Digestive Diseases and Sciences (2020) 65:1107–1110
https://doi.org/10.1007/s10620-019-05831-z

COMMENTARY

Promise of Fecal Microbiota Transplantation Therapy in Pouchitis

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Published online: 16 September 2019

Although restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is an important surgical treatment for medically refractory ulcerative colitis, it is frequently complicated by pouchitis, a condition responsible for up to 8.5% of pouch failures [1]. Though pouchitis comprises a spectrum of heterogenous disorders with diverse risk factors, clinical presentations, and prognoses, pouch dysbiosis appears to underlie initiation and progression of most forms of the disease [2]. While conducting a comprehensive meta-analysis to evaluate the efficacy of fecal microbiota transplantation (FMT) in IBD subtypes, we reported clinical remission in 21.5% (5/23) of patients with pouchitis who underwent FMT [3]. These analyses, however, were descriptive since only three small cohort studies with differing infusion regimens, endpoints, and conflicting outcomes were identified at the time [4–6].

In this issue of *Digestive Diseases and Sciences*, Selvig et al. [7] report on the largest study of FMT therapy in pouchitis to date. While post-FMT Pouchitis Disease Activity Index (PDAI) scores were not available for all patients and some had PDAI scores ≤ 6 pre-FMT [7], the slight improvements in endoscopic and histological outcomes are supported by the only other pouchitis study reporting these data. Specifically, Stallman et al. reported endoscopic response in all patients ($n=5$) and endoscopic remission in one patient (20%) following FMT infusions ($n=1$–7 instillations) [6]. Selvig et al. [7] also report statistically significant improvement in bowel frequency, which was particularly evident in patients receiving rifaximin pre-FMT and a second FMT instillation. These observations align well with a recent report of severe diversion ileitis and pouchitis in a patient with a history of ulcerative pancolitis, in whom multiple autologous FMT infusions were required for successful treatment, leading to an increase in *Firmicutes* and decrease in *Proteobacteria* in the ileal pouch [8].

At present, with respect to FMT for pouchitis, there is a paucity of available data, a high degree of heterogeneity among studies, and lack of randomized controlled trials for either induction or maintenance (Table 1) [4–7, 9, 10]. Though the study by Selvig et al. [7] provides further patient data, clarity is still missing in many aspects. The use of antibiotics (rifaximin) pre-FMT in pouchitis is interesting, although its impact is unclear as only a small subset of patients received this treatment (7/19). Assessment of clinical efficacy is also limited by inconsistency in the number of FMT infusions provided. Of the eleven patients receiving two FMT infusions, six received rifaximin. The current literature strongly suggests that the use of antibiotics pre-FMT in UC patients assists in the engraftment of beneficial xenomicrobiota, improving clinical and histological responses [3, 11]. Indeed, a recent prospective randomized placebo-controlled double-blind FMT trial in patients with pouchitis was stopped prematurely due to low donor FMT engraftment [10]. Given that antibiotic therapy is the primary treatment modality in pouchitis, the use of antibiotics pre-FMT in this context is promising but only if an adequate selection of antibiotics, dosage, and length of therapy are ensured.

Profiling of the bacteriome showed that community-level differences were restricted to comparisons between donors and patients with pouchitis regardless of FMT, with donors showing higher phylogenetic diversity [7]. No shifts in patients' community profiles toward donor profiles were evident, unlike previous studies examining FMT in pouchitis [5, 6]. Selvig et al. [7] identified specific bacterial taxa

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Table 1 Cohorts and clinical trials on fecal microbiota transplantation therapy in pouchitis

Year	Author	Study type	Sample size	Severity	Donor	Pre-antibiotic	Route	Dosage	Fresh/frozen	Frequency (no. of infusions)	Clinical remission	Clinical response	Endoscopic outcomes	Histological outcomes	Follow Up
2015	Landy et al.	Cohort	8	Chronic pouchitis (PDAI > 7)	Unrelated and related	Antibiotic free for 2 weeks prior to FMT	Nasogastric	30 g stool in 50 mL saline	Fresh	Single	0	2/8 (25%) (PDAI drop ≥ 3)	NA	NA	4 weeks
2016	Fang et al.	Cohort	1	Chronic antibiotic refractory pouchitis (mPDAI 10; clinical mPDAI 6)	NA	Antibiotics ceased 48 h prior to FMT	Pouchoscopy	Stool diluted in 250 mL saline	Fresh	Single	1 (clinical PDAI 0)	–	NA	NA	6 months
2016	El-Nachef et al.	Cohort	9 (4 week data on 7)	NA	Unrelated	NA	Pouchoscopy	NA	Frozen	Single	NA	5/7 (71%) (global symptom improvement)	NA	NA	4 weeks
2016	Stallmach et al.	Cohort	5	Chronic antibiotic refractory pouchitis	Unrelated	Not part of FMT protocol. All patients failed ≥ 3 cycles of metronidazole and ciprofloxacin ± rifaximin	UGI (jejunum) via endoscopy	75 g stool in 200 mL saline	Fresh for initial; either frozen or fresh for subsequent infusions	1–7 (at 3–4-week intervals)	4/5 (80%)	5/5 (100%)	Endoscopic remission: 1/5 (20%); endoscopic response: 5/5 (100%); [based on endoscopy subscore on PDAI]	0 (histology subscore of 0 on PDAI)	3 months
2019	Herfarth et al.	Randomized clinical trial	6	Chronic antibiotic refractory pouchitis (mPDAI ≥ 5 and a history of ≥ 4 antibiotic therapies for pouchitis in the last 12 months)	Unrelated	Clinical remission was induced in all patients with antibiotic therapy, which was stopped at least 24 h before FMT	Endoscopic (eFMT) and oral encapsulated (oFMT)	eFMT: 12 g in 30 mL; oFMT: 6 G3 capsules gave a total of 4.2 g of stool	Frozen	eFMT: 2; oFMT: daily for 14 days	1/6 (17%) (clinical PDAI 1 and no need of antibiotics)	1/6 (17%)	NA	NA	16 weeks
2019	Selvig et al.	Clinical trial	19	Chronic pouchitis (prior endoscopic evaluation confirming inflammation of the pouch and > 4 weeks of pouch symptoms)	Unrelated	FMT + pretreatment with rifaximin ($n = 8$); FMT without antibiotics ($n = 11$)	Pouchoscopy	250 mL donor fecal suspension (25 g stool)	NA	Single or double	0	1/11 (9%) (among patients receiving double FMT; PDAI drop ≥ 3)	No robust changes (pre-FMT median PDAI endoscopy subscore = 4, post-FMT median PDAI endoscopy subscore = 3)	No robust changes (pre-FMT median PDAI histology subscore = 1, post-FMT median PDAI histology subscore = 1)	12 months

PDAI, pouchitis disease activity index; NA, not available; FMT, fecal microbiota transplantation; eFMT, endoscopic FMT; oFMT, oral encapsulated FMT

that differed in relative abundances across groups, the most robust differences being higher levels of anaerobic fermenters that produce short-chain fatty acids in the donors. Nevertheless, the authors did not report any changes in taxa abundances post-FMT. Interpretation of these microbial data is difficult due to the use of probiotics in 50% of patients ($n=9$) with no available information on dosage, frequency, and composition. While not much is known about the impact of concurrent use of probiotics on FMT, given that probiotics can modulate the microbiome, even more when following antibiotic therapy, it can be speculated that this will confound the microbial analysis.

While much attention has been paid to changes in the diversity of the pouch microbiome, microbial metabolite profiling may also provide insights into disease pathogenesis and treatment. In this context, restoration of secondary bile metabolism using ursodeoxycholic acid (UDCA) was successful in treating a case of recurrent *Clostridioides difficile* pouchitis [12]. Nonetheless, it remains unclear if this has direct relevance to pouchitis, as secondary bile acids inhibit *C. difficile* spore germination and are toxic to the vegetative forms of the bacteria [13]. Supporting the importance of microbial metabolism in the pouch is the observation that exclusion of the fecal stream and subsequent lack of nutrients generated by luminal bacteria contribute to diversion ileitis and pouchitis [14].

As with any pilot study, interpretation of the primary, secondary, and microbial outcomes in this study by Selvig et al. [7] should be done with caution. Since current data do not discount FMT as a potential treatment option in pouchitis, it is possible that multiple FMT infusions may be required for clinical, endoscopic, and histological improvement in these patients. The use of antibiotics prior to FMT may also be beneficial. This study by Selvig et al. [7] also highlights the importance of using endoscopic criteria at the time of enrollment in order to avoid including patients with non-inflammatory symptoms (e.g., irritable pouch syndrome). Further, collection of biological specimens must be consistent among patients and controls, inflammatory biomarkers must be taken pre- and post-FMT, and differences in concurrent treatments (e.g., corticosteroids and biologics) should be documented and assessed as potential confounding variables.

The aim now is to build on the current literature and conduct well-designed randomized controlled trials of FMT in pouchitis to resolve the many questions that remain. Such questions include: (1) What is the optimal dosing regimen (frequency and interval of infusions)? (2) What is the impact of anaerobic processing of FMT infusions? and (3) Similar to UC, are there any benefits if employing multi-donor/pooled infusions as well as preselecting donors according to microbial profiles? At the time of this writing, 22 clinical trials on pouchitis are registered in ClinicalTrials.gov, of which five studies assessing the efficacy and safety of FMT in pouchitis are active/recruiting/recently completed. These are early but promising days indeed.

Acknowledgments NCR is supported by a NHMRC Early Career Fellowship (APP1111461). NOK is supported by a Cancer Institute NSW Career Development Fellowship (15/CDF/1-11) and a UNSW Scientia Fellowship.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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