FMT in UC: Spotlight on Patients' E'motions'

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Thomas J. Borody has a pecuniary interest in the Centre for Digestive Diseases, where fecal microbiota transplantation is a treatment option for patients.

Jordana Campbell has no financial interest or affiliation with any institution, organization, or company relating to the manuscript.

No support or funding, including pharmaceutical and industry support, was received for work undertaken relating to the manuscript.

Keywords: Fecal Microbiota Transplantation, Ulcerative Colitis, Probiotics, Microbiome, Microbiota

The etiology of ulcerative colitis (UC) is unknown. However, evidence suggests that host-microbial interactions play an important role in the pathogenesis of colitis, contributing to longstanding inflammation. The gastrointestinal bacterial flora may also be an important factor in the maintenance of IBD, but exact mechanisms remain elusive. Fecal bacteriotherapy, now termed Fecal Microbiota Transplantation (FMT), has gained prominence in light of the recent epidemic of *Clostridium difficile* infection (CDI) in North America and Europe. Coupled with the emergence of a hypervirulent strain of *C. difficile,* FMT is likely to feature prominently in the treatment of both relapsing and fulminant *C. difficile* colitis. Given that FMT is capable of successfully reversing CDI-associated colitis and is arguably the most complete and ideal probiotic, one can see the potential value of FMT in other bacteria-mediated diseases such as idiopathic ulcerative colitis. Khan and colleagues from the University of Chicago Inflammatory Bowel Disease Centre reported their results from a recent qualitative study assessing patients' readiness for FMT in UC [1]. The premise of the study was to assess patients' attitudes and concerns towards FMT therapy as a potential treatment option for the UC community. Their questioning encompassed five broad areas in relation to FMT treatment including: patient's impressions of treatment, benefits, risks, potential mechanisms and social concerns. The overwhelming majority of patients not only expressed their interest in FMT as a treatment option, but expressed their desire that the treatment was already readily available. Interestingly parents of children with colitis expressed fewer reservations about FMT than adult subjects, with FMT described as 'more natural' and therefore perceived as 'easier and safer' than current therapies, specifically steroids and biologics. There is no doubt that IBD poses considerable treatment challenges for physicians and patients alike, with a dearth of more specific therapeutic options currently available. Our current repertoire of various immunomodulators and antibiotics relied upon to induce and maintain remission remains imperfect in both efficacy and the level of adverse effects experienced.

A variety of probiotic agents have been used in the treatment of ulcerative colitis with some definite, albeit minor, success [2]. However the marked heterogeneity amongst various trials has provided one obstacle to advocating their use in UC. In addition, current oral probiotic doses are typically three to four orders of magnitude lower than the 100 trillion native microorganisms contained within the colon, a number likely to be even further reduced following passage through the harsh environments of the stomach and small bowel. Considerable research has been directed towards elucidated probiotics' exact mechanisms of action, and it is now generally accepted that their therapeutic effects are due to a number of diverse mechanisms including: the secretion of bactericidal substances, competition with pathogens and toxins for intestinal epithelium adherence, regulation of immune responses, and regulation of intestinal epithelial homeostasis through promotion of intestinal epithelial cell survival, enhancement of barrier

function, and stimulation of protective responses. Given the complexity of probiotic function, it appears unlikely that any one probiotic organism has the capacity to accomplish more than a few of these functions independently, suggesting that a combination of probiotic strains is likely required to achieve optimal therapeutic benefit.

The rationale for the employment of FMT in ulcerative colitis dates back more than 50 years to reports of FMT success aimed not towards treating *C. difficile* infection, but rather pseudomembraneous enterocolitis [3-6], as *C. difficile* was not recognized as the established cause of this phenomenon until 1978. Hence, a related colitis subgroup of patients may benefit from FMT, those with idiopathic colitis and *C. difficile* superinfection. Our previous experience in this patient population [7] indicates that post-FMT these patients experience a gradual diminution in UC severity following eradication of CDI and exhibit an improved response to their IBD medications. The proportion that *C. difficile* contributes to the severity of the UC varies from patient to patient. Bennet *et al.* reported the first successful case for FMT in non-CDI ulcerative colitis in 1989, documenting reversal of his own colitis following large volume retention enemas of healthy donor flora [8]. Prior to FMT he reported continuously active, severe ulcerative colitis of seven years duration, and had difficulty reducing his prednisone dosage below 30mg/day without experiencing relapse. At three months post-FMT, histology revealed no active inflammation, remaining asymptomatic in the absence of therapy for the first time in 11 years. The Lancet letter was followed in 2003 by a report from our group which published the first documented cases of FMT in six UC patients without concurrent *C. difficile* infection [9]. This treatment departure from *C. difficile* colitis to *idiopathic ulcerative colitis* resulted in their long-term remission of idiopathic colitis. The first patient was treated in 1989 and remained in histological remission 13 years later. Other patients had similar responses of variable duration. This long-term histological, deep mucosal healing leads one to believe that a cure for UC is possible. The definition of ‘cure’ is still to be determined. Although the composition of the colonic flora in an individual is relatively stable and difficult to alter permanently and the mechanism remains unclear as to how the reversal takes place, we do know that various deficiencies of the resident microbiota can be corrected with implantation of healthy flora, best shown in patients with relapsing *C. difficile* [10-11] and that the implantation appears to be durable [12].

These reports pave the way for novel UC therapies aimed at altering or restoring the resident microbiota. Khan *et al.* opens the door to this novel therapeutic possibility by informing patients that there may be an opportunity to improve the management of their UC and to prepare patients for what might be otherwise considered a distasteful treatment. Given the early successes of FMT in UC, the rationale that Khan *et al.* are proposing in preparing UC patients for future FMT trials in colitis is strongly supported by case evidence. Adequately designed, randomized controlled trials of FMT in UC by clinics specializing in IBD are now needed to provide the answers to several important questions to optimize FMT in UC. In our experience and that of

many others, a single trans-colonoscopic, naso-gastric, or enema infusion of donor stool is typically sufficient to cure CDI colitis [11, 13-16]. It is our current clinical impression that whilst *C. difficile* is easily eradicated with a single FMT infusion, this appears to generally not be the case in UC. From our initial publication in 2003 reporting on the treatment of 6 UC patients with 5 FMT infusions [9], our subsequent unpublished experience is that multiple and recurrent infusions are required to achieve prolonged remission or 'cure'. This observation raises a number of key questions to be answered: Which type of colitis will be most suitable for treatment? What should be the frequency pattern and duration of infusions be? Are younger patients more likely to achieve healing or cure? What proportion will actually achieve cure? Will colonoscopic histological healing be the signal for ceasing infusions?

It is, in a sense, fortuitous that the current epidemic of *C. difficile* has led to the recent resurgence of FMT, facilitating the expansion of this therapy to patients with *C. difficile* infection and at times in CDI in UC. From here, it may be easier to extend FMT to patients with idiopathic colitis and could help to uncover the mechanisms underpinning UC causality. Whatever the causality, the use of 'wild type' probiotics in FMT appears to control inflammation and re-colonize deficient UC flora [12,18] not previously reported using cultured probiotics. The challenge now is to capitalize on these early observations and see whether FMT can be positioned as an adjunct therapy in UC to further improve our patients' quality of life. Khan *et al.* have demonstrated insight in their paper in predicting the potential expansion of CDI to UC. Although further consensus regarding treatment methodology needs to be established, it would seem timely to ask the opinions of the patient population re: FMT. It is this group for whom we often prescribe taxing therapies in the form of multiple medications, enemas, intravenous and subcutaneous infusions, and ultimately colectomy. The participants in this study agreed that the 'yuck factor', whilst initially present, did in no way alter their interest or willingness to try FMT, as they agreed that UC was inherently unpleasant and had altered their perceptions and willingness to consider unpleasant treatments in the aid of disease improvement. This study has allowed us to gain valuable insight into the minds and opinions of patients we so often make decisions for. From these findings it appears that the social and ethical issues surrounding FMT are well understood by the consumer UC population who welcome this therapy – The unanswered question posed – "Are we, the gastroenterologists as a group – ready for delivering the emerging FMT therapy"?

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