Editorial

Editorial: Rejuvenating the Microbiome in Recurrent *Clostridioides difficile* Infection with Fecal Microbiota Transplant

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Clostridioides difficile is part of the normal microbiome kept in check by dominant anaerobes via competition for nutrients and mucosal niches. Alterations in gut microbiome, typically after antibiotic use, make the host susceptible to invasion, colonization, and infection. The symptoms range from diarrhea to life-threatening enterocolitis.

The recurrence of clinical symptoms within 2 to 8 weeks of successful therapy for the primary occurrence constitutes recurrent *Clostridioides difficile* infection CDI (rCDI).[1] Refractory CDI is defined by poor response to existing standard medical therapy usually presenting as severe or fulminant CDI (SFCDI). Severe CDI manifests with leucocytosis (total leucocyte count $\geq$15,000 cells/mL) or acute kidney injury (serum creatinine $>$1.5 mg/dL), and fulminant CDI leads to shock, ileus, and megacolon.[1]

Metronidazole and/or oral vancomycin is used to treat the first occurrence of CDI as is the first recurrence. For second recurrence, pulsed (every 2nd or 3rd day) and/or tapered vancomycin is recommended. Other agents are rifaximin, fidaxomicin, and cadazolid.[2]

In order to correct the intestinal dysbiosis, fecal microbiota transplant (FMT) wherein homogenized stool obtained from a healthy donor is instilled into the gastrointestinal tract of an ill recipient with a restorative objective has been successful as therapy of CDI. Multiple mechanisms of action include competing for niche and nutritional resources, production of bacteriocins, metabolizing primary bile acids into secondary bile acids inhibiting spore germination, and achieving enhanced gut barrier function and mucosal immune system following effective homeostasis with the host.[3]

Tixier et al in a meta-analysis demonstrated an overall cure rate of 61.3% after single FMT in SFCDI with a trend of low colectomy rate after FMT.[4] A meta-analysis done by Song et al showed that FMT is an effective treatment for SFCDI with low adverse events albeit multiple treatments and antibiotics may be required for complete resolution.[5] Baunwall et al in a meta-analysis projected that repeat FMT given for rCDI is 91% effective at 8 weeks with a number needed to treat of 1.5 compared to model therapy, thereby suggesting that all patients with rCDI may be treated with FMT.[6] Approximately 30% of patients with SFCDI undergo total abdominal colectomy (TAC). The approach of diverting loop ileostomy (DLI) with intraoperative colonic lavage and subsequent anterograde vancomycin flush was introduced by Neal et al.[7]

Subsequent retrospective studies showed no statistically significant difference between TAC and DLI. rCDI can develop in the rectal remnant or small intestine in patients who undergo TAC for SFCDI post-surgery. There was a 4.7% incidence of rCDI enteritis in colectomy cases with 45% occurring within the first 90 days in one study.[8] Thus, therapeutic options in rCDI and SFCDI are limited. Although surgery decreases mortality, the significant morbidity associated with the procedure itself makes it a difficult decision especially in presence of other options. Thus, FMT appears to be a promising candidate as a new noninvasive and yet effective treatment modality.

Role of FMT in post-colectomy CDI has been an area of ongoing research and some earlier reported studies highlight the potential benefits of FMT such as Orenstein et al in a case

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report described the successful FMT application for SFCDI remnant proctitis post-TAC with an excluded rectal stump with rectal swabs[9] and Lan et al subjected 13 patients with rCDI post-ileal pouch-anal anastomosis to 22 FMTs and their study showed the effectiveness of FMT in abolition of CDI in these patients.[10]

In the article, Cho et al[11] report descriptive analysis of FMT outcomes for rCDI from 2014 to 2020 performed in 29 patients with prior colectomy for varied indications including SFCDI. The routes of FMT included esophagogastroduodenoscopy (EGD), EGD and flexible sigmoidoscopy, EGD and pouchoscopy, enteroscopy and pouchoscopy and instillation through an ileostomy catheter. To maximize the time the donor fecal material stays in the recipient's intestines, a dual approach with upper and lower endoscopy was mostly utilized. They reported that two patients (6.9%) had rCDI within 8 weeks post-FMT, seven had CDI beyond 8 weeks (median 10 months) with 71% related to antibiotic exposure post-FMT, and resolution in others, thereby suggesting a 69% overall success.[11] Therefore, this study although a retrospective analysis does add to the sparse data on the role of FMT in this subset of patients.

FMT is an attractive therapeutic option in the management of rCDI with elevated effectiveness and low hazard of adverse events. In patients of rCDI with concomitant ischemia or perforation, colectomy will be indispensable. Novel means of using FMT described in this article present an alternative for managing cases of rCDI post-colectomy. On the other hand, due to limited sample size and small number of significant studies that deal with FMT post-colectomy, further research in frequency and administration route of FMT, standardized donor screening, and patient selection is required to establish this approach as a recommendation in the near future.

Ethical Statement
Not applicable.

Authors Contributions
M.M.: literature review, drafting, and revising the editorial. R.U.: literature review and initial drafting.

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