LETTER TO THE EDITOR

Can you cause inflammatory bowel disease with fecal transplantation? A 31-patient case-series of fecal transplantation using stool from a donor who later developed Crohn’s disease

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To the editor

Despite rigorous donor screening, the possibility that transmission of chronic inflammatory disorders could occur as a consequence of fecal microbiota transplantation (FMT) remains a serious potential concern. In Crohn’s disease, dysbiotic gut microbiota are characterized by decreases in Bacteroidetes and Firmicutes, with increases in Gammaproteobacteria. While our current understanding of the etiology of Crohn’s disease emphasizes the defective recognition, tolerance, or elimination of microbiota, the causal role of irregular gut microbiota in the development of Crohn’s disease is unclear. Despite extensive research, the “chicken or egg” conundrum persists: Do abnormal microbiota elicit and sustain an inappropriate immune response in genetically susceptible hosts or do unrelenting inflammatory processes create a pathologic milieu that selects for abnormal microbial communities? Promising data from FMT studies in ulcerative colitis suggest that microbial alterations can induce remission in inflammatory bowel disease (IBD), raising the concern that unfavorable changes could also cause disease in other contexts. While there is a paucity of human data evaluating the risks of such unfavorable changes, animal studies suggest that in genetically predisposed germ-free mice, transfer of dysbiotic microbiota can induce terminal ileitis or colitis.

We report a novel case-series of patients who received FMT for recurrent Clostridium difficile infections from a donor who was later diagnosed with ileocolonic Crohn’s disease. Between August and December 2013, 31 patients received FMT by colonoscopy for treatment of non-responsive C. difficile from this single, unrelated, on-site donor at an academic center. The donor was a healthy, 28-year-old male with unremarkable medical history on no prescription medications or supplements. He was evaluated using the Full-Length Donor History Questionnaire (DHQ) and underwent blood and stool testing per the FMT Working Group guidelines. In January 2014, the donor developed bloody diarrhea with elevated fecal calprotectin of 614 μg/g and was diagnosed with moderately severe ileocolonic Crohn’s with discontinuous areas of ulceration in the terminal ileum and rectosigmoid colon on colonoscopy. He was initiated on adalimumab.

Among the 31 FMT recipients, 22 were females (mean age: 58 y ± 18.8) with a mean follow-up of 19.8 (range 9–24) months. Five patients had pre-existing IBD (3 ulcerative colitis, 2 Crohn’s disease) and 7 were immunocompromised (Table 1). All FMT recipients were followed closely clinically. Importantly, none of the recipients developed new clinical IBD sequela. Among the pre-existing IBD patients, 1 UC patient and 1 Crohn’s patient had significant improvement in clinical and endoscopic disease activity post-FMT, while 3 had unchanged IBD symptoms. Among the cohort, 4 patients died within 30 d of FMT due to other causes (N = 2), but none were IBD associated.
Stool sample was collected from the donor before his first donation and after the diagnosis of Crohn’s disease while already in clinical remission on adalimumab and from 10 recipients post-FMT. Stool composition was compared with that of 89 healthy controls, participants of the OpenBiome donor program. The V-4 region of the 16S rRNA gene was amplified from DNA extracted from the stool samples and sequenced using an Illumina MiSeq. The Shannon diversity index was computed for each sample and t-distributed stochastic neighbor embedding (t-SNE) was performed on the full data set to visualize differences in taxonomic composition. The microbial diversity of follow-up stool samples from the donor and FMT recipients was not significantly different than the diversity in healthy controls (p \text{D} 0.07, U \text{D} 283.0 Mann Whitney U-test) (Fig. 1). No significant clusters or differences could be detected by t-SNEs between the population of healthy controls and the FMT recipients (Fig. 2).

Despite exposure to the microbial community from an FMT donor that went on to develop Crohn’s disease, no observed clinical or microbiological signatures of IBD in this recipient population were detected. While this observation is somewhat reassuring, due to its small size and intrinsic methodological limitations, our study does not resolve the question of whether Crohn’s can be induced by microbial transfer in humans. The lack of pre-FMT stool samples from these patients limited our understanding of the specific strains that may have engrafted during FMT and whether FMT normalized their gut microbiome. However, this experience does highlight the importance of careful donor selection beyond clinical evaluation and stool testing for infectious organisms. When screening donors, we believe fecal calprotectin should be included into the laboratory testing panel with a cutoff of ≤ 40 µg/g for it is associated with ≤ 1% probability of having occult IBD.7 Notably, in the case of universal donors when multiple recipients will be exposed, it is particularly important. Moreover, when banking universal donor material, consideration should be given to quarantining before usage – as practiced by stool banks – to allow for identification of latent disease and to increase the safety of FMT.

**Disclosure of potential conflicts of interest**

Eliseo Papa, Mark Smith and Zain Kassam are consultants for Finch Therapeutics. Mark Smith and Zain Kassam are employees of OpenBiome.

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**Author contributions**

Monika Fischer conceived the study, contributed to data acquisition and analysis, drafted and edited the manuscript. Mohamad Bittar contributed to data acquisition and drafting.
of the manuscript. Eliseo Papa performed metagenomic data analysis of stool samples. Zain Kassam contributed to conception of the study, data analysis and editing of the manuscript. Mark Smith contributed to data analysis, drafting and editing the manuscript. All authors approved the final version of the manuscript. Informed consent was obtained for this case-series.

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