Fecal Microbiota Transplantation
Techniques, Applications, and Issues

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KEYWORDS
• Fecal microbiota transplantation • Clostridium difficile • Ulcerative colitis
• Probiotics • Microbiome • Microbiota

KEY POINTS
• Fecal microbiota transplantation (FMT) is now arguably the most effective form of Clostridium difficile eradication, consistently achieving cure rates of greater than 90% in patients by numerous investigators.
• The therapy’s success in C difficile infection (CDI) colitis indicates the potential value of FMT in idiopathic ulcerative colitis (UC).
• The authors’ group treated the first UC patient in May 1988, which resulted in a durable clinical and histologic cure, suggesting a cure for UC is possible.
• It is the authors’ current clinical impression that although C difficile is easily eradicated with a single FMT infusion, multiple and recurrent infusions are required to achieve prolonged remission or cure in UC.
• Manipulation of the colonic microbiota represents an exciting therapeutic strategy in several conditions where the gut microbiota has been implicated, including UC, as well as previously unexpected applications, such as obesity, diabetes, and several neurologic disorders.

DESCRIPTION AND HISTORY OF FMT

FMT is the currently accepted term to describe the “infusion of a fecal suspension from a healthy individual into the gastrointestinal tract of an individual with colonic disease.”1–7 Although the notion of FMT is at first unpalatable and inconceivable to some, the concept has existed for many decades and has been used successfully
clinically. Historically, the first recorded case of enteric flora transplantation was described by the Italian anatomist, Fabricius Acquapendente, in the seventeenth century, when he reported, “I have heard of animals which lost the capacity to ruminate, which, when one puts into their mouth a portion of the materials from the mouth of another ruminant which that animal has already chewed, they immediately start chewing and recover their former health.” Since that time, transfaunation has been used in veterinary practice for cattle, horses, sheep, and various other animals suffering from rumination disorders and colitis. The first recorded use in humans dates back more than 50 years to its use for antibiotic-induced staphylococcal pseudomembranous colitis (PMC), where it resulted in rapid recovery of previously moribund patients. In the face of the rapidly worsening current CDI epidemic, this therapy has shown great promise as an inexpensive, safe, and highly efficient treatment for recurrent and refractory CDI, which achieves results current pharmaceuticals cannot achieve.

The first published case of FMT in humans was by Eiseman and colleagues in 1958, when they reported the successful treatment of 4 patients with severe PMC using fecal enemas. At the time, the investigators were unaware they were treating CDI because C. difficile was not recognized as a cause of PMC until 1978. Three of 4 patients were suffering with life-threatening fulminant PMC, which then carried a 75% mortality rate. The patients had failed all available therapies and in desperation the physicians resorted to fecal retention enemas, which resulted in prompt recovery of all patients and facilitated their discharge from hospital within days. At the time, the investigators expressed their hope that a “more complete evaluation of this simple therapeutic measure can be given further clinical trial by others.”

Since FMT’s first introduction into medical practice in 1958, more than 500 patients have been treated for CDI in 35 publications with a cumulative cure rate of 95%. The results are summarized in Table 2. At the authors’ center alone, approximately 100 patients have been treated for CDI, spanning 24 years.

**FMT BROUGHT INTO CLINICAL USE AFTER THE CDI EPIDEMIC**

Since 2000, there has been a steady increase in CDI rates in numerous health care facilities in the United States, Canada, and Europe, and CDI has reached epidemic proportions in the United States due in part to the emergence of the new hypervirulent toxigenic strains, such as the NAP1/BI/027 strain. This strain has increased toxins A and B production and high-level resistance to fluoroquinolones, secretes an additional binary toxin, and is associated with increased disease severity and worsening outcomes. It has been implicated in outbreaks of CDI worldwide and isolated from 82% of CDI cases during the 2001 to 2003 Quebec outbreaks, where hundreds of patients were infected and several deaths occurred, as well as the devastating outbreak in the Niagara, Ontario, area that caused more than 30 deaths in 2011.

An estimated 3 million new acute CDIs are diagnosed annually in the United States alone. Of these 3 million cases, up to 35%, or approximately 1.05 million patients, fail initial antibiotic treatment and experience a symptomatic relapse. Of this relapsing population, approximately 50% to 65% of patients go on to have multiple relapses (MR-CDI). More worrying is the subset of acute CDI patients who progress to severe CDI due to antibiotic nonresponse, particularly in the presence of the hypervirulent 027 strain and, from there, fulminant CDI (F-CDI), which is frequently fatal.

The rapidly changing epidemiology of CDI in recent years has largely caught the medical community off-guard, and the response has been generally ineffective. Strategies to counter this epidemic included discontinuing the inciting antibiotic and
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<th>Failed Therapies</th>
<th>Response to FMT</th>
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<tr>
<td>Case 1</td>
<td>Gastrectomy. Mixed antibiotic regimen postoperatively.</td>
<td>“Appeared to be in the terminal stages of his critical illness.” Abdominal distention, vomiting, bloody diarrhea, marked hypotension.</td>
<td>Vasopressors, hydrocortisone, fluid therapy, albamycin</td>
<td>1 d Post-FMT: marked improvement in condition, bloody diarrhea ceased.</td>
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<tr>
<td>Case 2</td>
<td>Subtotal gastrectomy. Achromycin postoperatively</td>
<td>“Desperately ill” with PMC. Frequent loose, mucoid, greenish bowel movements. On fourth postoperative day—“profound shock appeared moribund.”</td>
<td>Hydrocortisone, erythromycin, albamycin, lactobacillus</td>
<td>Diarrhea stopped within 48 h of FMT, “clinical response to fecal enemas was dramatic with disappearance of diarrhea.”</td>
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<tr>
<td>Case 3</td>
<td>Preoperative sulfasuxidine and neomycin. Postoperative achromycin, penicillin and streptomycin.</td>
<td>After left hemicolecotomy profuse watery diarrhea and fever.</td>
<td></td>
<td>48 h Post-FMT diarrhea completely ceased. Discharged 5 d later.</td>
</tr>
<tr>
<td>Case 4</td>
<td>Achromycin for sinusitis</td>
<td>Suddenly developed “severe and life-threatening” profuse watery and bloody diarrhea with fever.</td>
<td>IV fluid and electrolyte replacement. Intramuscular chloromycetin.</td>
<td>Within 24 h diarrhea had ceased. Patient made an “uneventful recovery.”</td>
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<tr>
<th>Study</th>
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<th>No. of Patients</th>
<th>Mode of Administration</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Eiseman et al, 1958</td>
<td>Severe PMC</td>
<td>4</td>
<td>Fecal enema</td>
<td>Dramatic resolution of PMC in all patients (100%)</td>
</tr>
<tr>
<td>Cutolo et al, 1959</td>
<td>PMC</td>
<td>1</td>
<td>Cantor tube, then fecal enema</td>
<td>Resolution</td>
</tr>
<tr>
<td>Fenton et al, 1974</td>
<td>PMC</td>
<td>1</td>
<td>Fecal enema</td>
<td>Symptom resolution within 24 h; sigmoidoscopy at 4 d revealed normal mucosa.</td>
</tr>
<tr>
<td>Bowden et al, 1981</td>
<td>PMC</td>
<td>16</td>
<td>Fecal enema (n = 15); enteric tube (n = 1)</td>
<td>Rapid/dramatic response in 13/20 (65%). 3/20 (15%) patients died; no PMC on autopsy in 2 the third patient had small-bowel PMC.</td>
</tr>
<tr>
<td>Schwan et al, 1984</td>
<td>Relapsing CDI</td>
<td>1</td>
<td>Fecal enema</td>
<td>Prompt/complete normalization of bowel function.</td>
</tr>
<tr>
<td>Tvede and Rask-Madsen, 1989</td>
<td>Relapsing CDI</td>
<td>6</td>
<td>Fecal enema</td>
<td>Prompt <em>C. difficile</em> eradication and symptom resolution. Normal bowel function within 24 h.</td>
</tr>
<tr>
<td>Flotterod and Hopen, 1991</td>
<td>Refractory CDI</td>
<td>1</td>
<td>Duodenal tube</td>
<td><em>C. difficile</em> eradication</td>
</tr>
<tr>
<td>Paterson et al, 1994</td>
<td>Chronic CDI</td>
<td>7</td>
<td>Colonoscope</td>
<td>Rapid symptom relief. Resolution in all (100%).</td>
</tr>
<tr>
<td>Harkonen, 1996</td>
<td>PMC</td>
<td>1</td>
<td>Colonoscope</td>
<td>Diarrhea ceased immediately and symptoms had not recurred by 8 mo post FMT.</td>
</tr>
<tr>
<td>Lund-Tonneson et al, 1998</td>
<td>CDI</td>
<td>18</td>
<td>Colonoscope (n = 17); gastrostoma (n = 1)</td>
<td>15/18 (83.3%) Clinically cured post-FMT without relapse.</td>
</tr>
<tr>
<td>Persky and Brandt, 2000</td>
<td>Recurrent CDI</td>
<td>1</td>
<td>Colonoscope</td>
<td>Immediate symptom resolution; <em>C. difficile</em> eradication persisted at 5-year follow-up.</td>
</tr>
<tr>
<td>Faust et al, 2002</td>
<td>Recurrent PMC</td>
<td>6</td>
<td>Unknown</td>
<td>All patients (100%) clinically cured postinfusion.</td>
</tr>
<tr>
<td>Aas et al, 2003</td>
<td>Recurrent <em>C. difficile</em> colitis</td>
<td>18</td>
<td>Nasogastric tube</td>
<td>15/18 (83.3%) Cured; 2 (11.1%) patients died of unrelated illnesses; 1 treatment failure (5.5%).</td>
</tr>
<tr>
<td>Borody et al, 2003</td>
<td>Chronic CDI</td>
<td>24</td>
<td>Colonoscope and/or rectal enema and/or nasojejunal tube</td>
<td>Eradicated CDI in 20/24 patients (83.3%) with negative toxins and stool culture.</td>
</tr>
<tr>
<td>Authors, Year</td>
<td>Type of CDI</td>
<td>Treatment</td>
<td>Number</td>
<td>Outcome</td>
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<tr>
<td>Jorup-Rönström et al, 2006</td>
<td>Recurrent CDI</td>
<td>Fecal enema</td>
<td>5</td>
<td>All (100%) patients clinically asymptomatic post-FMT.</td>
</tr>
<tr>
<td>Wettstein et al, 2007</td>
<td>Relapsing CDI</td>
<td>Colonoscopy (day 1), then enemas 5, 10, or 24 d.</td>
<td>16</td>
<td>Eradication of CDI in 15/16 pts (93.8%), confirmed via negative culture or toxin assay.</td>
</tr>
<tr>
<td>Louie et al, 2008</td>
<td>Relapsing CDI</td>
<td>Rectal catheter</td>
<td>45</td>
<td>CDI resolved in 43/45 (95.6%) patients.</td>
</tr>
<tr>
<td>Niewdorp et al, 2008</td>
<td>Recurrent CDI</td>
<td>Jejunal infusion via duodenal catheter</td>
<td>7 (2 of Whom with the 027 strain)</td>
<td>C difficile eradication in all patients (100%), confirmed via culture and/or toxin assay.</td>
</tr>
<tr>
<td>You et al, 2008</td>
<td>F-CDI</td>
<td>Fecal enema</td>
<td>1</td>
<td>Bowel function, BP, and leukocytosis normalized; oliguria resolved, and both vasopressin and venous hemofiltration were discontinued.</td>
</tr>
<tr>
<td>Hellemans et al, 2009</td>
<td>CDI</td>
<td>Colonoscopy</td>
<td>1</td>
<td>C difficile eradication</td>
</tr>
<tr>
<td>MacChonachie et al, 2009</td>
<td>Recurrent CDI</td>
<td>Nasogastric tube</td>
<td>15</td>
<td>13/15 (86.7%) Asymptomatic post-FMT.</td>
</tr>
<tr>
<td>Arkkila et al, 2010</td>
<td>Recurrent CDI</td>
<td>Colonoscopy</td>
<td>37 (11 of whom with the 027 strain)</td>
<td>C difficile eradication in 34/37(92%) patients.</td>
</tr>
<tr>
<td>Khoruts et al, 2010</td>
<td>Recurrent CDI</td>
<td>Colonoscopy</td>
<td>1</td>
<td>C difficile eradicated, confirmed via negative culture. Remained negative at 6-month follow-up.</td>
</tr>
<tr>
<td>Yoon and Brandt, 2010</td>
<td>Recurrent CDI/PMC</td>
<td>Colonoscopy</td>
<td>12, 2 of whom had PMC</td>
<td>12/12 (100%) Exhibited durable clinical response.</td>
</tr>
<tr>
<td>Rohlke et al, 2010</td>
<td>Recurrent CDI</td>
<td>Colonoscopy</td>
<td>19</td>
<td>18/19 (94.7%) Clinically asymptomatic between 6 mo and 5 y post-FMT.</td>
</tr>
<tr>
<td>Silverman et al, 2010</td>
<td>Chronic recurrent CDI</td>
<td>Low-volume fecal enema</td>
<td>7</td>
<td>All (100%) patients clinically asymptomatic.</td>
</tr>
<tr>
<td>Garborg et al, 2010</td>
<td>Recurrent CDI</td>
<td>Colonoscopy = 2; transduodenal = 38</td>
<td>40</td>
<td>Eradication of C difficile in 33/40 patients (82.5%).</td>
</tr>
<tr>
<td>Russel et al, 2010</td>
<td>Relapsing CDI</td>
<td>Nasogastric tube</td>
<td>1</td>
<td>Resolved diarrhea by 36 h. C difficile toxin negative.</td>
</tr>
<tr>
<td>Kelly and De Leon, 2010</td>
<td>Chronic, recurrent CDI</td>
<td>Colonoscopy</td>
<td>12</td>
<td>All (100%) patients exhibited clinical response.</td>
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<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Mellow and Kanatzar,37 2010</td>
<td>Recurrent and refractory CDI</td>
<td>13</td>
<td>Colonoscope</td>
<td>12/13 (92.3%) C difficile toxin negative with rapid resolution of diarrhea.</td>
</tr>
<tr>
<td>Kassam et al,38 2010</td>
<td>CDI</td>
<td>14</td>
<td>Fecal enema</td>
<td>All (100%) patients complete clinical resolution.</td>
</tr>
<tr>
<td>Kelly et al,39 2012</td>
<td>Relapsing CDI</td>
<td>26</td>
<td>Colonoscope</td>
<td>24/26 Cured of CDI with resolution of diarrhea.</td>
</tr>
<tr>
<td>Hamilton et al,40 2012</td>
<td>Recurrent CDI</td>
<td>43</td>
<td>Colonoscope</td>
<td>86% Eradication rate (37/43) by symptom resolution/negative PCR testing for CDI toxin.</td>
</tr>
<tr>
<td>Mattila et al,41 2012</td>
<td>Refractory CDI</td>
<td>70</td>
<td>Colonoscope</td>
<td>66/70 Recovered (94%) C difficile eradicated.</td>
</tr>
<tr>
<td>Brandt et al,42 2012</td>
<td>Recurrent CDI</td>
<td>77</td>
<td>Colonoscope</td>
<td>Primary cure rate of 91%. Secondary cure rate of 98%. Resolution of diarrhea in 74% of patients by day 3.</td>
</tr>
</tbody>
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**Abbreviation:** CDAD, C difficile-associated diarrhea.
restricting the use of high-risk antibiotics and use of specific antibiotic treatments once the etiology was known. These interventions, however, have failed to arrest the epidemic and, in retrospect, have not taken into account the pathophysiology of relapsing CDI. Despite CDI most commonly occurring after antibiotic exposure, first-line therapies rely heavily on antibiotics, such as vancomycin, metronidazole, and fidaxomicin, which fail to correct the underlying flora deficiencies. Once patients have failed first-line therapies, current CDI therapies lack a solution for the underlying bowel flora deficiencies driving the MR-CDI.

The inability of antibiotic-based measures to hinder the spread of infection suggests that unless drastic and novel therapeutic strategies are used that address the underlying microbiota defects, this epidemic will continue to spread unabated. The predictable consequences include rising morbidity, prolonged illness, greater risk of complications, and higher mortality rates. A crisis has been building in the past 2 decades due in part to the emerging epidemic strain and reducing efficacy of antibiotics, particularly in the face of the epidemic strains. Instead of predicting and preparing for this day by focusing on the cause, however, the medical community has continued to rely on antibiotics, incorporating new models, sophisticated combinations, and novel routes of administrations; reducing vancomycin protocols; and developing antitoxin antibodies. An alternative and more effective approach is to address the fundamental microbiota pathology—known since 1989. The industry is scrambling to develop new therapeutic strategies, such as toxin scavengers, immune stimulants, and newer antimicrobials, to counteract this epidemic rather than repairing the underlying microbiota defect. These therapies will unlikely be available for several years, leaving prescribing physicians limited in their choice of curative options while prolonging the duration of the epidemic. It is not hard to fully grasp this scenario, which demands focus and action to avert an ongoing global CDI health care crisis, the latest casualty being Australia with the start of its epidemic.

FMT offers the particularly attractive therapeutic solution of eradicating CDI through the re-establishment of normal intestinal flora composition via the implantation of missing fecal components provided from a healthy donor. Originally a last-ditch therapy for dying patients, the nearly 100% cure rates achieved in MR-CDI and F-CDI have driven institutions worldwide to adopt FMT earlier with an emphasis for FMT to become the first-line treatment option.

GUT MICROBIOTA—THE VIRTUAL ORGAN

The human gut microbiota is the term used to collectively describe the complex ecosystem of some $10^{14}$ bacterial cells housed within the gastrointestinal tract. Extensively more complex than previously believed, the number of microbial cells outnumber the human somatic cells by approximately 1 order of magnitude. Concurrently the microbiome, which is the collective genomes of the gut microbiota, outweighs the human genome by up to 2 orders of magnitude. Recent research has offered new insights into the microbial diversity of the gut microbiota, with the dominant organisms belonging to 7 main bacterial divisions (ie, Firmicutes, Bacteroides, Proteobacteria, Fusobacteria, Verrucomicrobia, Cyanobacteria, and Actinobacteria). Of these, Firmicutes and Bacteroides are the most abundant of the species, comprising approximately 70% of all gut bacteria.

Until recently, the function of the gut microbiota has been underestimated. Commonly believed a waste product of digestion destined for elimination, rarely was it considered an organ of microbial cells contained within humans with critical roles in immunity and energy metabolism—among other roles. With the development
of molecular-based metagenomics, metabolomics, and proteomics, various functions of the gastrointestinal microbiota are beginning to be unraveled. Several diverse functions can be ascribed to this microbial organ, summarized in 4 broad categories: (1) pathogen resistance and clearance, (2) immunomodulation, (3) control of epithelial cell proliferation and differentiation, and (4) nutrition and metabolism.

Constantly interfacing with the external environment, arguably one of the most important functions of the gut microbiota, is defense against invading pathogens. This occurs not only through competition for nutrients and adhesion sites, termed colonization resistance, but also through the production of bacteriocins and bacterial-derived immunomodulatory molecules. The intestinal microbiota has been identified as a rich source of protective probiotics, which produce novel antimicrobial and, more specifically, antipathogenic bacteriocins. Thuricin CD is a narrow-spectrum bacteriocin produced by Bacillus thuringiensis found to possess potent activity against C difficile. For the most part—similar to bacterially derived vancomycin—bacteriocins have a narrow spectrum of activity, inhibiting strains closely related to the producer. Some bacteriocins, however, such as nisin, possess a broad spectrum of inhibition, active against a vast array of gram-positive bacteria. In recent years, there has been a particular focus on bacteriocin-producing gut bacteria. Bacteriocin production is believed to provide strains with a competitive advantage within complex microbial environments as a consequence of their associated antimicrobial activity, enabling the establishment and prevalence of producing strains as well as directly inhibiting pathogens within the gut. The production of these antimicrobial peptides and associated intestinal producing strains is one likely mechanism contributing to FMT’s efficacy to beneficially influence the microbial communities of the gastrointestinal tract and facilitate durable implantation.

RATIONALE FOR FMT USE

Depletion in intestinal microbiota constituents, including Bacteroidetes and Firmicutes phyla, have been demonstrated in patients with initial or recurrent C difficile infection and seems to be associated, or perhaps causal, in several other conditions. The rationale behind FMT includes the reintroduction of a complete, stable community of gut microorganisms aimed at repairing or replacing the disrupted native microbiota to correct the underlying imbalance. It is presumed this microbiota repair eradicates or hinders pathogens, which may be causing the targeted condition (e.g., CDI). The current application of probiotics at best aims to alter the metabolic or immunologic activity of the residing native gut microbiota. A cultured single or few strains, which exist in low numbers and struggle to implant onto the bowel epithelium. FMT results in a durable, long-term implantation of donor flora. In one report by Khoruts and colleagues, transplantation of fecal microbiota from a healthy individual into a recipient with recurrent CDI resulted in resolution of symptoms and a fecal bacterial composition dominated by Bacteroides spp and an uncharacterized butyrate producing bacterium, which closely matched those of the healthy donor. Implantation of members of the Bifidobacterium genus, the Bacteroides and Clostridium coccoides groups, and the Clostridium leptum subgroup, has further been demonstrated after transplantation of donor stool for up to 24 weeks. These studies suggest that long-term restoration of the disrupted gut microbiota by fecal transplantation is achievable. Hence, FMT is likely not only to repair the depleted flora but also introduce species whose bacteriocins may eradicate susceptible pathogens with these antibiotic-like molecules and presumably restore the multiple functions of microbiota (enumerated previously).
FMT IN INFLAMMATORY BOWEL DISEASE

The central role of the gut microbiota in the pathogenesis of inflammatory bowel disease (IBD) is well established. Many studies have reported marked alterations in fecal and mucosal bacterial communities in IBD patients versus healthy controls, with several studies reporting a decreased abundance of dominant commensal members, such as Clostridium Ixa and IV groups, Bacteroides, and Bifidobacteria, and also a concomitant increase in detrimental bacteria, such as sulfate-reducing bacteria, Escherichia coli.66,67 Furthermore, some patients with Crohn disease have been shown to have reduced levels of Faecalibacterium prausnitzii in mucosa-associated microbiota.68 This microorganism—a prevalent Firmicutes species and an important butyrate producer—secretes metabolites that reduce proinflammatory cytokine production, such as interleukin (IL)-12 and interferon-γ; increases production of IL-10; and inhibits development of colitis in a mouse model. Qin and colleagues60 demonstrated low diversity in IBD, a feature of microbiota abnormality in UC and Crohn disease.

It is conceivable that an infective agent or agents could reduce diversity. Infection and inflammation have been shown to alter the composition of the intestinal microbiota in distinctive ways. Lupp and colleagues,69 in a murine model of enterohaemorrhagic E coli infection, showed that Citrobacter rodentium infection drastically reduced total numbers of colonic microbiota and extensively altered the composition of the indigenous microbiota. Similarly, Barman and colleagues,70 in a murine model of Salmonella typhimurium infection, reported a 95% decrease in total bacterial number in the cecum and large intestine of mice after S typhimurium infection (Borody TJ, Wettstein A, Torres M, et al, personal communication, 2011). In addition, alterations in microbiota composition preceded the onset of diarrhea, suggesting the involvement of pathogen-commensal interactions and/or host responses unrelated to diarrhea.

This article is not an exhaustive review of reported microbiota abnormalities in IBD; however, the balance has tipped in favor of the instrumental role that abnormal microbiota plays in IBD causality. This concept supersedes the older Podolsky theory, which stated, “Inflammatory bowel disease is thought to result from inappropriate and ongoing activation of the mucosal immune system driven by the presence of normal luminal flora.”71 An infectious cause has long been proposed for IBD but only recently has the complexity of the normal flora been better appreciated, which a realization of how difficult it would be to identify certain scarce pathogens among the enormous numbers of flora components. Known infective agents, such as a Campylobacter, Yersinia, and E coli, often result in a visible colitis, which heals after the causal bacterium departs the colon.72 CDI colitis also heals after successful eradication with FMT. This reversal of CDI colitis with FMT in part drove the authors’ FMT studies in idiopathic IBD. The rationale was that if C difficile can cause colitis and FMT can reverse it, a similar treatment should be applied to IBD. This seemed to work in some patients and the authors treated their first UC patient in 1988 with others soon following73 and detailed long-term follow-up in 6 cases reported in 2003.5 Today, approximately 23 years later, that first patient remains asymptomatic and in histologic remission. In January 1989, Bennet and Brinkman6 published a case of FMT in non-CDI UC, documenting reversal of Bennet’s own colitis after large-volume retention enemas of healthy donor flora 6 months prior. Before FMT, he reported continuously active, severe UC of 7 years’ duration. At 3 months post-FMT, however, the patient was asymptomatic in the absence of UC therapy for the first time in 11 years, with no active inflammation.

The marked success of FMT in UC in preliminary case reports was surprising and intriguing. Such remission and cure in several patients has rarely been reported with
current marketed therapies and lends further credence to an infective cause, disproving the previously accepted theory of an “aberrant reaction to normal colonic flora.”71 This may perhaps be one of the great breakthroughs in modern medicine and involves learning and accepting an entirely new concept involving a close co-existence with microbiota. If UC can be cured by infusing “normal colonic flora” from a healthy individual into the colon of a patient with UC, accepted etiologic dogma needs to be rethought and rejected. Unlike even recalcitrant CDI, however, in which a single shot of FMT is sufficient to eradicate the infection,58 the abnormal microbial communities in IBD—luminal as well as intramucosal74—are resistant to change, requiring not single, but recurrent, administration of scheduled infusions.2 It is this discovery of the need for repeated infusions of normal flora that reverses inflammation in most cases and in often medically unresponsive colitis (ulcerative and Crohn) and also gives insight into the mechanism of inflammation at the mucosal interface. Examples of representative cases of IBD reversal with FMT alone are shown in Figs. 1–5.

**Case 1**

A 21-year-old patient with a 10-year history of severe UC, uncontrolled with anti-inflammatory agents, steroids, antibiotics, and finally anti–tumor necrosis factor therapy underwent FMT. Pre-FMT symptoms included severe diarrhea with marked urgency and presence of blood and mucus. The patient underwent colonoscopy where the first FMT was administered. After this, daily rectal infusions were performed for 7 days followed by 26 weekly rectal infusions. The patient experienced an immediate reduction in symptoms, passing 2 formed stools daily without blood, urgency, or mucus. Follow-up colonoscopy at 12 months revealed virtually nil inflammation or edema and she remains clinically well at 12 months on no medication.

**Fig. 1.** (A) Pre-FMT: edema while on numerous combined therapies. (B) Pre-FMT: extensive psueopolyps.

**Fig. 2.** (A) Post-FMT: return to normal, uninflamed mucosa with return of vascular pattern. (B) Post-FMT: 1 pseudopolyp in another region.
Case 2

A 24-year-old man with a 5-year history of UC/Crohn disease, ultimately failing immuno-suppressants, antibiotics, and anti-tumor necrosis factor therapy, underwent FMT. Symptoms included anal fissures, severe abdominal pain, and bloody diarrhea up to 20 to 35 times daily, and colectomy had been advised. Patient commenced daily FMT rectal infusions for 2 months, followed by infusions of ever lessening frequency. One-week post-FMT, rectal bleeding had resolved, and diarrhea had ceased at 1 month. Follow-up colonoscopy revealed no inflammation with some residual pseudopolyps in the right colon.

Fig. 3. (A) Pre-FMT: severe luminal inflammatory changes initially. (B) Post-FMT.

Fig. 4. (A) Pre-FMT: some pseudopolyps in the ascending colon at 9 months. (B) Post-FMT: healed distal colon showing return of vasculature.

Case 3

A 54-year-old woman with 9 y history of refractory proctitis poorly responding to 5-aminosalicylate anti-inflammatory agents, antibiotics, acetarsol, and immunomodulators underwent 69 FMT infusions using her husband as her donor. She experienced rapid response within 10 days, progressive loss of bleeding, urgency, mucus, and diarrhea and she remains clinically, endoscopically, and histologically normal over 3 years without any therapy.
FMT—EMERGING APPLICATIONS

The current CDI epidemic, coupled with the burgeoning interest in the gut microbiota, has led to the recent resurgence of FMT as a powerful clinical therapy for CDI (Fig. 6). In a sense it is fortuitous that the CDI epidemic facilitated the use of FMT to other gastrointestinal conditions. Andrews and colleagues in the authors’ group treated 45 patients with chronic, severe constipation using FMT and reported a substantial improvement in 89% (40/45) of these patients, with improved defecation and resolution of bloating and abdominal pain. Of the 30 patients contacted at long-term follow-up (9–19 months), 18 (60%) continued to report normal defecation without laxative use. In a separate report of a constipated patient, both anorectal dysmotility and

Fig. 5. (A) Pre-FMT: figure rectal inflammation before FMT. (B) Post-FMT: normal mucosa in the rectum with no signs of protitis.

Fig. 6. Administration of FMT in syringes through the biopsy channel. FMT procedure. (Courtesy of The Centre for Digestive Diseases, Five Dock, New South Wales, Australia; with permission.)
deep pseudomelanosis coli were reversed after FMT. Borody and colleagues, in a case series of 55 patients with irritable bowel syndrome (IBS) and IBD treated with FMT, reported that 36% (20/55) patients were deemed cured post-FMT and 16% (9/55) patients reported a decrease in symptoms. Such clinical documentations open the door to a better understanding of the profound contribution abnormal microbiota plays in IBD and IBS and perhaps to channelling scarce funding into microbiota research both in the diagnostic and therapeutic fields.

There is also compelling evidence that the importance of the intestinal microbiota extends beyond the intestine. Several studies during the past decade have implicated the intestinal microbiota in the pathogenesis of several disorders, including obesity, diabetes, autism, myasthenia gravis, rheumatoid arthritis, and other conditions. The metabolic syndrome epidemic, associated with obesity and related health problems, is arguably the greatest single health care challenge in the industrialized world, rapidly spreading to encompass less developed nations. Energy metabolism is a well-recognized primary function of the gut microbiota. Differences in distal gut microbiota composition have been reported in human studies and mice models of obesity, with a shift in the ratio of Firmicutes and Bacteroidetes. Ley and colleagues, analyzing 5088 bacterial 16S rRNA gene sequences, reported that ob/ob animals have a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes. Turnbaugh and colleagues, transplanting lean and obese cecal microbiotas into germ-free wild-type mouse recipients, demonstrated that colonization of germ-free mice with an obese microbiota results in a significantly greater increase in total body fat than colonization with a lean microbiota and that this trait is transmissible. In 2010, Vrieze and colleagues reported the results of a double-blind, randomized controlled trial of FMT in 18 men with the metabolic syndrome. Fifty percent of patients received fecal material from lean male donors and the other 50% were implanted with their own feces as controls. Transplantation from lean donors resulted in a marked reduction of fasting triglyceride levels in patients with the metabolic syndrome. No effect was observed in the control group reinfusing their own feces. In addition, peripheral and hepatic insulin sensitivity markedly improved after 6 weeks in the lean donor group. This was again not observed in the control group. These findings suggest that intentional manipulation of community structure may be useful for regulating energy balance in obese individuals.

Along similar lines, the gut microbiota has been hypothesized as playing a role in the pathophysiology of eating disorders. Armougon and colleagues, analyzing the gut microbiota of individuals with anorexia nervosa, found increased levels of the methanogen Methanobrevibacter smithii in the anorexic patient population versus controls. At the authors’ clinic, 2 patients were treated with repeated home FMT for their IBS and coexisting anorexia nervosa, and both regained an interest in food and subsequently regained weight, one of them dramatically.

Several neurologic conditions have associated bowel dysfunction. Up to 80% of patients with Parkinson disease report constipation as an early symptom that can precede the onset of motor symptoms by up to 2 decades. In addition, men who experience less than 1 bowel movement daily have a 4-fold increase of developing Parkinson disease in later life. In 2009, the authors reported a 73-year-old man with chronic constipation who was treated with vancomycin, colchicine (Colgout), and metronidazole (Flagyl) for his constipation. His baseline motor symptoms included marked pillrolling hand tremor, micrographia, positive glabellar tap reflex, and cogwheel rigidity. When reviewed after 21 days on antibiotic treatment, he reported a marked improvement in his constipation symptoms, defecating daily with ease. Surprisingly, he also reported a marked improvement in his Parkinson disease
symptoms, with a visible decrease in tremor commencing 10 days into therapy. At 6 and 10 months on continuous therapy, he reported resolution of neurologic symptoms, including absence of persistent tremors and glabellar tap reflex, and he lost his cogwheel rigidity. The remarkable resolution of constipation coupled with neurologic near normalization with antibiotics, one of which is not absorbed, suggest that the gut microbiota is involved in the pathogenesis of this disease. Braak and colleagues\(^87\) postulated this from histopathologic data and suggested a microbial origin arising in the gut with brain pathology developing later.

This gut-brain connection is also clear in a case of a 28-year-old woman with myoclonic dystonia and long-standing diarrhea.\(^88\) The movement disorder began at the same time as the diarrhea, at age 6, and progressed in severity until age 18, when they plateaued. Predominant neurologic symptoms consisted of tremors of the hands, arms, and neck and muscle spasms, including severe writers cramps, all associated with worsening diarrhea. Consultation with several neurologists confirmed the diagnosis of myoclonic dystonia. Gastrointestinal symptoms included frequent diarrhea with daily loose motions (up to 10 per day), bloating, flatulence, and fatigue. Treatment of a presumed pathogen was initiated with vancomycin, rifaximin and metronidazole (Flagyl) for her diarrheal symptoms, which resulted in rapid improvement in diarrhea and gradual but then profound improvement in her movement disorder of 90% to where she could write continuously in excess of 5 minutes, carry mugs of coffee, and eat with a fork. At baseline, the patient could not write for more than 30 seconds, could not hold cups without dropping them, and could not use a knife and fork due to her symptoms.

Other gut-brain influence examples include the virtually complete and prolonged (>15 years) normalization of previously documented severe multiple sclerosis (MS) symptoms in 3 patients who underwent FMT for constipation.\(^3\) Such exceptional observations point to the potential role of the gut microbiota in promoting the pathologic inflammation that underlies MS. Using a mouse model of MS, Mazmanian and colleagues\(^89\) showed that the presence of segmented filamentous bacteria in the gut plays a central role in the development of experimental autoimmune encephalomyelitis through induction of Th17 cells and consequential IL-17 production in the gut and spinal cord. The association of elevated levels of IL-17 with MS is well established. Targeting the source of the autoimmune response (gut microbes) rather than the end result (elevated levels of IL-17) may be a valid approach to treating some cases of MS.

Several studies have described increased prevalence of gastrointestinal dysfunction and histologic changes in the gastrointestinal tract of autistic children versus healthy controls, with overgrowth of certain bacterial species or other changes in the gut microbiota frequently reported.\(^90,91\) In 1971, Goodwin and colleagues\(^92\) were among the first to make this observation, reporting on 15 autistic patients, 6 of whom had bulky, odorous, loose, or diarrheal stools. Horvath and Perman\(^93\) confirmed these findings in 2002 when they revealed a high prevalence of gastrointestinal dysfunction in 412 autistic children surveyed over a 6-year period from 1996 to 2002. The results reported that 84.1% of autistic patients had at least 1 gastrointestinal symptom comprising diarrhea, constipation, foul-smelling stools, abdominal discomfort, bloating, belching, or reflux versus only 31.2% of healthy siblings (\(P<.0001\)). Valicenti-McDermott and colleagues,\(^94\) comparing the prevalence of gut symptoms in autistic children versus developmentally disabled children and those with normal development in a cross-sectional study, found a history of gastrointestinal symptoms in 70% of children with ASD compared with 28% of children with typical development (\(P<.001\)) and 42% of children with DD.
Alterations in gut *Clostridium* species are commonly detected in autism. Finegold and colleagues, comparing fecal flora from children with regressive autism versus controls, found significantly higher *Clostridial* counts in autistic group. Additionally, the number of *Clostridial* species was much greater in the autistic group versus controls. Furthermore, 9 species of *Clostridium* were found in autistic children that were not found in controls. In a later study, Song and colleagues found statistically significant cell count differences between autistic and control children for *C. boletae* and clusters I and XI of the *Clostridium* groups. Mean counts of *C. boletae* and clusters I and XI in autistic children were 46-fold (P = .01), 9-fold (P = .014), and 3.5-fold (P = .004) greater than those in control children, respectively.

Parracho and colleagues surveying 58 ASD children and healthy controls not only found an overwhelming prevalence of gastrointestinal disorders in autism (91.4% vs 25% in siblings and 0% in unrelated healthy children (P < .05)) but also markedly increased levels of *C. histolyticum* in the ASD groups compared with healthy unrelated children and healthy siblings (P < .01 and P < .05, respectively). In another study, Finegold’s group detected *Desulfovibrio* bacteria specifically in the autistic group but not in the control group also susceptible to vancomycin. If *Clostridia* and *Desulfovibrio* contribute etiologically, treatment with oral vancomycin, which targets both species and has poor systemic absorption, should lead to significant improvement in these patients. This was the case when Sandler and colleagues treating a 4.5-year-old boy with autism and chronic diarrhea with vancomycin, reported dramatic results. The child had displayed normal motor, cognitive, and social development until the age of 18 months, when he received recurrent antibiotic treatments for otitis media and subsequently developed diarrhea with gradual decline in motor cognitive and social development. A 12-week therapeutic trial of vancomycin (125 mg 4 times per day) was initiated, which resulted in a rapid and significant clinical improvement. The child became affectionate and calm and promptly achieved toilet training and increased vocabulary. Follow-up behavioral assessments revealed an increase in on-task performance, compliance, and parental requests; awareness of environmental surrounds; and persistence when engaging in positive activities. After discontinuation of vancomycin therapy, behavioral deterioration was observed and although still improved over baseline, he eventually lost most of the gains. A follow-up study of 10 autistic children treated with oral vancomycin resulted in a short-term benefit in 8 of 10 patients. Efficacy was largely lost, however, after stopping vancomycin.

For many years, we have highlighted the brain-gut axis, especially in relation to functional bowel disorders, but much of this work has previously been focused on a top-down approach. New work involving the gut microbiota indicate that this communication network is bidirectional and that events occurring in the gut microbiota, not just the gut enteric nervous system, also can have an impact on the function of the central nervous system (CNS). Research has shown that this communication likely occurs via the vagus nerve. Examples include work by Bravo and colleagues, who demonstrated that *Lactobacillus rhamnosus* can modulate behavior and CNS biochemistry in healthy mice via the vagus nerve. Similarly McLean and colleagues previously showed that *Bifidobacterium longum* (BI NCC3001) normalizes behavior and CNS biochemistry in mice with mild colitis, also mediated via the vagus nerve. Several pathogens, however, also exploit this link. The vagus nerve provides the route of ascent to the CNS for transporting tetanus neurotoxin. Prion infections (including Creutzfeldt-Jakob disease in humans, bovine spongiform encephalopathy in cattle, and scrapie in sheep) use the enteric and peripheral nervous system to reach their ultimate target of the central nervous system. The new concept should also include gut
<table>
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<tr>
<th>Absolute Exclusion Criteria</th>
<th>Relative Exclusion Criteria</th>
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<tr>
<td>Risk of infectious agent&lt;sup&gt;a&lt;/sup&gt;</td>
<td>History of major gastrointestinal surgery (eg, gastric bypass)</td>
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<tr>
<td>Known HIV, hepatitis B or C infections</td>
<td>Metabolic syndrome</td>
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<tr>
<td>Known exposure to HIV or viral hepatitis within the previous 12 mo</td>
<td>Systemic autoimmunity (eg, MS, connective tissue disease)</td>
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<td>High-risk sexual behaviors (eg, sexual contact with anyone with HIV/acquired immune</td>
<td>Atopic diseases, including asthma and eczema, eosinophilic disorders of the gastrointestinal tract</td>
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<td>deficiency syndrome or hepatitis; men who have sex with men; prostitution for drugs or</td>
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<td>money)</td>
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<tr>
<td>Use of illicit drugs</td>
<td>Chronic pain syndromes (eg, chronic fatigue syndrome, fibromyalgia)</td>
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<tr>
<td>Tattoo or body piercing within 6 mo</td>
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<td>Incarceration or history of incarceration</td>
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<tr>
<td>Known current communicable disease (eg, upper respiratory tract infection)</td>
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<tr>
<td>Risk factors for variant Creutzfeldt-Jacob disease</td>
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<tr>
<td>Travel within the last 6 mo to areas of the world where diarrheal illnesses are endemic</td>
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<td>or risk of traveler's diarrhea is high</td>
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<tr>
<td>1. Gastrointestinal comorbidities</td>
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<td>a. History of IBD</td>
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<td>b. History of IBD, idiopathic chronic constipation or chronic diarrhea</td>
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<tr>
<td>c. History of gastrointestinal malignancy or known polyposis</td>
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<tr>
<td>2. Factors that can or do affect the composition of the intestinal microbiota</td>
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<tr>
<td>a. Antibiotics within the preceding 3 mo</td>
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<tr>
<td>b. Major immunosuppressive medication (calcineurin inhibitors, exogenous glucocorticosteroids, biologic agents, and so forth)</td>
<td></td>
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<tr>
<td>c. Systemic antineoplastic agents</td>
<td></td>
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<td>3. Additional recipient considerations</td>
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<tr>
<td>a. Recent ingestion of a potential allergen (eg, nuts) where recipient has a known</td>
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<td>allergy to this/these agent(s).</td>
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<sup>a</sup> May be appropriate to consider.

microbiota-brain axis but in the reverse direction. Hence, bacterially mediated autism is an example of such a mechanism.

Circulating antigen uptake from the bowel microbiota may explain the mechanism of ongoing autoimmune-like syndrome, as in an index case of idiopathic thrombocytopenia. The authors reported prolonged remission of idiopathic thrombocytopenia after FMT targeting UC and near-complete and prolonged (>15 years) normalization of previously severe MS symptoms in 3 patients who underwent FMT for constipation. Often marked improvement in chronic fatigue syndrome using FMT in 34 patients for IBS symptoms may point to a similar mechanism. These serendipitous results after FMT in extraintestinal conditions not previously considered to originate in gut microbiota may be pointing to studying the gut flora to uncover the underlying pathogenesis of these disorders and likely others.

HOW IS FMT CURRENTLY PERFORMED?

Recently, a group of international infectious disease and gastroenterology specialists published formal practice guidelines for performing FMT, outlining the rationale, methods, and indications of FMT, including screening procedures (see Table 1), material preparation, FMT administration, and other practical pointers. The investigators advise using the American Association of Blood Banks Donor History Questionnaire to screen potential donors in addition to the screening procedures listed in Table 3.

The infusate is prepared by homogenizing stool with a diluent, such as preservative-free normal saline, in a dedicated conventional household blender until the mixture reaches a liquid slurry consistency. The mixture is then filtered to remove particulate matter. Depending on the route of delivery, the slurry can then be poured into enema bags for rectal administration or drawn up into syringes for administration through the biopsy channel of the colonoscope. Methods used to administer FMT have included fecal suspensions via nasogastric and nasoduodenal tubes, through the colonoscope, or as a retention enema. No clear superiority of one method over another has yet been demonstrated. The selection of delivery method is up to the discretion of the infectious diseases specialist or the gastroenterologist and may vary with the needs and status of individual patients.

Universal precautions should be used when preparing FMT infusate, including a hood, if possible, because stool is a level 2 biohazard. Those involved with mixing and/or handling the fecal material should wear a fluid-resistant gown, gloves, and mask with goggles or eye shield. Stool should be administered as soon as possible after passage but within 24 hours and preferably within 6 hours.

HOW WILL FMT BE PERFORMED IN THE FUTURE?

As FMT development moves forward, in the foreseeable future, the authors envision the task being best conducted by a few centralized facilities, capable of filtering and processing the donor material and shipping it to individual providers in frozen, and ultimately in a lyophilized, form as powder for various ways of administration, including encapsulated form. This form of FMT can be used in carriers, such as yogurt or favored beverages, for administration to children or in a capsule for longer treatment in IBD or IBS.

SUMMARY

In summary, use of FMT in various conditions has opened the door to better understand the contributing mechanisms of previously idiopathic diseases. If some of the major diseases, such as the metabolic syndrome, IBD, and some neurologic and
perhaps autoimmune conditions, are causally linked to disordered microbiota, FMT in its various delivery forms can be anticipated to have a role in therapeutic gut microbiota restoration with far-reaching effects on a society-wide scale.

REFERENCES


