobial therapy. (8, 9) Therefore, in the absence of large prospective studies, the recommendations by Mezoff et al (9) to screen stool for C. difficile toxin in all children with diarrheal relapse of IBD and to begin antimicrobial therapy awaiting stool studies seems prudent.

The limitations of this study are related to its retrospective nature. First, we have included only those patients followed in our tertiary center. It is possible that our patients might have been seen and treated at local hospitals, which we may have missed. Second, the sensitivity of the immunoassay test for CDI is not 100%. Third, this is a retrospective study of a single institution involving small cohort of patients, which significantly limits the generalizability. Fourth, given that negative stool studies do not rule out infection, the true incidence of enteric infections could be significantly higher. Furthermore, CMV was not routinely investigated in our patients with refractory symptoms and it is possible that we could have missed CMV-associated IBD flares. Therefore, the incidence of enteric infections reported in our study may be an underestimate and should be considered an approximation. Finally, we used the most recent colonoscopy, labs, and clinic visit for assessment of disease severity. As patients may have had lab work and clinic visit in remission, this could have certainly introduced bias in the assessment of disease activity.

Despite these limitations, the current study has several clinical implications. It highlights the importance of examining stools for infectious organisms in IBD patients presenting with diarrheal relapse and also indicates that patients with CDI may have an aggressive disease course following infection.

We conclude that enteric infections can mimic or be associated with an IBD flares and could contribute to approximately 25% of all relapses in children; thus, it is advisable that stools are examined for enteropathogenic organisms in all IBD patients presenting with diarrheal relapse. CDI in IBD patients should be carefully followed and aggressively managed due to the possibility of increased severity of underlying disease. Parasitic and viral infections are not uncommon and should be investigated in suspected clinical situations. Large prospective studies are needed to further validate our results.

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