Title: Outcomes of Fecal Microbiota Transplantation in Patients With Inflammatory Bowel Diseases and Recurrent *Clostridioides difficile* Infection

Short Title: IBD and recurrent CDI: Outcomes after FMT

Jessica R. Allegretti[1,2], Colleen R. Kelly[3], Ari Grinspan[4], Benjamin H. Mullish[5], Zain Kassam[6], and Monika Fischer[7]

Collaborators: Jonathan Hurtado[1], Madeline Carrellas[1], Jenna Marcus[1], Julian R. Marchesi[5,8], Julie A.K. McDonald[5,9], Ylaine Gerardin[6], Michael Silverstein[6], Alexandros Pechlivanis[5,10], Grace F. Barker[5], Jesus Miguens Blanco[5], James L. Alexander[5], Kate I. Gallagher[5], Will Pettee[11], Emmalee Phelps[7], Sara Nemes[7], Sashidhar V. Sagi[7], Matthew Bohm[7]

1. Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston MA
2. Harvard Medical School, Boston, MA
3. Division of Gastroenterology, Alpert Medical School of Brown University, Providence, RI
4. The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY
5. Division of Digestive Diseases, Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, United Kingdom
6. Finch Therapeutics, Somerville, MA
7. Division of Gastroenterology, Indiana University School of Medicine, Indianapolis, IN
8. School of Biosciences, Cardiff University, Cardiff, UK
9. MRC Centre for Molecular Bacteriology and Infection, Imperial College London, London, UK.
10. Center for Interdisciplinary Research and Innovation, School of Chemistry, Aristotle University of Thessaloniki, Thessaloniki, Greece
11. OpenBiome, Cambridge, MA

Grant Support: The trial was funded by the Crohn's and Colitis Foundation. In addition, this work was supported in part by the Harvard Digestive Disease Center, NIH Grant P30 DK034854. Metabonomics studies were performed at the MRC-NIHR National Phenome Centre at Imperial College London; they receive financial support from the Medical Research Council (MRC) and National Institute of Health Research (NIHR) [grant number MC_PC_12025]. BHM is the recipient of a MRC Clinical Research Training Fellowship (grant reference: MR/R000875/1) and NIHR Academic Clinical Lectureship. The Division of Digestive Diseases and MRC-NIHR National Phenome Centre at Imperial College London receive financial and infrastructure support from the NIHR Imperial Biomedical Research Centre (BRC) based at Imperial College Healthcare NHS Trust and Imperial College London.

Corresponding Author:
Jessica R. Allegretti, MD, MPH
Brigham and Women's Hospital, Division of Gastroenterology
75 Francis Street, Boston, MA 02115, USA
Phone: +1-617-732-6389

This is the author's manuscript of the article published in final edited form as:

Allegretti, J. R., Kelly, C. R., Grinspan, A., Mullish, B. H., Kassam, Z., & Fischer, M. (2020). Outcomes of Fecal Microbiota Transplantation in Patients With Inflammatory Bowel Diseases and Recurrent Clostridioides difficile Infection. Gastroenterology. https://doi.org/10.1053/j.gastro.2020.07.045

Fax: +1-617-732-9198
jallegretti@bwh.harvard.edu
Disclosures: JRA consults for and has research support from Finch Therapeutics Group. JRA, MF, CRK have research support from Finch Therapeutics and serves as clinical advisors to OpenBiome. YG, MS and ZK are employees/shareholders of Finch Therapeutics. BHM consults for Finch Therapeutics.

Author and Collaborator Contributions: JRA initiated study concept and design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. MF participated in developing study concept, study design, data acquisition and critical revision of the manuscript. YG, MS analyzed and interpreted microbiome data. BHM, AP, JAKM, JM, GFB, JLA, KIG and JRM generated, analyzed and interpreted the metabolomics data. MC, JM and JH, EP, SN participated in data acquisition. ZK participated in developing study concept, study design, interpretation of data and critical revision of the manuscript. AG, SVS, MB and CRK participated in data acquisition, interpretation of data and critical revision of the manuscript.

Acknowledgements: The authors would like to acknowledge OpenBiome for providing the FMT material used in this trial. In addition, the authors would like to acknowledge Lynn Bry, Socheat Men, Mary Louise Delaney and Andrea DuBois from the BWH Pathology department and microbiology lab for coordinating the centralized stool testing efforts

Background:
There has been an increase in the burden of *Clostridioides difficile* infection (CDI)[1]; especially in high-risk populations such as patients with inflammatory bowel disease (IBD).[2] The prevalence of CDI in the IBD population is up to 8-fold higher than comparable controls with increased rates of recurrence and CDI-associated mortality.[3] Additionally, CDI may induce an IBD flare, worsen disease severity and clinical course.[4]

Fecal microbiota transplantation (FMT) is a guideline recommended therapy for recurrent CDI[5]; however, supportive randomized trials excluded IBD patients. In retrospective trials of IBD patients, FMT failure rates had been reported to be approximately 25-30%.[6] Additionally, Khoruts and colleagues reported that patients with IBD and CDI were more likely to fail FMT,[7] leading to further uncertainty regarding the safety and efficacy of FMT in IBD patients with concurrent CDI. Accordingly, we conducted the first prospective study examining the efficacy of FMT among patients with IBD and CDI.

Methods:
We conducted an open-label, prospective, single-arm, multicenter cohort study at 4 tertiary care FMT referral centers (Brigham and Women's Hospital, Indiana University, Brown University, and Mount Sinai Hospital; NCT03106844). Patients with a confirmed diagnosis of IBD and 2 or more confirmed CDI episodes within 12 months, including the most recent episode occurring within 3 months, were enrolled. In keeping with CDI clinical guidelines[5], polymerase chain reaction or glutamate dehydrogenase with toxin enzyme immunoassay were permitted for the qualifying CDI episode. Patients with a total or subtotal colectomy, isolated ileal or small bowel CD, those pregnant or breastfeeding, those treated with vancomycin or metronidazole for more than 60 days, or those that had undergone a prior FMT within 12 months were excluded. Baseline IBD and CDI data were collected. All patients underwent a single FMT via colonoscopy. Four robustly screened healthy donors were used (Openbiome, Cambridge, USA).[8]

Stool testing including glutamate dehydrogenase, toxin enzyme immunoassay and polymerase chain reaction were performed 1, 8 and 12 weeks post-FMT regardless of symptoms to assess for CDI and *C. difficile* colonization rates. All stool testing was performed at a central laboratory. The primary outcome was FMT failure through week 8, defined as diarrhea (3 or more loose stools daily for 3 or more days) and stool testing positive for C.*difficile* via two-step testing using glutamate dehydrogenase and toxin enzyme immunoassay. Patients who met the criteria for failure underwent a second FMT. Secondary outcomes included C. *difficile* colonization defined as patients without diarrhea whose stool remained positive via polymerase chain reaction post-FMT.

Results:

Fifty participants were enrolled (August 2017 to October 2019) among which 15 had Crohn's disease (CD) and 35 had ulcerative colitis (UC) (Table 1). The mean age of participants was 43 years (range 21-91) and the cohort was primarily female (58%). A total of 49 patients received treatment. One patient withdrew prior to treatment and was not replaced. Among the 49 participants, one patient was lost to follow-up after the week 1 visit and was treated as a FMT failure. Baseline CDI characteristics: 48% had 2 CDI episodes prior to entry, among which 87.5% (21/24) were diagnosed via polymerase chain reaction at the qualifying episode; 38% had 3 confirmed episodes, among which 78.9% (15/19) were diagnosed via polymerase chain reaction; and 14% had 4 prior CDI episodes among which 71% were diagnosed via polymerase chain reaction (5/7).

Overall, among 49 treated patients, 5 participants (10.2%) were FMT failures, 4 with confirmed diarrhea and a positive stool test via glutamate dehydrogenase and toxin enzyme immunoassay as well as the patient lost to follow up. Among the failures, 3 patients had 3 prior CDI episodes, and 2 patients has 2 prior CDI episodes. Notably, the failures were all primary non-responders with failure by week 1 post-FMT. All 4 underwent a second FMT from the same donor and achieved clinical cure through week 8. Two additional patients received a second FMT based on investigator discretion, but did not meet the criteria for FMT failure (toxin enzyme immunoassay and polymerase chain reaction negative, but ongoing symptoms). Importantly, 45 patients (91.8%) experienced C. *difficile* decolonization 1-week post-FMT and remained polymerase chain reaction negative.

Overall the treatment was safe and well-tolerated. Two serious adverse events were reported, both were determined to not be treatment-related by the treating physician.

Discussion: Overall, these data suggest the efficacy and safety profile of FMT in IBD-CDI is more favorable than previously reported. In this cohort, only 5 patients (10.2%) experienced FMT failure, which is significantly lower than the previous failure rates reported in retrospective trials, with a mean ~25%.[6] This discordant result may be for several reasons. First, patients with IBD are prone to diarrhea and patients who remain colonized with ongoing PCR positive stools may be mis-diagnosed as a FMT failure. Second, we enrolled patients with their first recurrence (2 CDI episodes) in contrast to second recurrence (3 CDI episodes) or further, which is common clinical practice. Importantly, we found that the majority of patients were decolonized post-FMT which may have public health implications in avoiding spreading *C. difficile.*

This study had several limitations. First, this trial was not controlled. We did not feel it was appropriate to compare clinical cure rates with standard of care alone given CDI guideline recommendations. Additionally, a strong placebo effect seems unlikely in participants with prolonged and severe symptoms and an objective laboratory test used for the primary outcome. Additionally, we estimated our sample size based on FMT failure rates from retrospective studies. We had a significantly lower rate of FMT failure, making subgroup analysis between failures and non-failures difficult.

We undertook the first prospective IBD-CDI trial to follow patients systematically post-FMT assessing for CDI eradication and decolonization. We were able to use a central lab and were able to perform robust testing on all stool samples for CDI (glutamate dehydrogenase, toxin

enzyme immunoassay and polymerase chain reaction). Overall, this study suggests FMT for the treatment of recurrent CDI in patients with IBD is safe and better tolerated than has been previously reported in retrospective studies, and results in a high rate of *C. difficile* decolonization. Additionally, positioning FMT earlier in the treatment course for patients with IBD-CDI may improve FMT failure rates.

References

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431-55.
2. Ananthakrishnan AN. Clostridium difficile infection: epidemiology, risk factors and management. Nat Rev Gastroenterol Hepatol 2011;8:17-26.
3. Razik R, Rumman A, Bahreini Z, et al. Recurrence of Clostridium difficile Infection in Patients with Inflammatory Bowel Disease: The RECIDIVISM Study. Am J Gastroenterol 2016;111:1141-6.
4. Kelsen JR, Kim J, Latta D, et al. Recurrence rate of clostridium difficile infection in hospitalized pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2011;17:50-5.
5. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018;66:987-994.
6. Newman KM, Rank KM, Vaughn BP, et al. Treatment of recurrent Clostridium difficile infection using fecal microbiota transplantation in patients with inflammatory bowel disease. Gut microbes 2017:1-7.
7. Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. Clin Gastroenterol Hepatol 2016;14:1433-8.
8. Kassam Z, Dubois N, Ramakrishna B, et al. Donor Screening for Fecal Microbiota Transplantation. N Engl J Med 2019;381:2070-2072.

Table 1: Enrolled Patient Characteristics

Variable	
Female % (n)	58% (29)
Mean Age	43.0 (range 21-91)
Crohn's % (n)	30% (15)
Colonic	20.0% (3)
Ileo-colonic	66.7% (10)
Unknown	13.3% (2)
UC % (n)	70% (35)
Proctitis	8.6% (3)
Left-sided	25.7% (9)
Pancolitis	60.0% (21)
Unknown	5.7% (2)
Race% (n)	
White	94.0% (47)
Black or African American	4.0% (2)
Asian	2.0% (1)
Mean Baseline Calprotectin (SD)	1918.23 +/- 2458.5
Mean Baseline CRP	5.8 +/- 10.1
Mean Daily BMs at Baseline	5.2 +/- 4.0
Mean Baseline Bristol Score	5.5 +/- 1.0
Mean Baseline Partial Mayo Score	4.2 +/- 2.1
Mean Baseline HBI score	5.9 +/- 3.5