Enteric Infection in Relapse of Inflammatory Bowel Disease: The Utility of Stool Microbial PCR Testing

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Background: The similar presentations in relapse of inflammatory bowel disease (IBD) and enteric infection pose substantial barriers to diagnosis and treatment. The objective of this study was to investigate the incidence, etiology, predictors, and treatment of enteric infection in patients with IBD.

Methods: We reviewed the records of 214 patients with IBD who underwent 295 gastrointestinal pathogen panel and Clostridium difficile infection (CDI) polymerase chain reaction (PCR) stool tests during an exacerbation of symptoms. We collected baseline characteristics, PCR outcomes, and medication exposures. We tested for associations via the Chi-square test and the *t*-test. Logistic regression analysis was used to identify predictors of enteric infection.

Results: Of 295 PCR tests ordered during an exacerbation of symptoms, 38 (12.9%) were positive for CDI and 41 (13.8%) were positive for 14 other pathogens, with E. coli species as the most common. A previous history of CDI or colonic involvement of IBD predicted CDI, whereas a previous colectomy predicted negative testing for CDI. The majority with CDI (24, 63.2%) received oral vancomycin and 15 (37.5%) with other enteric pathogens were treated for their infection. Patients with CDI had a longer median length of hospital stay (8.5 versus 4 days, $P = 0.041$). Patients who tested negative for enteric infections were more likely to have IBD medications added or up-titrated ($P = 0.027$).

Conclusions: Enteric infection was detected in 79 (26.8%) symptomatic patients with IBD , with CDI the most frequent followed by E. coli. Negative stool PCR testing was associated with changes in IBD management. Broad enteric PCR testing should be considered during relapse of IBD.

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Key Words: inflammatory bowel disease, Crohn's disease, ulcerative colitis, Clostridium difficile, enteric infection, flare, stool PCR testing

The similar clinical presentations and laboratory findings in relapse of inflammatory bowel disease (IBD) and enteric infection pose substantial barriers to diagnosis and treatment. A number of different enteric infections have demonstrated to cause symptoms that mimic those in exacerbation of IBD, including bacterial, viral, fungal, protozoal, and helminthic pathogens.[1] Of these infectious agents, Clostridium difficile infection (CDI) has been considered to be the most significant with regards to morbidity.[2–5]

In recent years, multiple studies have demonstrated increasing CDI rates in patients with IBD.[6,7] Established risk factors for CDI such as nosocomial acquisition, age, and recent antibiotic use may not be significant risk factors for CDI in patients with IBD.[8–11] Moreover, patients with IBD not only have a higher prevalence of CDI, but also significantly worse outcomes with studies reporting longer length of hospital stays, increased costs, higher colectomy rates, higher recurrence rates, and increased mortality.[2–5] Given the considerable morbidity and mortality of CDI in patients with IBD , early recognition of infection is crucial to improving outcomes.

Despite extensive recent studies examining the role of CDI in IBD, far less is known regarding the risks of acquisition and clinical impact of other enteric infections in IBD. Population studies have examined the role of enteric pathogens in the development of IBD, demonstrating a possible association between specific enteric infections, such as Campylobacter, Salmonella, and Escherichia coli species, and an increased incidence of IBD.[12,13] However, only a few studies have examined the prevalence and role of intestinal infections complicating known IBD with most reporting a minor role, and none have measured the prevalence of these infections using broad PCR-based infectious panel testing.[14–18]

The increasing availability of rapid, highly sensitive, and highly specific nucleic acid amplification tests have improved gastrointestinal pathogen diagnostics. The objective of this study was to investigate the incidence, etiology, predictors, and treatment of enteric infection detected by broad PCR testing in patients with relapse of IBD.

METHODS

Study Population, Variables, and Outcomes

We performed a cross-sectional study using the electronic medical records of inpatients and outpatients at New York Presbyterian-Columbia University Medical Center, a quaternary care

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institution in New York City. We identified all patients with a diagnosis of Crohn's disease, ulcerative colitis, or indeterminate colitis who underwent a gastrointestinal pathogen panel PCR and C. difficile PCR stool tests during an exacerbation of symptoms suggestive of a flare during the dates spanning January 1, 2015 and July 1, 2016. Patients with IBD were initially identified via International Classification of Disease codes and each patient's diagnosis was confirmed via manual review of the medical record based on accepted criteria including clinical symptoms, endoscopy, radiology, pathology, and operative reports. An exacerbation of symptoms was defined broadly, as any patient with IBD who presented with diarrhea and/or abdominal pain. For patients who underwent repeat PCR testing, repeat testing results were excluded if they occurred within 90 days of a positive previous test.

We recorded the following values from the medical record: age at IBD diagnosis, IBD subtype and phenotype, sex, ethnicity, duration of IBD, history of CDI, previous subtotal colectomy or total proctocolectomy, date of gastrointestinal pathogen panel and C. difficile PCR stool testing, hospitalization requirement, IBD medication exposure before and at PCR testing including 5-Aminosalicylate (5-ASA) agents, corticosteroids, immunomodulators, biologics, and other medication exposures such as previous and current use of a proton pump inhibitor, antibiotic use within 90 days before and at PCR testing, inflammatory markers at PCR testing including erythrocyte sedimentation rate (ESR) and C-reactive protein, active inflammation noted on computed tomography (CT) or magnetic resonance (MR) imaging within 2 weeks of PCR testing, active inflammation noted on flexible sigmoidoscopy or colonoscopy within 2 weeks of PCR testing, PCR results, treatment for positive PCR results, change in IBD management after the results of PCR testing including no change, holding IBD medications, adding or up-titrating IBD medications, and colectomy, and length of stay. Active inflammation on CT or MR imaging was defined by luminal wall thickening, mucosal hyperenhancement, or mesenteric fat stranding, as interpreted by a radiologist. Active inflammation on flexible sigmoidoscopy or colonoscopy was defined as any deep or superficial ulceration, erosion, friability, erythema, or decreased vascular pattern.

Enteric Pathogen Testing

The gastrointestinal pathogen panel PCR (BioFire FilmArray, Salt Lake City, Utah) tests for 22 analytes including 11 bacteria, 2 bacterial toxins, 5 viruses, and 4 parasites (Table 2). The gastrointestinal pathogen panel PCR is capable of the simultaneous detection and identification of nucleic acids from multiple bacteria, viruses, and parasites directly from stool samples in Cary Blair transport media. The multiplex PCR process takes about an hour. The clinical sensitivity and specificity is 94.5% to 100% for all targets.[19] C. difficile PCR testing (Cepheid Xpert, Sunnyvale, CA) detects toxin B, Binary Toxin (cdtA), and accessory gene tcdC deletion and can also provide results within 1 hour of specimen collection.

Statistical Analysis

The primary outcome was a positive gastrointestinal pathogen panel or C. difficile PCR result. Secondary analyses included specific gastrointestinal pathogen panel results, treatment regimens for positive PCR results, and change in IBD management after the results of PCR testing. We measured associations between variables and stool test results via the Chi-square test for categorical variables and the *t*-test for continuous variables. We used logistic regression to identify predictors of enteric infection and predictors of change in IBD management. All tests were considered significant at a 2-sided P-value < 0.05.

RESULTS

Over the data collection period, 214 patients with IBD underwent 295 gastrointestinal pathogen panel PCR with C. difficile PCR stool tests during an exacerbation of symptoms. This included 103 patients with Crohn's disease, 110 with ulcerative colitis, and 1 with indeterminate colitis, who underwent 127, 165, and 3 gastrointestinal pathogen panel with C. difficile PCR stool tests, respectively. Forty-nine patients experienced more than one relapse in symptoms and underwent repeat PCR testing at an interval greater than 90 days. Patients with a previous positive PCR test were not more likely to test positive on repeat testing. C. difficile was detected in 38 (12.9%) and other enteric pathogens were detected in 41 (13.9%) exacerbations of IBD (Table 1). Two patients had a positive gastrointestinal pathogen panel and a positive C. difficile PCR test. Seventy-two percent had an ESR or C-reactive protein checked at PCR testing, which was elevated in nearly 75% in patients who met our initial inclusion criteria. Fewer underwent CT or MR imaging (41%), or endoscopy (34%), within 2 weeks of PCR testing, with 73% demonstrating inflammatory changes on imaging and 91% on endoscopy.

Gastrointestinal Pathogen PCR Panel Results and Predictors of Enteric Infection

Forty-one positive gastrointestinal pathogen panels detected 51 enteric pathogens in 38 patients, with E. coli species (24, 47.1%) as the most common. Other enteric pathogens detected included Campylobacter species, Salmonella, Vibrio species, Shigella species, Pleisomonas shigelloides, Rotavirus, Norovirus, Sapovirus, and Adenovirus (Table 2). Nine patients tested positive for more than one pathogen. There were no statistically significant predictors of a positive pathogen PCR test including age, IBD subtype and phenotype, sex, ethnicity, duration of IBD, history of CDI, previous subtotal colectomy or total proctocolectomy, IBD medication exposure before and at PCR testing, previous and current use of a proton pump inhibitor, antibiotic use within 90 days before and at PCR testing, elevated inflammatory markers at PCR testing, inflammation on CT or MR imaging within 2 weeks of PCR testing, or inflammation on flexible sigmoidoscopy or colonoscopy within 2 weeks of PCR testing (Table 1).

Clostridium Difficile PCR Results and Predictors of CDI

Thirty-eight C. difficile PCR tests were positive in 32 patients. There was no significant association between positive

TABLE 1. Characteristics of Patients with Inflammatory Bowel Disease Who Underwent 294 Stool PCR Tests

	Negative Gastrointestinal Pathogen and Clostridium Difficile PCR Tests, n = 218 (73.9%)	Positive Gastrointestinal Pathogen PCR Test, n = 41 (13.9%)	P^a	Positive Clostridium Difficile PCR Test, n = 38 (12.9%)	P^a
IBD subtype, n (%)					
Crohn's disease	95 (43.6)	17 (41.5)		16 (42.1)	
Ulcerative Colitis	121 (55.5)	23 (56.1)		22 (57.9)	
Indeterminate colitis	2 (0.9)	1 (2.4)	0.614	0	0.788
IBD phenotype, n (%)					
Isolated ileal/upper GI only	41 (19)	7 (17.5)		1 (2.6)	
Any colonic involvement	167 (77.3)	31 (75.6)	0.855	37 (97.4)	0.010
Sex, n (%)					
Man	106 (48.6)	22 (53.7)		19 (50)	
Woman	112 (51.4)	19 (46.3)	0.534	19 (50)	0.928
Race/ethnicity, n (%)					
White	104 (47.7)	16 (39)		15 (39.5)	
Hispanic	67 (30.7)	16 (39)		13 (34.2)	
Black	27 (12.4)	7 (17.1)		7 (18.4)	
Asian	5 (2.3)	0		0	
Other/unknown	15 (6.9)	2 (4.9)	0.640	3 (7.9)	0.770
Duration of IBD (median in years)	4.4	5.2	0.855	3.4	0.669
Age, years, mean ± SD	40.1 ± 22.1	37.2 ± 19.4	0.661	37.9 ± 19.6	0.902
Previous CDI, n (%)	55 (25.2)	13 (31.7)	0.621	17 (44.7)	0.015
Previous colectomy, n (%)	42 (19.3)	3 (7.3)	0.115	2 (5.3)	0.040
Previous medication exposure, n (%)					
5-ASA	157 (74.4)	31 (75.6)	0.796	31 (83.8)	0.224
Corticosteroids	147 (69.3)	26 (63.4)	0.477	30 (78.9)	0.182
Immunomodulators	87 (41)	18 (43.9)	0.666	14 (36.8)	0.610
Biologics	80 (37.7)	15 (36.6)	0.869	17 (45.9)	0.316
Immunomodulator with biologic	53 (24.3)	10 (24.4)	0.843	9 (23.7)	0.762
Proton pump inhibitor	77 (36.3)	18 (43.9)	0.300	13 (35.1)	0.759
Antibiotic exposure within 90 days, n (%)	55 (25.9)	9 (22)	0.505	13 (35.1)	0.227
Medications at testing, n (%)					
5-ASA	126 (57.8)	16 (39)	0.575	20 (52.6)	0.208
Corticosteroids	52 (23.9)	7 (17.1)	0.303	11 (28.9)	0.393
Immunomodulators	46 (21.1)	14 (34.1)	0.060	8 (21.1)	0.825
Biologics	54 (24.8)	9 (22)	0.618	11 (28.9)	0.529
Immunomodulator with biologic	12 (5.5)	5 (12.2)	0.174	2 (5.4)	0.751
Proton pump inhibitor	58 (26.6)	14 (34.1)	0.228	8 (21.1)	0.118
Antibiotics	31 (14.4)	6 (14.6)	0.828	3 (7.9)	0.271
Inflammatory markers at testing					
Elevated ESR or C-RP, n (%)	117/157 (74.5)	22/28 (78.6)	0.878	23/29 (79.3)	0.879
Median ESR	35	37		39	
Median C-RP	15.3	6		33.6	
CT or MR imaging at testing, n (%)					
No active inflammation	20/81 (24.7)	11/23 (47.8)		2/17 (11.8)	
Active inflammation	61/81 (75.4)	12/23 (52.2)	0.351	15/17 (88.2)	0.689
Endoscopy at testing, n (%)					
No active disease	7/78 (9)	1/14 (7.1)		1/9 (11.1)	
Active disease	71/78 (91)	13/14 (92.9)	0.862	8/9 (88.9)	0.841

[a]Compared with those patients with negative stool PCR testing results for gastrointestinal pathogen panel and C. difficile.

C. difficile testing and IBD subtype, age, sex, ethnicity, duration of IBD, IBD medication exposure before and at PCR testing, previous and current use of a proton pump inhibitor, antibiotic use within 90 days, elevated inflammatory markers at PCR testing, inflammation on CT or MR imaging within 2 weeks of PCR testing, or inflammation on flexible sigmoidoscopy or colonoscopy within 2 weeks of PCR testing (Table 1). Positive testing was more common in patients with a previous history of C. difficile (20% versus 10% $P = 0.015$) or colonic involvement of IBD (15.7% versus 2%, $P = 0.010$). Patients with a previous subtotal colectomy or total proctocolectomy were less likely to test positive for C. difficile (4.3% versus 14.5%, $P = 0.042$).

Impact of Positive PCR Testing on Enteric Infection Management and IBD Management

Of 41 positive gastrointestinal pathogen PCR panels, 15 (36.6%) resulted in specific enteric infection treatment and 17 (41.5%) resulted in hospitalization. Of 36 bacterial pathogens detected, 18 (50%) received antimicrobials, whereas no viral infections received specific treatment. All patients with CDI received treatment with antimicrobials with activity against C. difficile and 22 (57.9%) resulted in hospitalization. The majority of CDI resulted in patients receiving oral vancomycin (24, 63.2%) as a part of the treatment regimen. Of 38 positive tests for CDI, 12 received oral metronidazole, 18 oral vancomycin, 5 oral metronidazole and vancomycin, 1 oral vancomycin followed by fecal transplant, 1 oral and intravenous metronidazole, and 1 underwent colectomy after treatment with oral vancomycin.

For patients with negative PCR testing, 112 (51.4%) tests resulted in hospitalization. Patients with CDI had a longer median length of hospital stay (8.5 days) compared with patients with a positive gastrointestinal pathogen panel (4.5 days) and compared with patients with fully negative PCR testing (4 days; $P = 0.041$). Patients who tested negative for all enteric infections were more likely to have IBD medications added or up-titrated (48.6%) compared with patients with a positive gastrointestinal pathogen panel (29.3%; $P = 0.027$; Table 3). Compared with patients who testing negative for infections, CDI was not associated with IBD medications being held, added, or up-titrated. There were no differences in 90-days mortality.

TABLE 2. Types of Enteric Infections Among Those with a Positive Gastrointestinal Pathogen Panel PCR Result

Enteric Infection	Number Identified (n = 51), n (%)
Bacteria	36 (70.6)
Escherichia coli (E. coli) species	24 (47.1)
Enteropathogenic E. coli	14 (27.5)
Enteroaggregative E. coli	6 (11.8)
Entertoxigenic E. coli	2 (3.9)
Enteroinvasive E. coli	1 (2)
Shiga toxin-producing E. coli	1 (2)
Campylobacter species	8 (15.7)
Salmonella	1 (2)
Vibrio species	1 (2)
Shigella species	1 (2)
Pleisomonas shigelloides	1 (2)
Yersinia enterocolitica	0
Parasites	0
Cryptosporidium	0
Cyclospora cayetanensis	0
Entamoeba histolytica	0
Giardia lamblia	0
Viral	15 (29.4)
Norovirus (genogroups GI, GII)	9 (17.6)
Rotavirus A	3 (5.9)
Sapovirus (serotypes I, II, IV, V)	2 (3.9)
Adenovirus	1 (2)
Astrovirus	0

DISCUSSION

In this cross-sectional study of patients with IBD and exacerbation in symptoms over an 18-month period, enteric infection was detected in 26.8% of PCR tests. Of all tests, CDI was the most common (12.9%) followed by E. coli species (8.1%) and viruses (5.1%). To our knowledge, this is the first study evaluating the utility of broad stool PCR testing in patients with relapse of IBD. These findings indicate that in patients with IBD and symptoms suggestive of flare, enteric infection may be the sole etiology for presentation or coexist as a complicating factor in over one-fourth of presentations.

We did not find any association between previous exposure to and current use of medications for IBD, such as 5-ASA, antibiotics, corticosteroids, immunomodulators, biologic agents, or combination immunomodulation with biologic therapy, with enteric infection. The recent use of gut specific anti-integrin therapies has caused concern regarding whether these drugs may increase the risk of intestinal and systemic infections from enteric pathogens. Although few patients undergoing PCR testing in the present cohort were exposed to the anti-integrin vedolizumab (n = 16), this exposure was not associated with an increased risk of C. difficile or other enteric infection. Moreover, we did not find any association between previous exposure to and current use of proton pump inhibitors and antibiotics with enteric infection in patients with IBD.

Despite conflicting studies regarding the risk of CDI acquisition in patients with IBD as a result of exposure to antibiotics and immunosuppressive medications such as biologics and corticosteroids, our results suggest a less important role for medication exposure as risk factors for CDI.[10,11] In addition, although a recent report described similar outcomes for patients with and without CDI during relapse of IBD,[20]

TABLE 3. Association of Stool PCR Test Results with Management and Outcomes in Patients with IBD

	Negative Gastrointestinal Pathogen and Clostridium Difficile PCR Tests, n = 218 (73.9%)	Positive Gastrointestinal Pathogen PCR Test, n = 41 (13.9%)	P^a	Positive Clostridium Difficile PCR Test, n = 38 (12.9%)	P^a
Change in IBD management, n (%)					
None	104 (48.1)	26 (63.4)	0.088	22 (57.9)	0.267
Medications held	5 (2.3)	3 (7.3)		0	
Medications added or up-titrated	105 (48.6)	12 (29.3)	0.027	15 (39.5)	0.362
Colectomy	2 (0.9)	0		1 (2.6)	
Required hospitalization, n (%)	112 (51.4)	17 (41.5)	0.180	22 (57.9)	0.376
Length of stay if hospitalized (median in days)	4	4.5	0.854	8.5	0.041
Death, n (%)	3 (1.4)	0		1 (2.6)	0.897

[a]Compared with those patients with negative stool PCR testing results for gastrointestinal pathogen panel and C. difficile.

our findings reflect most studies confirming significantly worse outcomes for patients with CDI, with these patients having the highest proportion requiring hospitalization and the longest length of hospital stays.[2–5]

Our findings also suggest that microbiological and virological diagnosis of infection during an exacerbation in symptoms impacts IBD management such that negative gastrointestinal pathogen panel and C. difficile PCR tests resulted in largest proportion of patients having medications for IBD added or increased. Diagnosis of infection in relapse of IBD may prevent unnecessary exposure to immunosuppression, which may be especially harmful in the setting of certain enteric infections.

Overall, most patients with non-C. difficile enteric infections did not receive antimicrobial treatment. Treatment regiments for patients with bacterial infections included varying doses and durations of quinolones, cephalosporins, sulfonamides, macrolides, and nitroimidazoles. The present study highlights the importance for further study in this area to establish the significance of identifying the presence of these pathogens and the appropriate treatment protocols for specific infections.

There are several limitations to the current study inherent to a retrospective study design. Our analyses do not prove a cause-and-effect relationship between exacerbation in symptoms and enteric infections. The observed associations could have been because of the presence of factors that contribute to enteric infection and individualized decision-making in IBD management, especially for those patients who underwent inflammatory marker testing, imaging, or endoscopy. Moreover, PCR testing fails to discriminate between active infection and asymptomatic colonization. This is further complicated by high rates of reported asymptomatic enteric infection colonization in IBD.[21] Although PCR testing typically has a high negative predictive value for CDI, its specificity is limited as it detects genes rather than the presence of free toxins.[22] In addition, our study population consisted of patients cared for at an urban, academic referral center, and as such, our results may not be generalizable to the community.

In conclusion, in this analysis of patients with IBD symptom exacerbations, enteric infection with an array of bacterial and viral pathogens was detected via stool PCR during exacerbation of symptoms. These results suggest that PCR testing should be considered as a diagnostic step in patients with an apparent relapse of IBD. Although broad PCR testing impacted IBD management, it is unclear if the presence of intestinal pathogens other than C. difficile has an important effect on the course of IBD. Future studies should include determining of the prevalence of enteric pathogens in patients with IBD who are not experiencing an exacerbation in symptoms. In addition, there needs to be a uniform examination of IBD activity with endoscopic and pathologic assessment in patients with and without enteric infection to measure the clinical consequence of specific enteric infections on the course of IBD. This will help address the appropriate treatment of patients with IBD in whom relapse is complicated by enteric infection. The increasing widespread availability of this testing modality should facilitate these studies.

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