Over the past decade, the incidence of Clostridium difficile infection (CDI) has more than doubled. Fecal microbiota transplant (FMT) has emerged as a guideline-based treatment for recurrent and refractory disease. However, the role of FMT for the treatment of CDI in patients with underlying inflammatory bowel disease (IBD) is controversial despite higher CDI-related complication rates in this population including mortality, colectomy, and recurrent infection. A recent multicenter study demonstrated safety and efficacy of FMT for the treatment of recurrent or refractory CDI in IBD patients with cure rates comparable to the general population, but questions still remain regarding the impact of FMT on underlying IBD and its position in the treatment paradigm.

INTRODUCTION

Clostridium difficile infection (CDI) is the most prevalent cause of nosocomial infectious diarrhea in developed countries. Over the past decade its incidence has doubled, a phenomenon attributed to the emergence of an epidemic strain of C. difficile known as North American pulsed-field type 1, PCR ribotype 027 (NAP1/BI/027), an accelerated toxin producer associated with greater disease severity, higher relapse rates, and significant mortality. Its financial burden on the healthcare system is estimated to be up to $3.2 billion annually in the United States. The impact of CDI on patients with inflammatory bowel disease (IBD) is even more pronounced. Over the past decade, the incidence of CDI has doubled in Crohn’s disease (CD) and tripled in ulcerative colitis (UC). More importantly, the prevalence of CDI in the IBD population (CDI-IBD)
is estimated to be 2.5 to 8-fold higher than the general population, with a 10% lifetime chance of infection.\textsuperscript{8-10} In 2007, 2.9% of all IBD hospitalizations in the US were complicated by CDI.\textsuperscript{11} Beyond the alarming rise of CDI incidence disproportionate to the general population, hospital admissions for CDI-IBD result in worse outcomes when compared with CDI alone or IBD alone. In-hospital mortality is four to six times greater for patients admitted for CDI-IBD compared to IBD alone.\textsuperscript{12,13} Furthermore, patients with CDI-IBD have a twenty-fold increase in colectomy rate compared to patients with IBD alone,\textsuperscript{11} and six times greater colectomy rate compared to patients with CDI alone.\textsuperscript{12} Length of hospital stay and costs associated with hospitalization are also significantly higher when CDI-IBD is compared to IBD or CDI-related admissions.\textsuperscript{12,13}

Fecal microbiota transplant (FMT) has emerged as a highly effective therapy for recurrent CDI.\textsuperscript{14} There is also strong evidence that FMT is safe and rarely associated with adverse events even within immunosuppressed populations.\textsuperscript{15-17} Treatment guidelines published in 2013 by the American College of Gastroenterology recommend FMT for the third CDI recurrence.\textsuperscript{18} This is predicated on treatment success rates surpassing 90% for recurrent and refractory CDI after just one FMT delivered via colonoscopy to the ascending colon or cecum.\textsuperscript{19,20} Fecal microbiota transplant via other routes have also demonstrated efficacy rates of roughly 85% when delivered through nasoduodenal tube\textsuperscript{21,22} or via enema.\textsuperscript{23,24} More recent studies suggest a role for FMT in hospitalized patients with severe and severe-complicated CDI; cure rates are as high as 88% after a single FMT\textsuperscript{25} and over 90% when utilized in a sequential manner.\textsuperscript{26,27}

Despite the disproportionately high incidence and poor outcomes associated with CDI in patients with IBD, only a handful of studies have described outcomes after FMT therapy in this population. Among IBD patients on immunosuppressive therapy (N=36), Kelly and colleagues demonstrated CDI resolution in 86% of patients after a single FMT, with an overall cure of 94%.\textsuperscript{28} More recently, Khoruts et al. showed patients with IBD were more likely to fail a single FMT and that immunosuppressive therapy did not influence the outcome.\textsuperscript{29} In their study, a single colonoscopic FMT cleared CDI from 74% of patients with IBD compared to 92% of patients without IBD ($P = 0.0018$). A multicenter study on the use of FMT specifically in IBD patients with recurrent or refractory CDI, the largest study on this subject to date, had the primary goal of assessing treatment success rates for CDI in this unique population, and to describe secondary outcomes pertaining to safety and effect on IBD disease activity.\textsuperscript{30}

**Methods**

In this retrospective study, patients from seven medical centers with a history of IBD and recurrent or refractory CDI were treated with FMT delivered via colonoscopy or sigmoidoscopy. Protocols for donor selection and stool processing were performed as outlined by the Fecal Microbiota Transplantation Working group.\textsuperscript{31} IBD activity and severity was assessed based on the judgement of the treating physician, endoscopic findings, and clinical disease activity scores. Results of these assessments were recorded at 1 month pre-FMT, at the time of FMT, and 3 months post-FMT. Changes in IBD clinical course after FMT were categorized by the treating physician as improved, no change, or worsened.

**Outcomes of CDI Treatment**

A total of 67 patients were included, 35 with CD, 31 with UC, and 1 with indeterminate colitis among which 64% were being treated with immunosuppressive agents at time of FMT. All patients in this group had a history of recurrent or refractory CDI with an average of four episodes. The majority of patients (94%) were previously treated with vancomycin. The indication for FMT was recurrent CDI in 80% and severe or severe-complicated CDI in 9%. Overall, 79% were treated successfully after one single FMT, while 90% achieved success after a maximum of three FMTs. The only independent predictor for a repeat FMT was low serum albumin concentration.

**Impact of FMT on IBD**

Seventy-six percent of this CDI-IBD population had endoscopic evidence of active IBD during FMT. After 3 months, the majority of patients were “doing well”; the IBD clinical course had improved in 46.3% and went unchanged in 35.8% of patients. Clinical disease activity score (Harvey-Bradshaw index) was available for 23 CD patients and decreased significantly from a mean of 7 pre-FMT to 2 post-FMT ($P = 0.004$). However, a significant minority of patients (17.9%) had worsening of their IBD clinical course. Among those
patients considered to be worse, three had extensive colitis at the time of FMT and were hospitalized for an IBD flare in the ensuing 2 weeks post-FMT, but responded promptly to a short course (10-30 days) of systemic steroids. Two patients proceeded to colectomy within 1 month, both for severe Crohn’s colitis and therapy-refractory CDI. Two other ulcerative colitis patients underwent proctocolectomy, but were noted to be negative for CDI by PCR at the time of surgery. Nineteen patients were started on a new IBD therapy during the 12 week follow up period.

Overall, 12% (8/67) of patients experienced a serious adverse event (SAE), two of which were IBD flares requiring hospitalization. Only one patient experienced an SAE directly attributable to FMT; this immunocompromised CD patient in clinical and endoscopic remission at the time of FMT, developed a flare 1-week post-FMT and was found to have active inflammation and CMV-positive cells on subsequent colonic biopsies. CMV could have been transmitted through the stool transplant; neither the donor nor recipient was tested for CMV prior to the FMT. Notably, no other infectious complications related to FMT were reported.

How Will FMT Change the Treatment Paradigm For CDI-IBD?

This study demonstrated the efficacy of FMT as an adjunct to medical therapy for the treatment of CDI in the IBD population. It reaffirms success previously documented in case series and derives a cure rate comparable to the general population. The majority of patients had an improved or unchanged IBD course post-FMT, but a significant minority developed an IBD flare or had worsening disease activity. These findings are consistent with a previous study on immunocompromised patients where 14% of patients in the IBD subset experienced an IBD exacerbation after FMT. More recently, Khoruts et al. reported that 25% of IBD patients had a flare requiring systemic steroid therapy after FMT. Importantly, a majority of these patients had severe colonic inflammation at the time of FMT. Given the considerable portion of patients who experienced an IBD flare post-FMT, the authors adopted the practice of increasing anti-inflammatory/immunosuppressive therapy in patients with severe underlying colitis to mitigate the risk of post-FMT IBD flare. In another study, Chin and colleagues administered FMT to 35 CDI-IBD patients primarily via oral capsules. While FMT was well tolerated by all patients, a large portion (54%) required therapy escalation for IBD after FMT. Interestingly, two patients developed de novo disease in the form of perianal fistula and abscess post-FMT. The cause of post-FMT IBD flare and worsening disease activity is unknown. Conceivably, the flares could be precipitated by *Clostridium difficile* infection itself versus natural IBD progression, and/or an immune reaction triggered by FMT administration. Prospective studies on temporal changes in the gut microbiota composition are needed to gain mechanistic insights.

Patients with IBD have multiple risk factors for CDI including dysbiotic gut flora and higher rates of exposure to immunosuppressive medications, antibiotics, and hospitalization, which collectively lead to conspicuously worse morbidity and mortality outcomes. Yet, patients with CDI-IBD are treated under the same guidelines as their non-CDI counterparts. There is a role for a more aggressive treatment methodology. Mounting evidence supports the use of vancomycin in CDI-IBD as first line therapy even for non-severe CDI. In one study, patients with UC and non-severe CDI had fewer readmissions and shorter length of stay when treated with vancomycin-containing regimens than those with metronidazole alone. Lower rates of colectomy were reported when CDI-IBD patients were treated with oral vancomycin. There is a need for CDI disease severity stratification specific to the IBD population. Both elevated white blood cell count (WBC) and serum albumin concentration below 3g/dL are characteristic of severe disease and independently associated with colectomy and death in the general population. In the CDI-IBD population, serum albumin below 3g/dL was associated with a three-fold increase in the primary outcomes of colectomy and death, irrespective of the white blood cell count.

There are improved outcomes in CDI-IBD patients after usage of vancomycin even for non-severe cases. The severity of disease may possibly be masked by the concurrent use of immunosuppressive medications and delayed recognition of CDI due to the similarities in patient symptomatology during an IBD flare and CDI. Further, delay in recognition of CDI severity even after colonoscopy may be due to the lower frequency of pseudomembranous colitis in CDI-IBD patients. Fifty percent of non-IBD patients with CDI have pseudomembranous disease, but only 13% of
patients with CDI-IBD in a large cohort study had pseudomembranes identified during colonoscopy. Pseudomembranes, as a marker of disease severity in non-IBD patients, did not have an association with length of stay or adverse clinical outcomes in this set of CDI-IBD patients. These factors may result in suboptimal treatment, which is further exacerbated by declining response rates to metronidazole even in non-severe patients. Initial CDI response to metronidazole was >90% in 1983, but have now dropped to roughly 50%.

There may be a role for earlier positioning of FMT for the treatment of CDI in the IBD population even though current evidence for FMT in the treatment of IBD without concurrent CDI is weak at best. Rates of admission for CDI recurrence are much higher for patients with IBD (8.7%) versus the general population (0.1%). However, there still appears to be unpredictability in the response to FMT in the IBD population. Our patients also had variable responses in IBD activity after FMT therapy with 17.9% citing worse symptoms. The variable clinical courses of IBD after FMT could well be explained by a “donor effect,” which has been raised after a recent randomized controlled trial using FMT to treat patients with mild to moderate UC, documented a particular donor being particularly effective at inducing remission in these patients. Fluctuations in the composition of commensal organisms occur over time, combined with the idiosyncratic response to therapy due to the heterogeneity of recipients’ underlying IBD, may explain why only some patients have improved IBD activity after FMT. Prospective, longitudinal studies are required to determine the optimal timing for FMT in the treatment of CDI-IBD, to ensure the best outcomes while curtailing worsening IBD activity post-FMT.

CONCLUSION

Current data suggest that FMT for the treatment of recurrent or refractory CDI is effective and safe in patients with inflammatory bowel disease. The overall cure rate in CDI-IBD patients is comparable to non-IBD patients, however IBD patients may need more than one FMT for cure. While the majority of CDI-IBD patients’ clinical course improves following FMT, some remain unchanged despite CDI clearance and a significant minority may experience an IBD flare. Hospitalizations related to CDI-IBD portend much higher rates of mortality, colectomy, and hospital length of stay compared with CDI or IBD alone, therefore FMT may need to be considered earlier on in this population. To effectively treat these patients and decide where to position FMT in the treatment paradigm, further studies of FMT on CDI and IBD outcomes are needed.

References

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