Fecal microbiota transplantation for ulcerative colitis—where to from here?

Thomas J. Borody, Annabel Clancy

Centre for Digestive Diseases, Five Dock, Sydney, NSW, Australia

Correspondence to: Dr. Annabel Clancy. Centre for Digestive Diseases, 1/229 Great North Rd., Five Dock, Sydney, NSW, Australia. Email: annabel.clancy@cdd.com.au.

Ulcerative colitis (UC) is one of several chronic inflammatory bowel diseases (IBD) characterised by intermittent exacerbations and remission of inflammation symptoms and the progressive development of complications over the course of the disease. Most current therapies focus on the suppression of inflammation, addressing the aberrant immune response aspect of UC. However, such inflammation-directed therapies are met with increasing concerns by both physicians and patients who do not perceive a long term solution in biologics but rather increased risk of serious infection, malignancy, high costs and significant loss of response (1).

There has been little hope of cure with immunosuppression, but treating an underlying infection in UC, championed by Ohkusa (2), has made that prospect more achievable—analogous to the story of the multifactorial peptic ulcer disease where a single factor required attention; *Helicobacter pylori* infection. While the aetiology and pathogenesis of IBD remains unclear the clinical observation that UC can respond to antibiotic treatment, combined with the documented differences in gut microbiota composition between patients with IBD and healthy controls supports a key role for the gut microbiota (3).

Fecal Microbiota Transplantation (FMT) is the process of introducing faecal material from a highly screened, healthy donor into an unwell recipient's gastrointestinal tract to restore the healthy homeostatic properties of the gut ecosystem and alleviate symptoms. For decades, it has been used in various forms and is currently the most effective treatment for recurrent *Clostridioides difficile*, with investigation into other disorders associated with an altered gut microbiota evolving. The most common methods of FMT administration involve liquefying donor stool in saline, filtering to remove solid components, and then infusing the contents either colonoscopically, via enema or less commonly through the upper gastrointestinal tract via nasojejunal tube. Colonoscopically delivered FMT has shown higher resolution of recurrent *Clostridioides difficile* compared to other delivery methods, however, enemas may be preferred as they are less costly, readily available and enable repeat administrations. More recently, encapsulated forms of FMT have been investigated. This less invasive method is more desirable for patients and holds promise for greater FMT availability (4).

Appropriate donor selection and screening is an essential component of FMT treatment to ensure patient safety (4) and potentially maximise clinical outcomes (super donor phenomena) (5). Current consensus guidelines focus on reducing the risk of potentially transmittable disease. The minimum recommended requirements for screening potential donors are outlined in *Table 1* and include medical history interview, blood and stool testing for infectious, gastrointestinal, metabolic and neurological diseases, as well as medications, which may impair gut microbiota composition. Regular re-testing and monitoring is also

Table 1 Summary of recommendations for stool donor screening [Adapted from Cammarota *et al.* 2017 (4)]

Screening phase	Key selection/exclusion criteria
Preliminary medical history interview	**Infectious disease** • History of, or known exposure to, HIV, HBV or HCV, syphilis, human T-lymphotropic virus I and II, malaria, trypanosomiasis, tuberculosis • Known systemic infection not controlled at the time of donation • Use of illegal drugs • Risky sexual behaviour (anonymous sexual contacts; sexual contacts with prostitutes, drug addicts, individuals with HIV, viral hepatitis, syphilis; work as prostitute; history of sexually transmittable disease) • Previous reception of tissue/organ transplant • Previous (<12 months) reception of blood products • Recent (<6 months) needle stick accident • Recent (<6 months) body tattoo, piercing, earring, acupuncture • Recent medical treatment in poorly hygienic conditions • Risk of transmission of diseases caused by prions • Recent parasitosis or infection from rotavirus, Giardia lamblia and other microbes with GI involvement • Recent (<6 months) travel in tropical countries, countries at high risk of communicable diseases or traveller's diarrhoea • Recent (<6 months) history of vaccination with a live attenuated virus, if there is a possible risk of transmission • Healthcare workers (to exclude the risk of transmission of multidrug-resistant organisms) • Individual working with animals (to exclude the risk of transmission of zoonotic infections) **Gastrointestinal disease** • History of IBS, IBD, functional chronic constipation, coeliac disease, other chronic GI disorders • History of chronic, systemic autoimmune disorders with GI involvement • History of, or high risk for, GI cancer or polyposis • Recent appearance of diarrhoea, hematochezia **Metabolic** • Overweight and obesity (body mass index >25) **Neurologic disease** • History of neurological/neurodegenerative disorders • History of psychiatric conditions **Medications** • Recent (<3 months) exposure to antibiotics, immunosuppressants, chemotherapy • Chronic therapy with proton pump inhibitors

Table 1 (*continued*)

Table 1 (*continued*)

Screening phase	Key selection/exclusion criteria
Blood testing	• Cytomegalovirus
	• Epstein-Barr virus
	• Hepatitis A
	• HBV
	• HCV
	• Hepatitis E virus
	• Syphilis
	• HIV-1 and HIV-2
	• Entamoeba histolytica
	• Complete blood cell count with differential
	• C-reactive protein and erythrocyte sedimentation rate
	• Albumin
	• Creatinine and electrolytes
	• Aminotransferases, bilirubin, gamma-glutamyltransferase, alkaline phosphatase
Stool testing	• Detection of Clostridium difficile
	• Detection of enteric pathogens, including Salmonella, Shigella
	• Campylobacter, Escherichia coli O157 H7, Yersinia, vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, Gram-negative multidrug-resistant bacteria
	• Norovirus
	• Antigens and/or acid-fast staining for Giardia lamblia and Criptosporidium parvum
	• Protozoa (including Blastocystis hominis) and helminths
	• Faecal occult blood testing

advised. Due to the stringent requirements, stool donor bank programmes are becoming increasingly in demand (4).

Case reports of prolonged, complete off-treatment remissions in UC following FMT (6-8), and colitis caused by *Clostridioides difficile* (9) being curable using (FMT), point to the need to address an infective cause for UC residing within the gut microbiota and to examine more closely the use of FMT as a treatment for UC. With our first case approximately 30 years ago remaining in remission off all UC treatment (7) and first reported cured UC in 1989 (6,8) FMT it is the only non-immunosuppressive and non-pharmacological treatment for what appears to be the cause of the disease. A recent landmark study, completed by our group, showed that FMT was associated with a four-fold improvement in the likelihood of achieving the combined primary endpoint of endoscopic response and steroid-free clinical remission in UC compared to placebo when given as a single colonoscopic infusion followed by an intensive regime of home-based enemas (10). Subsequent microbiome examination in these patients pointed to an association with *Fusobacterium*, *Sutterella*, and *E. coli* in those who failed to achieve remission (11), in line with Ohkusa antibiotic targeting of *Fusobacterium varium* (2).

In their recent study, "Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial" Costello and colleagues examined the efficacy of a one week treatment (consisting of three FMTs) in patients with active UC with either anaerobically prepared pooled donor stool (dFMT) or aerobically, autologous prepared stool (aFMT). The study demonstrated that patients receiving dFMT were more likely to have clinical and endoscopic response

at eight weeks. More specifically, steroid free remission was achieved in 12/38 (32%) of the dFMT group *vs.* 3/35 (9%) of the aFMT group (12).

These results are in line with previously reported randomised control trials and cohort studies of FMT treatment in UC, with 36% of UC patients achieving clinical remission reported in a recent systematic review and meta-analysis (13). In comparison, results from clinical trials of biological therapies provide response rates of up to 17%, although perhaps in more severe cases (6). Whilst current FMT results are encouraging, around 60% of patients do not achieve remission using current methods. Thus, as Costello and colleagues describe, establishing methods that enhance the clinical effect of FMT therapy is paramount (12). Kelly *et al.* (6) list further potential enhancements by combining FMT with immunomodulators and biologics.

The majority of colonic bacteria and archaea are extremely oxygen sensitive and are diminished when stool is processed under aerobic conditions. Thus, as hypothesised in this study, production under anaerobic conditions may assist in preserving viability of these oxygen-sensitive species (12) and has been recommended in the 2017 Consensus guidelines (4). Patients with UC, in previous studies, have been shown to require multiple FMT doses (up to 40) (10), to achieve similar remission rates to those of Costello *et al.* Thus, it is possible that the donor-derived anaerobes (which were shown to be maintained and associated with clinical response) may explain the similar clinical effect demonstrated with the lower frequency FMT dosing regimens (12). However, this study design provided comparison of not only anaerobically prepared *vs.* aerobically prepared stool, but also pooled homologous *vs.* autologous stool and this has affected clarity and interpretation.

Rossen *et al.* showed similar response rates (7/23, 30%), at 12 weeks, in patients with UC receiving two doses, of aerobically prepared donor stool, 3 weeks apart. This study did not achieve significance, due to the high placebo response (5/25, 20%) in the control group receiving autologous stool (14). Kelly *et al.* described a similar phenomena in the treatment of patients with recurrent *Clostridioides difficile* infection (CDI), with 15/24 (63%) of the control group receiving autologous stool achieving clinical cure (15). Thus, autologous stool may not be the best comparator, albeit for unclear reasons. Further studies comparing anaerobically prepared vs. aerobically prepared homologous donor stool would be required to better understand the clinical impact of anaerobic processing for UC treatment.

Pooled donor stool was found to possess the greatest microbial diversity, followed by individual donor stool, then autologous stool (12). Previous studies have shown positive outcomes using both pooled (10,16) and single donors (17). Currently, the use of pooled donor stool is thought to be advantageous in providing greater microbial diversity and thus greater chance of implantation (16). However, comparative studies of pooled vs. single donor FMT have yet to be conducted. Pooled donor stool also has the advantage of mitigating the "super-donor effect," in which individual donors may have a greater success in inducing remission than other donors (17). Characterised, rationalised donor selection has also been proposed as an alternative to donor pooling. However, a recent trial in recurrent hepatic encephalothapy, only achieved partial success (5). Thus, additional efforts to enhance engraftment may be required.

The use of antibiotics before treatment with FMT is hypothesized to improve the efficacy and engraftment of FMT by reducing the host's dysbiotic bacterial load, creating an ecological niche for donor microbiota engraftment. In CDI, the use of vancomycin before FMT is thought to increase success by reducing the burden of CDI in the gut and its use has been incorporated into international guidelines (4). The use of antibiotics as a therapeutic strategy in IBD has been assessed in cohort studies as well as multicentre trials showing improvement in fecal biomarkers, favourable changes in gut microbial composition as well as clinical and endoscopic response (18-24). In one study, targeting of *Fusobacterium* with a combination of amoxicillin, tetracycline and metronidazole led to development of prolonged remission of UC even after the cessation of therapy (2). Furthermore, a recent study from Japan has shown that combination antibiotics (fosfomycin, amoxycillin and metronidazole) in patients with UC prior to FMT leads to a clear reduction of pro-inflammatory bacteria as well as improved engraftment of the donor microbiome (25). Based on these findings, many of the more recent registered trials on Clinicaltrials.gov utilising FMT are now incorporating pre-treatment antibiotics.

Dietary fibre is a key candidate in facilitating changes in the gut microbiota. Fibres with fermentable characteristics are substrates for microbial populations in the colon, leading to the production of various metabolites. Dietary fibre interventions in healthy participants can influence bacterial abundance (26). Costello et al. is unique in its reporting of the dietary fibre intake of participants at baseline. Dietary fibre intake reported at baseline was well below the Australian recommendations of 25–30 g/day (27) for both groups (19 *vs.* 21 g for dFMT and aFMT respectively). Unfortunately, dietary fibre intake post-treatment nor the relationship

between dietary fibre intake and FMT outcomes were not reported in this study (12). A study by Wei *et al.* 2016 compared the outcomes of UC patients receiving FMT and a known prebiotic fibre (pectin) supplement or FMT alone. Their results suggested that supplementation with pectin delayed the loss of diversity of transplanted gut flora and enhanced the effects of the FMT (28). Further research is required to establish the role of dietary fibre and prebiotics as an adjunct therapy to FMT to prolong remission.

Costello and colleagues have provided further valuable data, to support designing future trials in this field. Given that FMT in patients with UC is effective in inducing clinical remission in approximately one-third of patients, further research to establish methods that enhance the clinical effect of FMT therapy is paramount. Consideration should be given to comparing the use of anaerobic *vs.* aerobic stool, identification of "super donors", antibiotic pre-treatment and adjunct dietary therapy, with the ultimate aim being lifelong remission in UC, which appears possible, as it has already been reported anecdotally.

Acknowledgments

None.

Footnote

Conflicts of Interest: Thomas J. Borody has a pecuniary interest in the Centre for Digestive Diseases and has filed patents in fecal microbiota therapies. He also holds a gratis advisory board position with Finch Therapeutics. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011;60:571-607.
2. Ohkusa T, Nomura T, Terai T, et al. Effectiveness of antibiotic combination therapy in patients with active ulcerative colitis: A randomized, controlled pilot trial with long-term follow-up. Scand J Gastroenterol 2005;40:1334-42.
3. Ni J, Wu GD, Albenberg L, et al. Gut microbiota and IBD: Causation or correlation? Nat Rev Gastroenterol Hepatol 2017;14:573-84.
4. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut 2017;66:569-80.
5. Wilson BC, Vatanen T, Cutfield WS, O'Sullivan JM. The Super-Donor Phenomenon in Fecal Microbiota Transplantation. Front Cell Infect Microbiol 2019;9:2.
6. Kelly CR, Ananthakrishnan AN. Manipulating the Microbiome With Fecal Transplantation to Treat Ulcerative Colitis. JAMA 2019;321:151-2.
7. Borody TJ, Campbell J. Fecal microbiota transplantation: techniques, applications, and issues. Gastroenterol Clin North Am 2012;41:781-803.
8. Bennet JD, Brinkman M. Treatment of ulcerative colitis by implantation of normal colonic flora. Lancet 1989;1:164.
9. Fordtran JS. Colitis due to clostridium difficle toxins: underdiagnosed, highly virulent and nosocomial. Proc (Bayl Univ med Cent) 2006;19:3-12.
10. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet 2017;389:1218-28.
11. Paramsothy S, Nielsen S, Kamm MA, et al. Specific Bacteria and Metabolites Associated With Response to Fecal Microbiota Transplantation in Patients With Ulcerative Colitis. Gastroenterology 2019;156:1440-54.e2.
12. Costello SP, Hughes PA, Waters O, et al. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. JAMA 2019;321:156-64.
13. Paramsothy S, Paramsothy R, Rubin DT, et al. Faecal Microbiota Transplantation for Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. J Crohns Colitis 2017;11:1180-99.
14. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. Gastroenterology 2015;149:110-8.e4.
15. Kelly CR, Khoruts A, Staley C, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial. Ann Intern Med 2016;165:609-16.
16. Jacob V, Crawford C, Cohen-Mekelburg S, et al. Single Delivery of High-Diversity Fecal Microbiota Preparation by Colonoscopy Is Safe and Effective in Increasing Microbial Diversity in Active Ulcerative Colitis. Inflamm

Bowel Dis 2017;23:903-11.

17. Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. Gastroenterology 2015;149:102-9.e6.

18. Borody TJ, Warren EF, Leis S, et al. Treatment of ulcerative colitis using fecal bacteriotherapy. J Clin Gastroenterol 2003;37:42-7.

19. Borody T, Wettstein A, Campbell J. Fecal microbiota transplantation in ulcerative colitis: Review of 24 years experience. Am J Gastroenterol 2012;107:S665.

20. Lorenzetti R, Prantera C. Rationale for the use of rifaximin in inflammatory bowel diseases based on clinical trial results. Clin Invest 2013;3:1187-93.

21. Turner D, Levine A, Kolho KL, et al. Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: a preliminary report. J Crohns Colitis 2014;8:1464-70.

22. Prantera C, Lochs H, Grimaldi M, et al. Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease. Gastroenterology 2012;142:473-81.e4.

23. Guslandi M. Rifaximin in the treatment of inflammatory bowel disease. World J Gastroenterol 2011;17:4643-6.

24. Perencevich M, Burakoff R. Use of antibiotics in the treatment of inflammatory bowel disease. Inflamm Bowel Dis 2006;12:651-64.

25. Ishikawa D, Takahashi M, Ito S, et al. P863 Eradication of dysbiotic indigenous species by multiple antibiotic pre-treatment contribute to effective faecal microbiota transplantation. J Crohns Colitis 2018;12:S553.

26. So D, Whelan K, Rossi M, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. Am J Clin Nutr 2018;107:965-83.

27. National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand including Recommended Dietary Intakes. Canberra, Australia; 2006.

28. Wei Y, Gong J, Zhu W, et al. Pectin enhances the effect of fecal microbiota transplantation in ulcerative colitis by delaying the loss of diversity of gut flora. BMC Microbiol 2016;16:255.