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Treatment of Ulcerative Colitis Using Fecal Bacteriotherapy

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Abstract

Background: Although the etiology of idiopathic ulcerative colitis (UC) remains poorly understood, the intestinal flora is suspected to play an important role. Specific, consistent abnormalities in flora composition peculiar to UC have not yet been described, however *Clostridium difficile* colitis has been cured by the infusion of human fecal flora into the colon. This approach may also be applicable to the treatment of UC on the basis of restoration of flora imbalances. **Goal:** To observe the clinical, colonoscopic and histologic effects of human probiotic infusions (HPI) in 6 selected patients with UC. **Case Reports:** Six patients (3 men and 3 women aged 25–53 years) with UC for less than 5 years were treated with HPI. All patients had suffered severe, recurrent symptoms and UC had been confirmed on colonoscopy and histology. Fecal flora donors were healthy adults who were extensively screened for parasites and bacterial pathogens. Patients were prepared with antibiotics and oral polyethylene glycol lavage. Fecal suspensions were administered as retention enemas within 10 minutes of preparation and the process repeated daily for 5 days. By 1 week post-HPI some symptoms of UC had improved. Complete reversal of symptoms was achieved in all patients by 4 months post-HPI, by which time all other UC medications had been ceased. At 1 to 13 years post-HPI and without any UC medication, there was no clinical, colonoscopic, or histologic evidence of UC in any patient. **Conclusions:** Colonic infusion of donor human intestinal flora can reverse UC in selected patients. These anecdotal results support the concept of abnormal bowel flora or even a specific, albeit unidentified, bacterial pathogen causing UC.

Key Words: bacteriotherapy, probiotics, inflammatory bowel disease, ulcerative colitis, intestinal flora

The use of human fecal flora to treat gastrointestinal (GI) disorders is not a novel concept, having been practiced periodically for more than 40 years.[1] Bacteriotherapy utilizing human feces has been reported to achieve success where antibiotics have failed. While the best known application of bacteriotherapy is in the treatment of unresponsive *Clostridium difficile* diarrhea and pseudomembranous colitis,[1–10] significant clinical improvements have also been reported in other GI conditions including constipation, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD).[3,6,11–14]

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Although the pathogenesis of ulcerative colitis (UC) is unclear, one hypothesis attributes the etiology and persistence of the inflammatory process to the intestinal flora.[15,16] Perhaps a viral, bacterial or chemical "trigger" invokes an overly aggressive host immune response that is perpetuated by the resident flora long after the initial infection has resolved.[17–19] Loss of tolerance to the normal luminal contents caused by abnormalities in mucosal permeability or a lack of regulatory cells/mediators is also thought to give rise to chronic inflammation in genetically susceptible individuals.[20,21] Given the complex composition of the intestinal flora, it is also feasible that the chronic recurrent inflammation associated with UC is the result of a persistent infection with a specific, but as yet unidentified, pathogen.[22,23]

The use of human fecal bacteriotherapy may have a role in the treatment of UC since it has consistently demonstrated efficacy against *C. difficile* colitis.[1–10] Furthermore, Bennet and Brinkman[11] reported prolonged remission of UC in the absence of *C. difficile* after the administration of a single fecal enema. With this in mind, we carried out fecal bacteriotherapy in 6 patients suffering longstanding idiopathic UC. Because human feces may be regarded as the ultimate probiotic mixture, the procedure itself was termed a human probiotic infusion (HPI). The results and long-term follow-up are compiled here as a series of 6 case reports.

MATERIALS AND METHODS

Fecal bacteriotherapy was performed in 6 patients (3 male, 3 female; aged 25–53). Because this was not a prospective, pre-set trial there were no distinct inclusion criteria. However, there were certain characteristics shared by all patients prior to receiving treatment. All patients had established UC for more than 5 years with active inflammation present at initial diagnosis on colonoscopy and histology. Stool culture and microscopy tests for each patient were negative for common detectable enteric pathogens including *C. difficile* and its toxins. All patients had failed maximum tolerated standard UC therapies or suffered partially controlled disease that readily relapsed on withdrawal of medication.

Patient pre-treatment characteristics and dose and duration of previous medications are detailed in Table 1. Previous medications for all patients included moderate to high-dose steroids and anti-inflammatory agents. Although these drugs were partly effective in reducing the severity of symptoms in 5 of 6 patients, the underlying disease remained active. When these medications were reduced or discontinued marked symptoms recurred. These patients were eager to avoid the use of long-term anti-inflammatory and

TABLE 1. *Patient pre-treatment characteristics and medications*

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age/sex	25/M	53/F	27/M	28/F	40/F	42/M
Duration of disease (years)	6	20	5	14	15	10
Disease site						
Rectum	+	+	+	+	+	+
Sigmoid colon	+	+	+	+	+	+
Descending colon	+	+	+	+	+	+
Transverse colon	+	–	–	+	+	+
Ascending colon	+	–	–	+	–	–
Histological evidence of active UC	+	+	+	+	+	+
Previous UC medications	P—25 mg/d S—3 g/d PE—20 mg/ml/d CP—30 mg/d	P—25 mg/d S—2 g/d PE—20 mg/ml/d M—600 mg/d	P—30–50 g/d A—200 mg/d ME—4–6 g/d O—3–4 g/d S—3 g/d V—1 g/d CY—? dose C—500 mg/d CF—100 mg/d E—800 mg/d R—300 mg/d	P—40 mg/d A—175 mg/d O—3 g/d MP—75 mg/d	P—25–40 mg/d A—200 mg/d ME—1.5 g/d O—3 g/d S—2 g/d M—>800 mg/d PE—20 mg/ml/d	P—25–50 g/d A—125 mg/d ME—1–2 g/d S—2 g/d
Concurrent medication at HPI (Dose duration prior to HPI)	P—25 mg/d S—1 g/d (28 mths)	S—2 g/d (12 mths)	P—30 g/d A—200 mg/d ME—6 g/d L—12 mg/d (5 mths)	P—40 mg/d O—3 g/d MP—75 mg/d (14 mths)	P—25 mg/d A—200 mg/d ME—1.5 g/d (7 mths)	P—25 mg/d A—125 mg/d ME—2 g/d (44 mths)
UC standard medication ceased	5 wks post-HPI	At HPI	4 wks post-HPI	6 wks post-HPI	6 wks post-HPI	6 wks post-HPI

A, azathioprine; C, clarithromycin; CF, clofazimine; CP, codeine phosphate; CY, cyclosporin; E, ethambutol; HPI, human probiotic infusion; L, loperamide hydrochloride; M, metronidazole; ME, mesalamine; MP, mercaptopurine; O, olsalazine; P, prednisone; PE, prednisolone sodium phosphate enema; R, rifabutin; S, salazopyrin.

immunosuppressive therapy and inquired about possible non-drug treatments. They were supplied with all available published material detailing the use of bacteriotherapy for GI disorders and subsequently gave written witnessed informed consent.

Available pre-treatment tests included full blood count (FBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function tests (LFTs), iron studies, colonoscopy and histology. Most parameters were reviewed at 4 months after HPI and then again at 1 to 2 years. In patients 1, 2, 3 and 4, parameters were measured again at 13, 12, 4 and 2 years respectively. All patients were reviewed to monitor clinical symptoms.

Selection of Donors

Patients were requested to nominate a suitable donor for HPI. Donors were required to be healthy adults with normal bowel function and no other ailments, having taken no antibiotics for at least 6 weeks. They were considered for selection if FBC and LFTs were within normal ranges and if viral screening was negative for HIV, hepatitis A, B, and C, cytomegalovirus, Epstein-Barr virus and syphilis. Donor fecal specimens were screened on selective media for common pathogens including *Salmonella, Shigella* and *Campylobacter* sp., *Aeromonas hydrophila, Yersinia* sp., *Vibrio parahaemolyticus, Vibrio cholerae*, *Candida albicans,* enterohaemorrhagic *E. coli* O157, and *Clostridium difficile* and its toxins. Microscopy was negative for protozoa (trophozoites and cysts), helminths and ova including *Entamoeba histolytica, Giardia lamblia*, *Cryptosporidium* sp., *Dientamoeba fragilis, Blastocystis hominis, Ascaris lumbricoides*, trematodes and tape worms.

Administration of Fecal Suspension

Prior to HPI, patients received antibiotics intended for the suppression of clostridia (vancomycin 500 mg bid, metronidazole 400 mg bid and rifampicin 150 mg bid for 7–10 days) followed by a single orthostatic lavage with 3 L of polyethylene glycol-based oral solution.

Donor feces (200–300 g) was diluted in 200 to 300 mL normal saline and administered to the patient via enema within 10 minutes of preparation. Patients were encouraged to retain the enema for as long as possible (at least 6–8 h). This process was repeated daily for 5 days. A high-fiber diet was advised in an attempt to stimulate proliferation of the infused bacteria. All anti-inflammatory therapy was withdrawn immediately post-HPI treatment in patient 2 and at 4 to 6 weeks in patients 1 and 3 to 6.

CASE REPORTS

Patient 1

A 25-year-old man presented with a 6-year history of UC. He had experienced frequent blood in stools, diarrhea (6–7 motions per day), abdominal pain, cramping, urgency, nausea, fevers, fatigue, and weight loss of 6 kg over 2 years. He had previously been treated with prednisone 25 mg/d, salazopyrin 3 g/d, codeine phos-

phate 30 mg/d, and nightly prednisolone sodium phosphate enemas, (see Table 1), but he refused azathioprine. A number of attempts to reduce steroid dosage resulted in recurrence of diarrhea and bleeding. Colonoscopy confirmed pancolitis with granular mucosa, contact bleeding, microulceration and histologically active chronic colitis. The patient had low serum iron and elevated alanine aminotransferase (ALT) levels, at times up to 10-fold above normal, together with elevated alkaline phosphatase (ALP) and g-glutamyl transpeptidase (GGT), presumed (no liver biopsy performed) to be due to associated sclerosing cholangitis.

Immediately preceding HPI, his symptoms were moderately controlled using prednisone 25 mg/d and salazopyrin 1 g/d. The patient was infused with bowel flora donated by his female partner via retention enemas. He ceased taking salazopyrin on the final day of infusion. Prednisone was withdrawn stepwise at a rate of 5 mg per week over 5 weeks. One week following HPI, his symptoms had improved markedly with an accompanying reduction in stool frequency and rectal bleeding. Four months post-HPI, he remained asymptomatic without treatment, defecating 2 to 3 times per day with no bleeding. The patient had not experienced a recurrence of symptoms since the infusion. Serum ALT, ALP, GGT and iron levels progressively returned to normal. He claimed markedly increased energy levels and regained weight. On his most recent review after 13 years follow-up without other therapy he had no clinical or colonoscopic evidence of UC and histopathology samples from several sites around the colon were normal.

Patient 2

This 53-year-old woman had a 20-year history of chronic UC, initially diagnosed at another institution. She had previously used salazopyrin, prednisone orally and steroid enemas in various combinations with inadequate follow-up. Treatment on review included prednisone 25 mg/d, metronidazole 200 mg tid together with salazopyrin 2 g/d which was subsequently self-administered with fluctuating doses (highest doses reached over the years remained unclear). On presentation, she complained of rectal bleeding and diarrhea (2–3 motions per day) with intermittent constipation, abdominal cramping, urgency, and flatulence. She preferred to self-treat, refused trial of azathioprine, and requested information on alternative therapies favoring the flora manipulation approach of Bennett and Brinkman.[11]

Prior to HPI and in symptomatic remission colonoscopy revealed patchy inflammatory changes indicative of ongoing IBD. Histology was consistent with UC of moderate-grade activity. HPI retention enemas were administered over 5 consecutive days. The fecal flora originated from an unrelated adult male donor. Salazopyrin, the only concurrent medication at that time, was ceased immediately and within days symptoms had improved markedly. At 4 months post-HPI, colonoscopy and histology showed no active and greatly reduced chronic inflammation. The patient had an entirely normal bowel habit consisting of 1 to 2 formed stools per day with no associated symptoms. At follow-up consultation 10 years later she continued to be asymptomatic. Twelve years post-HPI, there was no clinical or colonoscopic evidence of ulcerative colitis. Histology was negative for both active and chronic inflammation.

Patient 3

A 27-year-old male engineer presented with a 5-year history of severe UC symptoms including 10 to 15 bloody motions with mucus per day with intermittent abdominal pain, urgency, nausea, flatulence, and fatigue. These symptoms were particularly difficult to control on maximal standard available medications including high-dose steroids 50 mg/d, mesalamine 4 to 6 g/d, olsalazine 3 to 4 g/d, salazopyrin 3 g/d, azathioprine 200 mg/d, vancomycin 1 g/d and ultimately cyclosporine (dose unknown). An anti-mycobacterial combination of rifabutin (300 mg/d), clarithromycin (500 mg/d), clofazimine (100 mg/d), and ethambutol (800 mg/d) had also previously been administered on the basis of the possibility of *Mycobacterium avium* subspecies *paratuberculosis* involvement but was ceased due to fevers. In spite of these therapies, the patient was unable to reduce his daily prednisone dosage below 20 mg in conjunction with other drugs without symptom recurrence. Colonoscopy at this time confirmed gross active colitis with contact bleeding and histology typical of active chronic IBD. Blood tests revealed mild lymphopenia and neutrophilia.

Attempts to control symptoms with prednisone, azathioprine, mesalamine, and loperamide hydrochloride before HPI were unsuccessful. Despite the persistence of diarrhea and rectal bleeding, HPI was commenced using flora donated by the patient's brother and continued for 5 consecutive days. One week post-HPI, the patient noted decreased pain, urgency and bleeding. While still taking azathioprine and mesalamine, prednisone was reduced stepwise at a rate of 5 mg per week. One month after HPI, all medications were ceased. After 4 months, the patient was defecating twice daily with minimal blood and no urgency. He had gained 5 kg since the infusions and claimed profound improvement in symptoms and general health. One year post-HPI, the patient was asymptomatic and continued to require no medication, having 1 to 2 formed stools per day without bleeding or pain. After a 4-year follow-up period, he remained in complete clinical and colonoscopic remission with biopsies of the distal rectum showing minor architectural changes consistent with past chronic inflammation but without any active inflammation.

Patient 4

A 28-year-old woman presented with a 14-year history of UC including diarrhea with mucus and bleeding (3–5 motions per day), cramping, nausea, vomiting, sensation of fever at times, and fatigue. Despite therapy, severe symptoms recurred every few months, especially during times of stress. Intense inflammation was visible colonoscopically with active chronic inflammation on histology. Symptoms were partly controlled over several months on prednisone 40 mg/d, olsalazine 3 g/d, azathioprine 175 mg/d (above which thrombocytopenia developed), and later changed to mercaptopurine 75 mg/d.

Prior to HPI, prednisone was reduced to 20 mg/d at a rate of 5 mg/wk. HPI was administered using flora donated by the patient's brother-in-law over 5 consecutive days. Mercaptopurine was ceased immediately, while olsalazine was continued for a further 6 weeks. Immediate improvements included reduced bleeding, urgency, nausea, and vomiting, while abdominal cramping persisted for 1 week. The patient experienced 1 episode of bleeding 3 weeks post-HPI and the total withdrawal of prednisone was delayed until week 6. Two months following HPI, the patient was well, with no urgency or bleeding. Colonoscopy and histopathology was normal 1 year after HPI. At 2 years follow-up, she had had no more UC relapses despite episodes of stress and continued to be clinically, colonoscopically, and histologically disease-free without treatment.

Patient 5

A 40-year-old woman presented with a 15-year history of severe UC involving frequent episodes of diarrhea with rectal bleeding and mucus (>6 motions per day) with abdominal pain, arthralgia, anorexia, and weight loss. She was treated for over 2 years with prednisone 40 mg/d, azathioprine 200 mg/d, metroni-

dazole at times (max. 800 mg), prednisolone sodium phosphate enemas, and olsalazine 3 g/d combined with mesalamine 1.5 g/d or salazopyrin 2 g/d and reached good clinical control. At each review however, she desired to cease all medications. She attempted this periodically, but symptoms relapsed on withdrawal of treatment. Pre-HPI colonoscopy (see Fig. 1) showed intense colitis to mid-transverse colon with contact bleeding and histologically active and chronic inflammation consistent with UC. Using fecal flora donated by the patient's brother, HPI was administered via enema over 5 consecutive days. An improvement in symptoms was observed immediately and all concurrent standard medications (prednisone 25 mg/d, azathioprine 200 mg, and mesalamine 1.5 mg/d) were withdrawn over the next 6 weeks. Four months after HPI, the patient was defecating once a day with no bleeding, although abdominal discomfort and minor arthralgia persisted. This abdominal discomfort and arthralgia progressively recovered to normal over the course of 1 year, the patient's appetite improved and she was consequently able to gain weight. At 1 year following HPI, the patient was clinically disease-free without treatment and at colonoscopy inflammation was absent with the presence of some scarring (see Fig. 2). Histology showed no evidence of active or chronic UC.

Patient 6

A 42-year-old man had suffered severe, active UC for 10 years with diarrhea and rectal bleeding (4–5 motions per day) cramping, fatigue, and weight loss diagnosed and treated at another institution. Adequate control of his disease was reached using maximum tolerated therapies, including prednisone 50 mg/d, azathioprine 125 mg/d (adverse effects, including hair loss, with higher dose), mesalamine 1 to 2 g/d and salazopyrin 2 g/d, although he desired to use an alternate approach with few or no drugs. Colitis to mid-sigmoid was re-confirmed on colonoscopy and histology as active, chronic colitis.

Prior to HPI, prednisone was withdrawn step-wise to zero at 10 mg per week, while azathioprine and mesalamine were continued.

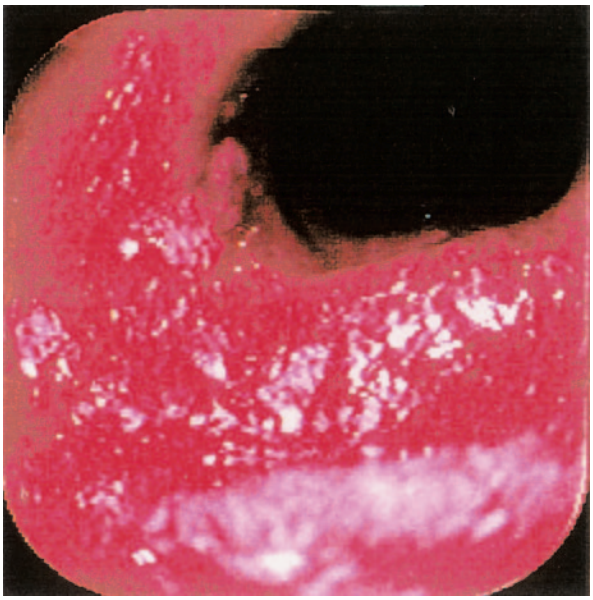

FIGURE 1. Patient 5, prior to HPI: Descending colon with intense UC visible on colonoscopy.

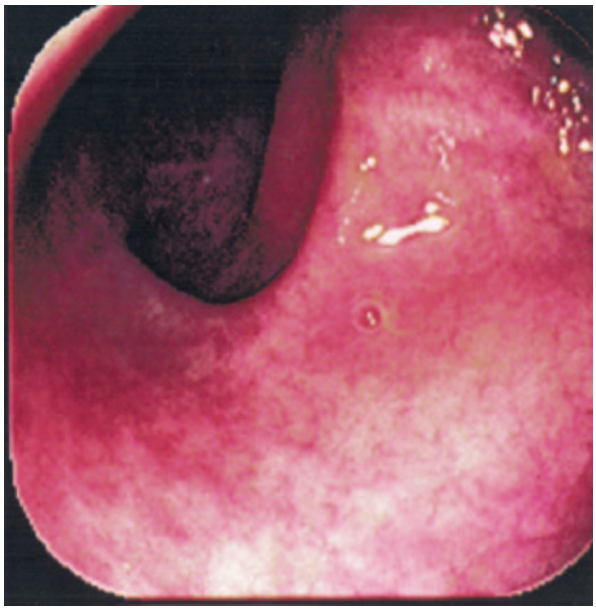

FIGURE 2. Patient 5, 1 year post-HPI: Normal mucosa with some scarring.

HPI consisted of 5 consecutive daily infusions and the use of his brother's fecal flora. Six weeks following HPI, symptoms had regressed to normal and all medications were ceased. At 6 months the patient's weight had increased by 4 kg. After 1 year without treatment normal bowel habit continued with 1 formed motion per day with no bleeding or urgency. Colonoscopy showed a normal bowel to the cecum with no evidence of colitis. Histopathology was negative for both active and chronic inflammation.

DISCUSSION

Although these are case reports several observations can be made. All patients had documented idiopathic UC with an absence of detectable infective agents. Complete reversal of UC was achieved in all 6 patients following the infusion of human fecal flora. All patients ceased anti-inflammatory therapy within 6 weeks and did not require further treatment during the extended follow-up period. After 1 to 13 years, patients remained asymptomatic with a healthy colonoscopic appearance and normal histology. Though there is little doubt that UC can go into clinical remission, chronic UC has not been known to spontaneously resolve both colonoscopically and histologically without relapse for up to 13 years, as observed here. To our knowledge, these 6 cases document for the first time the total disappearance of chronic UC without the need for maintenance treatment. This is an unprecedented finding that demands explanation through further research.

Our cases differ from the remissions commonly seen in clinical practice. Remission in UC is a term describing significant clinical improvement often measured by an activity index. There is currently no definition of remission that demands colonoscopic and histologic normality with no re-

currence after a prolonged period without medication. Perhaps in the future, if such a therapy can achieve prolonged absence of UC without maintenance drugs, the result should be considered a "cure".

Before postulating the therapeutic mechanism of fecal bacteriotherapy it should first be noted that the etiology of UC remains the topic of much conjecture. The pathogenesis of UC may involve the presence of an as yet undescribed pathogen.[22] Specific intestinal infections caused by *Salmonella*, *shigella*, *yersinia*, *Campylobacter*, *Entamoeba histolytica* and *Dientamoeba fragilis* often resemble those of UC.[24–28] Similarly, colonoscopic and histologic appearances of the bowel in idiopathic UC can at times mimic those present in acute infections.

Since UC is characterized by persistent inflammation, it is conceivable that the disease process is driven by a chronic infection aided perhaps by the absence of important luminal anaerobes constituting the colonization resistance of the bowel.[29] If the ability of the normal flora to resist colonization by pathogens is reduced, by previous antibiotic use for example, the numbers of protective anaerobes in the bowel, such as *Bacteroides* spp., decline. This would permit the implantation of other pathogenic anaerobes or spore-bearing bacteria and a form of recurrent, chronic colitis would ensue.

The chronicity of UC could be due to the implantation of spores in the mucosal surface, analogous to *Clostridium difficile* infection. Antibiotics may help transiently but are unlikely to be curative because the spores are not eradicated.[30] Fecal bacteriotherapy however is capable of curing *C. difficile* infection and the associated colitis.[8] Since a similar phenomenon has been observed here, it seems feasible to suggest that UC may also be sustained by a persistent gastrointestinal infection with some undiagnosed bacterium, perhaps invasive or spore-bearing, which is virtually impossible to eradicate with current antibiotics. Though no pathogen has been identified as the definitive cause of UC, some differences between normal and UC flora have been reported. Patients with UC are known to have abnormally elevated numbers of facultatively anaerobic bacteria.[31] Adhesive *Escherichia coli*[32] and more recently, invasive *Fusobacterium varium* have been nominated as possible UC pathogens.[23]

Assuming then that UC, in at least a proportion of patients, is the result of a chronic infection with a specific pathogen, fecal bacteriotherapy might aid in the reversal of the condition by reintroducing species that are capable of antagonizing the putative causal agent. This has been known to occur by competitive exclusion whereby the incoming microbes compete with the pathogen for either nutrients or epithelial adhesion sites[33] or by the production of metabolites that are inhibitory to the growth or adhesion of the pathogen.[34] Fecal bacteriotherapy may act through the re-establishment of essential anaerobes, restoring imbalances of composition and metabolism.[9,10]

The broad-spectrum antimicrobial activity of fecal flora is also thought to protect the bowel from invasive pathogens. A single study has examined the antimicrobial action of the complete fecal flora,[35] while its individual components, such as Group D streptococci, and certain strains of *Escherichia coli, Lactobacillus* and *Bifidobacterium* sp., have been shown to separately exert profound inhibitory effects against a range of pathogenic bacteria, including *C. difficile*.[36–40] In addition, some normal flora components produce bacteriocins that inhibit the growth of pathogens.[41]

It has been proposed that abnormalities in mucosal permeability may also give rise to UC by allowing inflammatory bacterial components to access the intestinal immune system.[16,21] Probiotics reintroduced to the bowel by fecal bacteriotherapy may act to enhance intestinal barrier function and down-regulate the production of pro-inflammatory cytokines.[42,43] Probiotics have also been suspected to alter the mucosal immune status through bacterial "priming" of gut-associated lymphoid tissue and by modulating gut-associated lymphoid and epithelial tissue response.[44–46] The ability of probiotics to improve the activity of intestinal macrophages and natural killer cells, incite the proliferation of lymphocytes, and increase sIgA production, could also be factors contributing to the success of bacteriotherapy.[47] Selected strains of probiotics are also able to modify mucosal and systemic immune function, including stimulating mucosal production of IL-10 and systemic Th-2 responses, leading to the readjustment of the Th-1/Th-2 mucosal balance.[45,48] Fecal bacteriotherapy may implant and propagate bacterial species that alter the immune balance within the mucosa resulting in the reversal of UC.

There exists only 1 previously published case of UC where symptoms improved by fecal bacteriotherapy.[11] It differed from our cases in that no colonoscopic or histologic evidence of UC disappearance was provided in the letter to the Lancet. Nevertheless, combined with our case reports, an argument could be made to support further research into the mechanisms of bacteriotherapy in UC especially since anecdotal reports have outlined the benefits of fecal flora infusions for other GI conditions, such as antibiotic-associated diarrhea, constipation, and IBS, without the demonstrated presence of specific etiological pathogens.[5,9,10,12–14]

The isolation of the hypothesized pathogen responsible for initiation and persistence of UC would enable future therapies to target a specific causal agent. Unfortunately, due to the complexity of the intestinal flora, complete analysis of the composition of flora and identification of putative UC pathogens remains problematic. Furthermore, complete analysis of donor feces was also not possible for donor specimens using conventional culture techniques. However, recent advances in molecular biology should progressively enable the identification and quantification of fecal bacterial

species in future studies, including pathogens, via polymerase chain reaction (PCR), and other nucleic-acid-based detection methods. In combination with randomized controlled trials against a putative causal agent, this avenue has potential to decipher the precise role of the luminal contents in the pathogenesis of UC.

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