Fecal microbiota transplantation: a new standard treatment option for *Clostridium difficile* infection

Thomas J Borody

Author for correspondence: Centre for Digestive Diseases, Sydney, NSW 2046, Australia Tel.: +61 297 134 011 Fax: +61 297 121 675 thomas.borody@cdd.com.au

Lawrence J Brandt

Albert Einstein College of Medicine, Bronx NY 10461 USA; Emeritus Chief of Gastroenterology, Montefiore Medical Center, Bronx, NY 10467, USA

Sudarshan Paramsothy

St Vincent's Hospital Clinical School, Darlinghurst, NSW 2010, Australia

Gaurav Agrawal

Centre for Digestive Diseases, Sydney, NSW 2046, Australia

> **"…the most rational therapy for *Clostridium difficile* infection in patients with a relapsing or refractory pattern of infection is the restoration of antibiotic-damaged microbiota."**

The last 20 years have seen a progressive increase in the global incidence and severity of *Clostridium difficile* infection (CDI), particularly in North America and Europe. This increase has been accompanied by the identification and increased prevalence of new, hypervirulent toxigenic strains such as NAP1/BI/027 [1], which in the USA alone is responsible for worsened outcomes and a mortality reaching some 300 deaths per day from 3 million new cases annually [2]. It is within the context of the CDI epidemic that fecal microbiota transplantation (FMT) has gained acceptance as the most effective therapy for CDI [3].

This editorial makes the case that the

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most rational therapy for CDI in patients with a relapsing or refractory pattern of infection is the restoration of antibiotic-damaged microbiota rather than pharmacologic therapy.

CDI pathogenesis

Risk factors for developing CDI include advanced age, proton-pump inhibitor therapy, serious underlying diseases, for example, inflammatory bowel disease and cirrhosis, and contact with infected patients, staff and surfaces, for example,

during extended hospitalization or institutionalization in a nursing home [4]. The key factor remains recurrent use of antibiotics, especially broad-spectrum agents.

Antibiotic use over the past 60 years has led to significant inadvertent damage to the human enteric microbiome, an extraordinarily complex composition of highly concentrated and diverse microorganisms that serves as a major defense against gastrointestinal infections. In relapsing CDI, distinct abnormalities have been noted in the microfloral composition including the reduction or absence of members of *Bacteroidetes* and *Firmicutes* phyla [5,6]. Loss of normal gastrointestinal microbiota volume and diversity appears to be the root cause of CDI.

Current therapies for CDI

First-line therapy for CDI is traditionally either oral metronidazole or vancomycin for 10–14 days. After relapse, a longer tapered or pulsed course of vancomycin is often employed. Alternative antibiotics include fidaxomicin, rifaximin, nitazoxanide, tigecycline, teicoplanin and the ansamycins. A recent (prefidaxomicin) Cochrane review and meta-analysis found no single antibiotic clearly superior to others in the treatment of CDI, although teicoplanin and vancomycin were among the best [7]. Other treatment options that have been explored include antibiotic

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enema with vancomycin, along with adjunctive use of intravenous monoclonal antibodies against *C. difficile* toxins A and B.

Rationale for use of FMT versus pharmacologic therapies

While anti-*C. difficile* antibiotics theoretically target Clostridial species, in relapsing CDI they often fail to eradicate the organism because of the presence of resistant spores. Such treatment is counter-intuitive, as antibiotics are utilized to treat a disease that largely results from antibiotic-induced disruption of gut microbiota and therefore, in a sense, maintain the condition of which they are the cause.

Even with narrow-spectrum agents, such as fidaxomicin, antibiotics are not selective enough to target *C. difficile* specifically and they invariably further damage the microbiota. Approximately, 20% of the patients experience a second bout of CDI after initial antibiotic therapy, presumably due to spores that reinitiate infection. Approximately 40% of these 'second infection' patients develop recurrent CDI despite repeated antibiotic therapy, and 65–80% of such recurrent CDI patients fail antibiotic therapy for their third *C. difficile* infection. For patients who experience ≥three CDIs, there is essentially no hope that antibiotics will prevent further recurrence. CDI recurs or persists when the underlying gut microbiota deficiency has not been properly replenished. Hence, antibiotics are an inappropriate therapy for CDI, particularly for relapsing *C. difficile* infection that results from persistent intestinal dysbiosis and the inability to eradicate spore forms.

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The human colonic microbiota contains over 3.3 million non-redundant genes with each individual harboring around 160 species with up to 1150 prevalent bacterial species in the entire cohort as studied by Qin *et al.* [8]. Reintroduction of such a rich flora by FMT restores diversity and colonization resistance in recurrent CDI, thereby enabling recovery of normal bowel function and eradication of CDI.

There is now a wealth of noncontrolled data from a variety of centers and one randomized controlled study that highlights the efficacy of FMT for recurrent CDI. A single FMT administration cures the majority of patients, while the remainder are successfully treated with a second infusion. A recent *New England Journal of Medicine* paper, which reports the first randomized controlled trial of FMT, demonstrated the superiority of microbiota transplantation over traditional antibiotic therapy [3]. FMT had a success rate of 81% following a single nasoduodenal infusion and 94% following a second infusion, whereas vancomycin 500 mg four-times daily for 2 weeks with or without bowel lavage resulted in only a 23–31% success rate. Regulatory authorities stopped the trial early, after interim analysis and a judgment that it was

unethical to continue to deny patients FMT. This trial provides the highest-level evidence of superiority of FMT over optimal antibiotic therapy and has also brought FMT further into the general medical spotlight and public arena.

Recent review of over 300 FMT cases administered via colonoscopy or retention enema revealed mean cure rates were consistently around 91% [9,10]. The route of FMT administration seems quite influential, with one infusion via upper GI tract endoscopy or nasogastric/duodenal tube resulting in 76–79% cure [10] but a single colonoscopic infusion affording a cure rate of over 90% [11]. Hence, FMT, particularly transcolonoscopically, is the appropriate therapy for relapsing CDI [12].

Rationale for the use of complete microbiota FMT versus probiotics or limited cultured FMT

The term FMT implies use of the full spectrum of human colonic microbiota and is associated with numerous advantages over other forms of microbiota therapy. Probiotics are perceived to correct intestinal microbiota compositional imbalance and have been investigated as a treatment option for CDI. Available probiotics have limitations because they are generally not anaerobes, represent only few strains, do not implant and are not standardized. The human gastrointestinal microbiome meanwhile is largely anaerobic, highly complex, and specific deficiencies that require replacement are difficult to measure. The fact that FMT replaces all microbiota groups means that even though the missing/deficient microbiota components in a recipient may be unknown, FMT can deliver lacking components by providing a complete human intestinal microbiota. Additionally, the 'wild-types' from donor microbiota in FMT durably implant in the recipient [13] in contrast to cultured probiotics. Cultured probiotics progressively change during the process of 'passaging', when bacteria are successively recultured. They subsequently lose their capability to implant and to inhibit pathogen growth, as exemplified by the anti-CDI *Lactobacillus GG* [14] that progressively lost anti-CDI activity. Thus, FMT results in sustained correction of intestinal dysbiosis and protects against future recurrent CDI infection whereas cultured probiotics do not.

Cultured, 'mini' versions of the complete human gut microbiota have been developed in the hope of avoiding treatment with material of fecal origin and these preparations have succeeded in treating CDI in a handful of human cases [5,15]. In fact, there is a multitude of potential human microbiota components that could be grouped and developed into 'mini' versions of the full flora that could still eradicate CDI. However, difficulty in maintaining identical bacterial characteristics and function in the long term after prolonged serial passaging during the manufacturing process prevents such a product from retaining its original efficacy and such cell cultures continue to smell like their fecal origin [16].

Microbiota-based therapies are now being explored as a treatment option for numerous other medical conditions besides CDI, including inflammatory bowel disease, irritable bowel syndrome, autism, metabolic syndrome and other disorders [17]. Until the specific defects of the gastrointestinal microbiome in these various conditions are clearly defined, use of a complete human

intestinal microbiota will remain a better approach to exploring the therapeutic potential for FMT in these non-CDI disorders.

Ongoing issues & the future of FMT

In spite of growing interest in FMT, many questions and challenges remain. The exact features of what makes a 'good donor' are not well understood. Currently, donor selection is limited to healthy individuals with no comorbidities who have satisfied an infectious screen for transmissible diseases and do not have obvious factors that will affect intestinal composition, such as recent antibiotic therapy [18]. One could define a 'good donor' as an individual whose colonic microbiota can reverse a specific microbiota-related condition. The actual microbiological characteristics that define a 'good donor' are unknown at present due to the complexity of the gastrointestinal microbiome, and are not identifiable by standard laboratory techniques. Furthermore, a 'good donor' for one disease may not be a 'good donor' for another. Advances in metagenomics along with further targeted research may answer some of these questions in the future.

Recent advances suggest that an FMT floral product can be produced by repeated filtering, washing, freezing and even freeze-drying feces – and yet still deliver a clinical result equivalent to that of fresh crude fecal homogenate in treating CDI [19], and implanting healthy microbiota components into the recipient [20] while removing the fecal odor. In the future, lyophilized full spectrum human donor microbiota may be available in capsule formulation to treat CDI (even initial episodes) and perhaps be used routinely after all antibiotic usage to prevent gut flora damage.

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