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ORIGINAL ARTICLE

Experience and Outcomes at a Specialized *Clostridium difficile* Clinical Practice

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Abstract

Objective: To report our experience with and outcomes among patients referred to a specialized *Clostridium difficile* clinical practice.

Patients and Methods: We retrospectively identified consecutive patients referred for *Clostridium difficile* infection (CDI) management from January 1, 2013, through May 30, 2015. Data were collected for demographic characteristics, CDI history, final diagnoses, and management.

Results: Overall, 211 patients (median age, 65 years; 66.4% women) were included. The most common indications for referral were recurrent CDI in 199 patients (94.3%), first CDI episode in 5 patients (2.4%), and chronic diarrhea in 7 patients (3.3%). After evaluation, the diagnoses were recurrent CDI in 127 patients (60.2%), resolved CDI in 36 patients (17.1%), first-episode CDI in 5 patients (2.4%), and non-CDI in 43 patients (20.4%). The most common non-CDI diagnoses were postinfection irritable bowel syndrome (PI-IBS) in 32 patients (15.2% overall), inflammatory bowel disease (n=3), small intestinal bacterial overgrowth (n=2), microscopic colitis (n=1), and asymptomatic *C difficile* colonization (n=2). Two patients had diabetic gastroparesis and food intolerances, and 1 had chronic constipation with overflow diarrhea. Of 127 patients with recurrent CDI, 30 (23.6%) received antibiotics; of these 30, 12 had antibiotic treatment failure and received fecal microbiota transplantation (FMT) for recurrent CDI. Among 97 patients (76.4%) who underwent FMT, 85 (87.6%) were cured after the first FMT, 5 were cured after the second FMT, and 7 were treated with antibiotics for FMT failure, with resolution of symptoms.

Conclusion: A substantial proportion of patients referred for CDI subsequently received alternative diagnoses; PI-IBS was the most common. Patients being referred for recurrent CDI should be evaluated carefully for alternative diagnoses.

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During the past 3 decades, the incidence of *Clostridium difficile* infection (CDI) has increased substantially in both hospital and community settings, and it is now the most common cause of hospital-acquired infection in the United States, with an overall cost in excess of $3.2 billion annually.[1,2] The severity and recurrence rates of CDI have increased markedly, with resulting poor outcomes.[3-6] The risk of recurrent CDI is approximately 20% to 25% after an initial episode and increases to more than 60% after 2 or more CDI episodes and with the use of additional systemic antibiotics.[6-8] The pathophysiology of recurrent CDI involves alteration of the gut microbiome, which is exacerbated by the use of antibiotics and which leads to further disruption of the protective intestinal microbiome and increased susceptibility to CDI. Treatment options for recurrent CDI include the use of tapered and pulsed courses of vancomycin, fidaxomicin, or rifaximin regimens. Fecal microbiota transplantation (FMT) has emerged as a safe, effective, and cost-effective treatment for recurrent and refractory CDI. It works by restoring the gut microbial diversity. Case series and observational studies have shown efficacy rates of 85% to 90%[9-11]; randomized controlled trials have demonstrated efficacy ranging from 50% with 1 stool enema[12] to more than 90% after multiple donor stool enemas or stool transplants with colonoscopy in patients with recurrent CDI.[13]

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Diagnosing recurrent CDI can be challenging because diagnostic test results can remain positive even after successful treatment.[14,15] Nucleic acid amplification (polymerase chain reaction [PCR]) testing is extremely sensitive and may give false-positive results. Also, the risk of postinfection irritable bowel syndrome (PI-IBS) after resolved CDI is as high as 25%, and PI-IBS has symptoms similar to recurrent CDI.[16] Patients with a diagnosis of recurrent CDI may, in fact, have functional gastrointestinal symptoms as a result of recent CDI and may have a positive stool test result due to colonization or a false-positive result, rather than true recurrent or persistent CDI. In a study of 117 patients referred with a diagnosis of recurrent CDI, 25% had an alternative cause for their diarrhea.[17] We have demonstrated that 25% of patients with CDI have development of PI-IBS at least 6 months after their last CDI episode, which makes PI-IBS a possible cause of symptoms in patients with a history of CDI and ongoing gastrointestinal tract (GI) symptoms.[16]

Although FMT is not approved by the US Food and Drug Administration, several hospitals and medical centers offer it as a therapy for CDI owing to its efficacy in preventing recurrent CDI.[10] At our center, we established a *C difficile* Clinic in August 2012 to evaluate patients with recurrent CDI for FMT. This specialized clinic is designed to improve patient care and provide newer treatment options, including clinical trials and conventional FMT, for the treatment of patients with multiple recurrent episodes and refractory CDI.

In this study, we report our experience with and outcomes in patients referred to our specialized *C difficile* clinical practice, including final diagnoses and management.

PATIENTS AND METHODS

Data Collection

The Mayo Clinic Institutional Review Board (IRB) approved prospective and retrospective data collection for this study. We first retrospectively identified all consecutive patients aged 18 years or older who were referred to our clinic for CDI management from January 1, 2013, through May 30, 2015. No patients were excluded on any basis. Data were collected and reviewed from the initial consultation and included demographic characteristics, referring diagnosis, CDI history, concurrent GI illness, final diagnoses, and management. Outcomes of interest included frequency of non-CDI diagnoses. For patients who received non-CDI diagnoses, additional information was collected regarding symptoms that might suggest alternate diagnoses and investigations to determine the exact cause of diarrhea. The PI-IBS was diagnosed on the basis of the Rome III criteria (improvement in abdominal pain with defecation or the onset of abdominal pain associated with a change in the frequency or form of the stool) and a recent history of CDI.[18] Inflammatory bowel disease was diagnosed on the basis of endoscopic and histologic findings of Crohn disease or ulcerative colitis, and microscopic colitis was diagnosed on the basis of findings of normal colon on endoscopy and histologic findings consistent with lymphocytic or collagenous colitis. For patients who received FMT, the rate of prevention of future recurrent CDI was calculated.

Patient Selection and Screening

Patients referred to the *C difficile* Clinic at Mayo Clinic in Rochester, Minnesota, were evaluated for eligibility for conventional FMT and clinical trials by physicians staffing the clinic (S.K. and D.S.P.). Patients underwent a complete diagnostic evaluation to ascertain whether they truly met criteria for recurrent CDI, which included thorough history and physical examination, serologic and stool tests to rule out other causes of diarrhea, and, if needed, radiographic and endoscopic evaluation.[19] The various aspects of patient history considered while making a diagnosis of CDI and distinguishing it from other causes of diarrhea are shown in Figure 1. The diagnosis of CDI was made on the basis of the presence of watery diarrhea ($\geq$3 watery stools/d) with a positive CDI stool test result. Eligibility criteria for FMT included patients with 3 or more CDI episodes established by a positive *C difficile* stool assay in the presence of diarrhea, and previous treatment with first-line therapies for CDI (metronidazole, vancomycin, or fidaxomicin), or a 6- to 8-week tapering course of vancomycin or vancomycin followed by rifaximin chaser, with a

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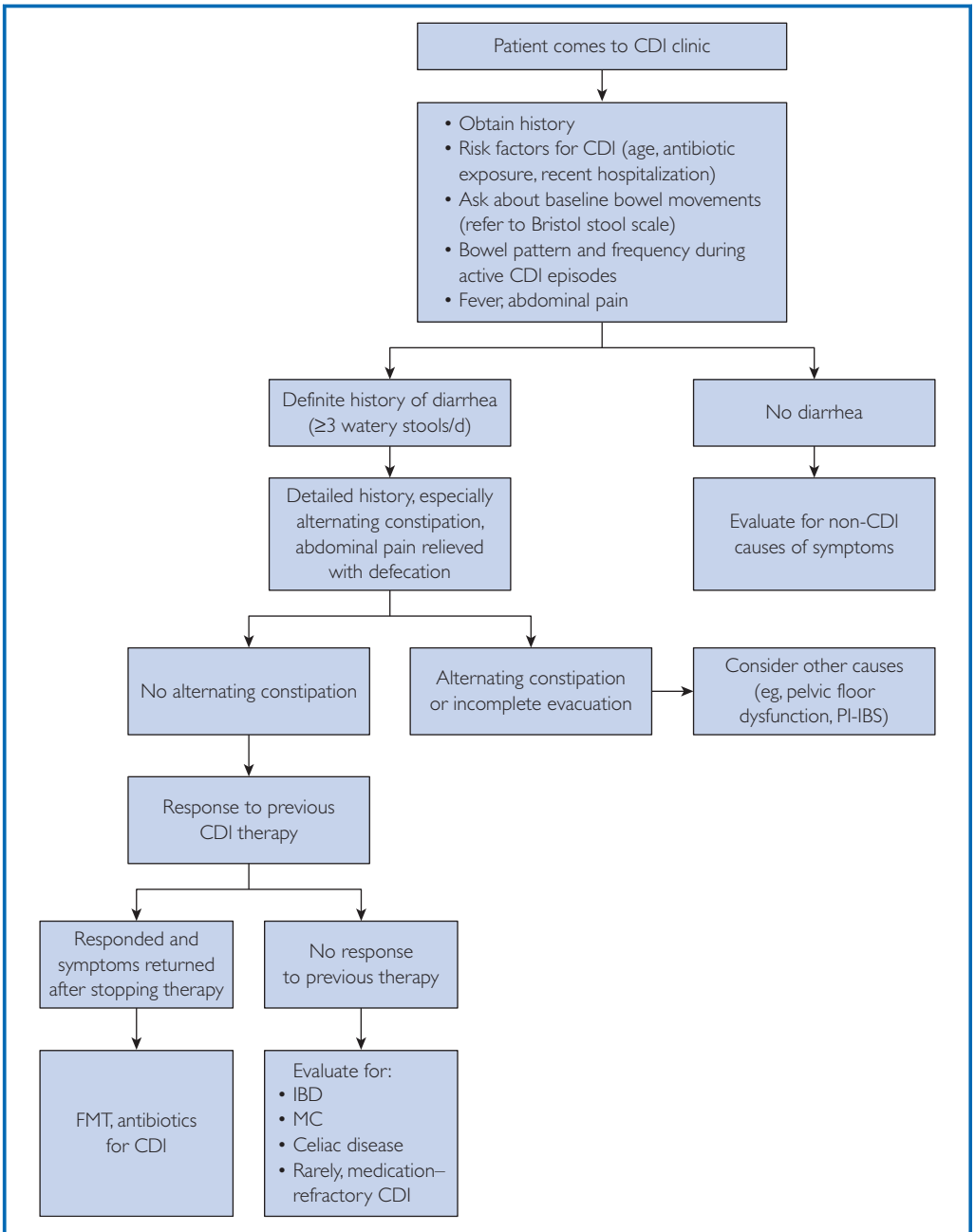

FIGURE 1. Diagnostic algorithm. A simplified approach for evaluation of patients to distinguish clinically between CDI recurrence and alternative causes of diarrhea. CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; IBD = inflammatory bowel disease; MC = microscopic colitis; PI-IBS = postinfection irritable bowel syndrome.

demonstrated treatment response.[20] If deemed appropriate candidates for FMT, patients received education and detailed informed consent that outlined the risks and benefits of, and alternatives to, FMT before the procedure. Because FMT was a clinical procedure, IRB approval was not needed for the procedure.

Donor Recruitment and Screening

In the initial stage of the program, FMT recipients identified a known stool donor, but this was later deemed an unfeasible approach.[19] First, every selected known donor had to undergo screening to determine eligibility, which created delays and high cost. Second, there were ethical issues; some patients were more comfortable using an anonymous donor, and some identified donors were found to have exclusions on preliminary testing.[19] To overcome these barriers, a standard donor pool was created. The creation of the donor pool was approved by the IRB. All donors underwent informed consent for screening before proceeding to stool donation. Donor screening (which included history and blood and stool testing) was performed with a well-defined protocol adapted from the published literature and vetted by providers within the departments of gastroenterology and infectious diseases and the Mayo Clinic Microbiome Program.[21] The donors were screened for specific exclusion criteria.[19] Recipients were then given the option to choose a known or a standard donor. In our program, most patients receive FMT via colonoscopy; a minority of patients receive FMT via retention enema or via endoscopy into the duodenum.

Statistical Analyses

Data were entered into JMP version 11.0 (SAS Institute Inc), which was used for statistical analyses. Demographic and clinical variables were summarized using descriptive statistics. Continuous variables are reported as median (range), and categorical variables are reported as count (percentage).

RESULTS

A total of 211 patients were identified and included in the study; patients' demographic characteristics, concurrent GI illnesses, CDI history, and CDI-related medication history are presented in Table 1. The most common indication for referral was recurrent CDI (199 patients; 94.3%). The most common established GI illnesses included inflammatory bowel disease in 16 patients (7.6%), irritable bowel syndrome (IBS) in 8 patients (3.8%), and microscopic colitis in 7 patients (3.3%). None of the patients was taking concomitant systemic antibiotics along with CDI treatment at the time of consultation.

TABLE 1. Characteristics of Patients Referred to CDI Clinic[a]

Characteristic	Value (N=211)[b]
Age (y)	65 (18-93)
Sex: women	140 (66.4)
Indication for referral	
Recurrent CDI	199 (94.3)
First episode of CDI	5 (2.4)
Nonspecific diarrhea	7 (3.3)
Most common concurrent GI illness	
IBD	16 (7.6)
IBS	8 (3.8)
Microscopic colitis	7 (3.3)
Previous CDI episodes	
0	5 (2.4)
1	18 (8.5)
2	58 (27.5)
≥3	130 (61.6)
CDI medications at presentation	
Vancomycin	99 (46.9)
Metronidazole	10 (4.7)
Fidaxomicin	3 (1.4)
Vancomycin and metronidazole	2 (0.9)
Loperamide	1 (0.5)
Previous CDI medications	
≥1 course of vancomycin	168 (79.6)
≥1 course of metronidazole	149 (70.6)
≥1 course of fidaxomicin	31 (14.7)

[a]CDI = *Clostridium difficile* infection; GI = gastrointestinal tract; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome.
[b]Values are median (range) or No. of patients (%).

Of the 211 patients, 43 (20.4%) received a non-CDI diagnosis as a cause of their diarrhea, on the basis of clinical evaluation and diagnostic investigations (Table 2). Features consistent among most of the patients with alternative diagnoses included a history of nonresponsiveness to CDI therapy and negative CDI stool testing results. The most common alternative diagnosis was PI-IBS (32 [74.4%] of non-CDI patients; 15.2% overall) after recent CDI. Of the 32 patients with PI-IBS, 3 had positive CDI PCR test results and were considered to be CDI carriers with PI-IBS; the other 29 patients had negative CDI stool test results (Table 3). Sixteen patients had ongoing symptoms at the time of follow-up and were using symptomatic therapies, including fiber, antidiarrheals, antispasmodics, and tricyclic antidepressants; 7 of these patients had resolution of symptoms, and

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TABLE 2. Final Diagnoses Among Patients Referred to CDI Clinic[a]

Diagnosis	No. of patients (%) (N=211)
Recurrent CDI	127 (60.2)
Resolved CDI	36 (17.1)
First episode of CDI	5 (2.4)
Non-CDI diagnosis	43 (20.4)
Postinfection IBS	32 (74.4)
IBD	3 (7.0)
SIBO	2 (4.7)
Multiple diagnoses[b]	2 (4.7)
Microscopic colitis	1 (2.3)
Chronic constipation with overflow diarrhea	1 (2.3)
CDI colonization	2 (4.7)

[a]CDI = *Clostridium difficile* infection; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; SIBO = small intestinal bacterial overgrowth.
[b]Diabetic gastroparesis, multiple food intolerances, and chronic functional diarrhea.

9 were lost to follow-up. The median follow-up period for patients with PI-IBS was 2 years (range, 1-3 years). Among patients who received non-CDI diagnoses, 2 had multiple diagnoses, including diabetic gastroparesis, multiple food intolerances, and chronic functional diarrhea, and 1 had chronic constipation with overflow diarrhea. In addition to the 3 patients with PI-IBS and CDI colonization, 2 other patients were deemed to have asymptomatic CDI colonization owing to the absence of watery diarrhea and positive stool PCR test results.

Of the other patients, 127 (60.2%) were determined to have recurrent CDI, 36 (17.1%) had resolved CDI, and 5 (2.4%) were asymptomatic after their first episode of CDI. Table 2 presents the final diagnoses for all patients referred to the CDI clinic. Of the patients with recurrent CDI, 97 (76.4%) were treated with FMT and 30 (23.6%) had medical management, either because of patient preference or because they had not had 3 or more episodes of CDI (Figure 2). Among patients with medical management, 12 (40%) subsequently underwent FMT after failure of antibiotic treatment. Among patients who received FMT, 87.6% (n=85) were cured after the first FMT, 5 were cured after the second FMT, and 7 were treated with antibiotics for FMT failure. Of the 7 patients with FMT failure, 5 had early FMT failure (within 3 months); post-FMT antibiotic exposure was the cause of FMT failure in all patients.

TABLE 3. Characteristics of Patients With Post-infection Irritable Bowel Syndrome[a]

Characteristic	Value (n=32)[b]
Age (y)	53 (23-83)
Sex: female	21 (65.6)
>2 Episodes of CDI	21 (65.6)
Treated with ≥1 course of vancomycin	24 (75)
Treated with ≥1 course of metronidazole	20 (62.5)
No response to CDI treatment	8 (25)
CDI positive	3 (9)

[a]CDI = *Clostridium difficile* infection.
[b]Values are median (range) or No. of patients (%).

DISCUSSION

With an increase in the incidence of recurrent CDI, more patients are being referred for FMT owing to its high efficacy in preventing recurrent CDI.[10] The purpose of specialized clinics is to accept referrals and treat patients with CDI, including those not responding to traditional therapies. In the present study, we report our experience with patients referred to our specialized *C difficile* clinic. A substantial proportion, 20.4%, did not have recurrent CDI and ultimately received a non-CDI diagnosis. The most common alternative diagnosis was PI-IBS. Most of the patients with PI-IBS had a recent CDI episode and had negative results of CDI stool tests. A few patients with PI-IBS had a positive CDI stool test result and were considered to be CDI colonizers. These patients were treated according to their symptoms, and none was offered FMT.

A few studies have described PI-IBS after infectious diarrhea caused by *Campylobacter*, *Salmonella*, *Escherichia*, and *Shigella* species,[22-24] but the data describing PI-IBS after CDI are limited. One study described the rate of PI-IBS after CDI to be 35%, but 3 months after the initial CDI episode only 4.3% had symptoms indicative of PI-IBS.[25] One recent study described sequelae of CDI in a US military population and found that 14.1% of patients had development of functional gastrointestinal symptoms (eg, IBS, gastroesophageal reflux disorder, and

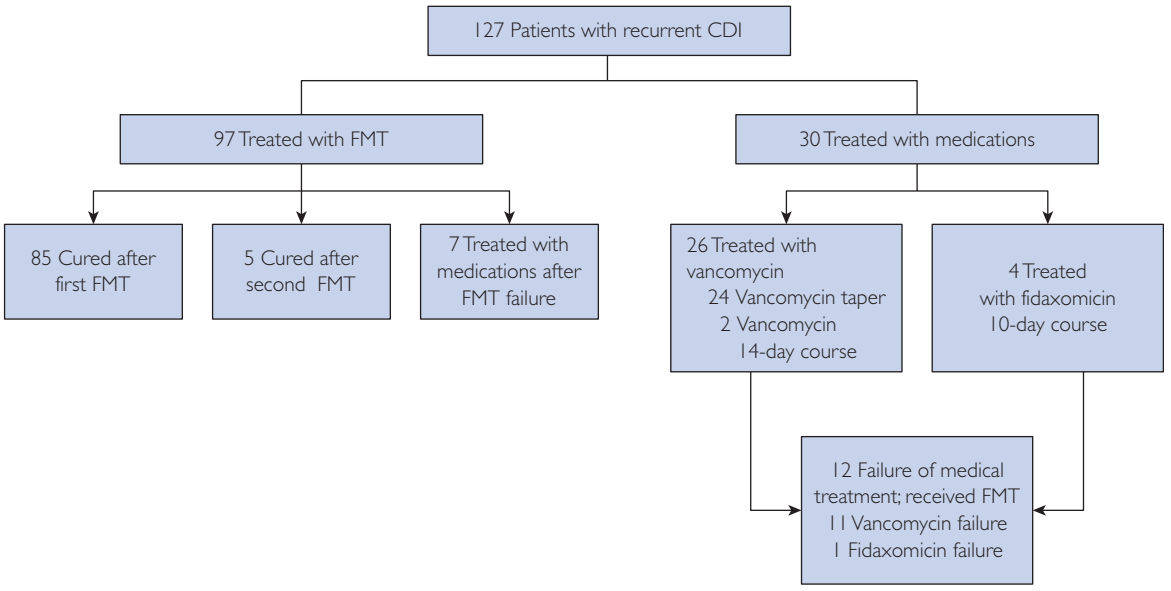

FIGURE 2. Outcomes among patients with recurrent CDI (n=127). CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation.

dyspepsia), whereas only 6% among a matched unexposed population had similar symptoms.[26] Another recent study reported the incidence of new-onset PI-IBS 6 months or longer after an episode of CDI to be 25%.[16] Finally, in a study evaluating outcomes in patients referred to their FMT center for recurrent CDI, a large percentage of the population did not have CDI but had an alternative cause of diarrhea, with IBS and PI-IBS being the most common.[17] Our results are generally in line with these previous studies and demonstrate that PI-IBS is common after CDI.

A careful and thorough clinical evaluation is needed to diagnose CDI. History taking should include an estimation of baseline bowel pattern and stool consistency using the Bristol stool scale, comparing it with bowel pattern and consistency during an active CDI episode, and previous response to anti-CDI therapy. The presence or absence of other symptoms such as alternating constipation or difficult defecation should be elucidated (Figure 1). In some patients, laboratory evaluation including assessment of the white blood cell count, serum creatinine and albumin levels, and upper GI endoscopy or diagnostic flexible sigmoidoscopy or colonoscopy may be helpful to rule out alternative causes of diarrhea.

It is imperative to understand the different interpretations of stool testing for *C difficile*, and such testing should be performed only in the presence of symptoms suggestive of CDI. *C difficile* colonization and false-positive test results are common after a treated episode of CDI, with studies reporting positive CDI test results in about 63% of patients after successful treatment of a CDI episode.[27] About 3% of outpatients and 4% to 29% of inpatients without infection may be colonized with *C difficile*.[27,28] If these patients have diarrhea at initial evaluation, it is difficult to distinguish between an alternate cause of diarrhea, such as PI-IBS, and true CDI recurrence. Several diagnostic tests are available to diagnose CDI. Enzyme immunoassay for toxin detection lacks sensitivity and, used alone, is considered insufficient for diagnosis of CDI. A 2-step algorithm using glutamate dehydrogenase antigen detection followed by enzyme immunoassay testing for toxin A or B has variable specificity (0.32-0.99).[29] The PCR test for detection of *tcdB* is widely used and is the preferred diagnostic test because of its

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high sensitivity and specificity and fast turnaround time.[30] However, a limitation of PCR testing is its lack of ability to distinguish between true CDI and colonization.[14,15,27,28] A multistep algorithm using PCR for confirmation after initial testing of glutamate dehydrogenase and toxin A and B with enzyme immunoassay has good sensitivity (0.68-1.0) and specificity (0.92-1.0). This is most likely the best strategy for diagnosing CDI and may help in distinguishing true CDI from colonization.[15]

The high rate of an alternate diagnosis in patients with presumed CDI is also associated with increased financial burden. Several studies have estimated the cost of medical care for each episode of CDI at between $2000 and $5000.[31-33] Hence, an accurate diagnosis of recurrent CDI is essential to decrease the financial burden and prevent unnecessary use of anti-CDI treatments, including FMT.

Our study highlights that all patients referred to a CDI clinic as potential candidates for FMT for presumed recurrent CDI should undergo thorough clinical evaluation, and providers should have a high degree of clinical suspicion for an alternative cause of diarrhea. This is especially true in those with atypical CDI symptoms, including absence of watery diarrhea or nonresponse to typically effective CDI treatments. In addition, it is difficult to distinguish symptomatic patients with a positive CDI stool test result due to true CDI recurrence from patients with PI-IBS with CDI colonization. Current data do not support the use of FMT as treatment, outside of research settings, for diagnoses other than recurrent CDI, especially for PI-IBS, which was the most common alternative diagnosis in our cohort.

Our study has several limitations. Data were incomplete in certain aspects, including details regarding CDI history and management, because they were collected retrospectively. The diagnosis of PI-IBS was mostly based on clinical history, and there is no confirmatory clinical test. Our study reports a single-center experience, and the study should be replicated at other centers.

In conclusion, a considerable proportion of patients referred to our CDI clinic subsequently received an alternative diagnosis, with PI-IBS being the most common. Clinicians should consider this diagnosis, especially in patients with symptoms refractory to CDI treatment and with ongoing symptoms but negative test results. Further prospective cohort studies with longer follow-up of patients with CDI who have PI-IBS development versus those who have symptom resolution might be helpful in understanding and exploring ways to distinguish PI-IBS from true CDI recurrence. These studies should focus on the role of gut microbiota and changes that are associated with the development of PI-IBS after CDI.

Abbreviations and Acronyms: **CDI** = *Clostridium difficile* infection; **FMT** = fecal microbiota transplantation; **GI** = gastrointestinal tract; **IBS** = irritable bowel syndrome; **IRB** = institutional review board; **PCR** = polymerase chain reaction; **PI-IBS** = postinfection irritable bowel syndrome

Potential Competing Interests: Dr Khanna has served as a consultant for Rebiotix, Inc, Assembly Biosciences, Inc, and Summit Pharmaceuticals International. Dr Pardi has served as a consultant for Assembly Biosciences, Inc, Merck, Seres Therapeutics, C3J Therapeutics, Nestlé, and Salix Pharmaceuticals. The rest of the authors report no competing interests.

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