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Fecal transplant is as effective and safe in immunocompromised as non-immunocompromised patients for *Clostridium difficile*

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Dear Editor

Clostridium difficile infection (CDI) is a leading cause of nosocomial infection and is associated with significant morbidity and mortality. Immunocompromised (IC) patients are particularly at higher risk. Recurrence rates of up to 60 % have been reported after the third episode despite treatment with antibiotics. Recent published reports of fecal microbiota transplantation (FMT) in the IC population have shed light that the procedure proves to be effective and safe. No studies that compare the efficacy and adverse event rate of FMT between IC and non-IC patients currently exist. The aim of our study is to compare the response and serious adverse event (SAE) rates of FMT for recurrent or refractory CDI (RCDI) between IC patients and non-IC patients.

We performed a single-center retrospective study on patients who received FMT for RCDI in a single tertiary care center. Donor stool was obtained from a universal donor, friend, or relative. We used a standardized protocol for preparation of stool used for FMT. Patients received FMT through the upper gastrointestinal route or by colonoscopy. Those who failed initial FMT were eligible to receive additional FMT.

Patients were considered IC as a result of one or more of the following: HIV infection (any CD4 count), AIDS-defining diagnosis or CD4<200/mm³, inherited or primary immune disorders, active malignancy, and immunodeficient or immunosuppressed from a medical condition/medication including current or recent (<3 months) treatment with anti-neoplastic

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Compliance with ethical standards

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agent or immunosuppressant medications. Immunosuppressant medications included but were not limited to monoclonal antibodies to B and T cells, anti-tumor necrosis factor agents, glucocorticoids, antimetabolites (azathioprine, 6-mercaptopurine, methotrexate), calcineurin inhibitors (tacrolimus and cyclosporine), and mycophenolate mofetil.

Outcomes compared between the two populations included rates of overall and primary 12-week CDI response post-FMT and percentage of patients who experienced SAEs within 12 weeks of FMT. Overall response was defined as lack of relapse with diarrhea associated with a positive *C. difficile* PCR within 12 weeks of the last FMT (patients were eligible to have up to three FMT prior to being considered as a FMT non-responder). Primary response was defined as lack of relapse with diarrhea associated with a positive *C. difficile* PCR testing within 12 weeks post single FMT. SAEs were defined as any death, life-threatening experience, hospitalization, or important medical event such as infection of inflammatory bowel disease flare within 12 weeks post-FMT. Patients were excluded from efficacy analysis if they did not have a minimum of 12 weeks post-FMT follow up.

Data was collected from a total of 122 FMTs performed on 107 patients. Six patients were excluded due to loss of follow up during the post-FMT follow up period. Six were excluded from the efficacy analysis due to death prior to 12 weeks post-FMT, but were used to analyze the rate of SAE.

Of the 95 patients used to analyze response rate, 93 (97.9 %) patients in both groups achieved overall 12-week response. The rate of overall response between the non-IC, 58 patients (100 %), and the IC group, 35 patients (94.6 %), was not statistically different ($p=0.15$). Primary response was achieved in 52 (89.7 %) of the non-IC patients versus 33 (89.2 %) of the IC patients, and this was also not statistically different ($p=1.00$). A total of 11 patients with inflammatory bowel disease (IBD) received FMT with all achieving response with FMT. Of these, nine (82.0 %) were on concomitant immunosuppression.

Of the 101 patients included in the analysis for SAEs, 11 (10.9 %) experienced a SAE. Of these, seven (63.6 %) patients were IC and four (36.4 %) were non-IC. Of the seven IC patients, three with IBD on concomitant immunosuppression experienced a flare of their disease post-FMT. One patient, who had quiescent IBD while on a tumor necrosis factor alpha agent at the time of FMT, developed a flare more than 4 weeks after her FMT but within 12 weeks of her FMT. The other patient had moderate Crohn's related inflammatory changes on colonoscopy while on tumor necrosis factor alpha agent at the time of FMT and developed a flare within 48 h of FMT. The third patient had mild ulcerative proctitis while on tumor necrosis factor alpha agent and 6-mercaptopurine and developed a flare a month after FMT. One IBD patient with a history of recurrent diverticulitis who was also on chronic prednisone for Crohn's disease developed diverticulitis within a few hours after her FMT, which responded to antibiotics. The patient had no recurrence of CDI within the study period. None of the patients who had active IBD at the time of the FMT had resolution of their IBD post-FMT and each proceeded with starting, changing, or continuing their biologic agent. No patient required surgery within the timeframe of the study. Based on our findings, it appears that most IBD patients appear to tolerate FMT and may be cured of their CDI with FMT; however, there is a potential risk of precipitating a flare, which is well reported in the

current literature. Whether the flares may have been directly related to FMT, the natural course of the patients' IBD, or related to the colonoscopy procedure is unclear based on our current data. One non-IC patient with a history of irritable bowel syndrome (TBS) was hospitalized for severe abdominal pain and constipation 9 days after her FMT and had an uneventful recovery. These five SAEs were felt to be possibly related to FMT as changes in microbiota have been associated with the reported SAEs.

Six deaths occurred within the follow up period. However, none of these were felt to be directly related to FMT. Three deaths occurred in IC patients. A bilateral lung transplant patient developed bronchiolitis obliterans syndrome and subsequently died. A Churg-Strauss patient on chronic steroid therapy developed a Churg-Strauss flare during her hospitalization and also died from her condition. The third IC patient passed away from complications related to malignancy 8 weeks after FMT but cleared his CDI after a single FMT. One death occurred in a non-IC inpatient 95-year-old male due to continued CDI that did not respond to FMT. One death occurred in a non-IC 22-year-old female with multiple co-morbidities including chronic kidney disease and hypertension. Her death occurred from Candidemia related to self-injecting of unknown substances into her peripheral line. One non-IC patient died 6 weeks after her FMT due to a myocardial infarction. When comparing percentage of patients with SAEs in the IC and non-IC population, no difference was seen (17.5 vs 6.5 %, $p=0.11$).

We conclude that response to FMT is equivalent in the IC and non-IC population. When comparing the percentage of SAEs between IC and non-IC patients, no significant difference was found.

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