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GUT IN FOCUS: EXTENDED ABSTRACT

Feces transplantation for recurrent *Clostridium difficile* infection: US experience and recommendations

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Patients who have failed to respond to repeated antibiotic treatment for recurrent *Clostridium difficile* infection (RCDI) present a particularly difficult challenge. Recent investigations of patients with RCDI have demonstrated significant disruption of the intestinal microbiome diversity as well as bacterial richness (1). Following the initial report on fecal microbiota transplantation (FMT) published by Eiseman in 1958 (2), instillation of stool collected from a healthy donor into the intestinal tract of patients with RCDI has been used increasingly and with a high degree of success to correct the intestinal dysbiosis brought about by repeated courses of antibiotic treatment. By now, multiple case reports and case series describing the outcome of FMT for more than 1,200 patients from around the Western world have been published. FMT treatment success rates are high and have ranged between 77 and 98% (3); the highest success rates have been observed with instillation of stool via the lower GI tract (4). A prospective randomized controlled trial was recently conducted in Holland (5), demonstrating superior treatment outcomes with FMT when compared to conventional therapy with oral vancomycin. FMT has been universally well accepted by patients and represents a low cost alternative treatment approach to an increasing clinical problem, with unlimited supply of the raw material (human stool). FMT appears to be safe, as no report of severe adverse events directly attributed to the instillation procedure itself has been reported so far (6). However, possible long-term consequences of FMT are unknown, and the US Food and Drug Administration currently considers FMT to be investigational therapy.

Materials and methods

A literature search of the Ovid MEDLINE database was conducted using search terms and synonyms for FMT. The search was limited to articles published in the English language or with an English language abstract between 1958 and December 31, 2014.

Experience with FMT

A total of 66 articles were identified; there were 15 single case reports, 50 case series and one randomized controlled clinical trial for a total case number of 1,212 cases. Prior to 2010 the annual number of reported cases of RCDI treated with FMT was fairly stable and averaged three cases per year. However, during the last 4 years more than 1,100 additional cases have been reported for an average of more than 250 cases per year. The majority of cases have been treated in North America (3, 6), and by the end of 2014 at least 105 practice centers in Canada and the USA were offering FMT for a variety of indications, including RCDI (www.idsociety.org/FMT/). Fecal samples may be instilled via the upper as well as the lower intestinal tract, but the majority of the published cases have had their fecal sample delivered either through a colonoscope or via a retention enema catheter (Table 1).

A recent survey of US infectious disease physicians indicated that patients with RCDI who failed to resolve their infection with standard antibiotic therapy should be considered for FMT after the third infection recurrence (7). The source of human feces for FMT administration has varied from a sample donated by a pre-screened close family member (e.g. spouse or intimate partner) to an unrelated donor (sample provided via a commercial 'stool bank' such as OpenBiome, www.openbiome.org). More recently well-defined suspensions of enteric bacteria have also been utilized with a high degree of success (8, 9). Recently a US consensus group recommended that stool donors should be screened through a detailed interview followed by examination of blood and feces for presence of occult contagious agents before being accepted for FMT donation (10, 11); however, screening practices have varied around the world, and routine screening of stool donors have not been practiced routinely in, e.g. Norway and Sweden (D. Berild, T. Noren; personal communication).

Anecdotal reports strongly suggest that the clinical response to FMT for the treatment of RCDI is superior

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Table 1. Routes of administration of Fecal Microbiota Transplantation (FMT) as reported in 66 published scientific articles between 1958 and December 31, 2014

Feces administration route	Cases	Success	%
Enema/colonoscopy	691	667	96
NGT/NDT/gastroscope	292	234	80
Mixed route: upper GI tract/colonoscopy	162	143	88
Oral capsules	20	14	70
Total	1,212	1,061	88

Mixed route refers to multiple published case series where the fecal sample was administered either via the upper or the lower gastrointestinal tract.

to standard antibiotic therapy (3, 12). The highest success rates (86–100%) have been noted when the fecal sample has been administered into the colon via the colonoscope or as a fecal enema (13–16). Slightly lower success rates (77–94%) have been reported when the fecal sample was administered into the gastric cavity or proximal portion of the small intestinal tract (17, 18). Only one randomized controlled trial has been published to date. Van Nood and coworkers compared vancomycin to FMT for treatment of RCDI. The trial was terminated prior to the planned stop date as interim data analysis demonstrated superiority of FMT over vancomycin (5). Youngster recently reported that human feces may also be successfully administered using pre-screened frozen fecal gel capsules, noting a success-rate of 70% (19).

The practice of administering FMT was unregulated in the United States until February 2013, when the Federal Drug Administration (FDA) classified human stool as a biological drug and imposed restrictions on prescribers of FMT by requiring all providers of FMT to hold an approved new investigational drug (IND) permit (20). The requirement for a valid IND was relaxed in July 2013, when the FDA declared that the agency would use 'enforcement discretion' when FMT was being prescribed as therapy for RCDI, providing that all patients sign an informed consent form that clearly outlines the potential risks of FMT and states that FMT is considered investigational therapy. The efficacy of FMT for gastrointestinal illnesses other than RCDI is currently not well defined, and use of FMT in the United States for treatment of inflammatory bowel disease and other less well-defined indications requires the provider to possess an IND approved by the FDA.

FMT has been tolerated remarkably well, and no significant infectious adverse effects directly attributed to the transfer of human feces from one individual to another have been described to date. Two cases of norovirus gastrointestinal infection was reported in 2012 for two FMT recipients despite asymptomatic stool donors and lack of recent sick contacts (21). The potential for long-term infectious and non-infectious consequences from FMT is currently unknown, but a recent publication reported new-onset obesity in a woman who had been successfully treated for RCDI with stool donated by her obese daughter (22). Physical complications from the FMT instillation procedure (upper gastrointestinal bleeding after nasogastric tube insertion, colon perforation during colonoscopy) has been occasionally reported and may occur with the same frequency as when these procedures are performed for illnesses other than RCDI.

Conclusions

FMT offers a highly effective treatment modality for patients who have failed to resolve their RCDI with standard courses of recommended antibiotic administration. In the United States, individualized FMT may be administered to patients with RCDI by medical providers without an FDA approved IND. However, an IND is required to administer FMT for all other indications. The optimal source of human stool for FMT administration continues to be debated, but stored, frozen stool samples that have been collected from carefully prescreened donors have become increasingly available from commercial biotech companies. Immuno-compromised patients with RCDI have tolerated FMT without reports of increased adverse effects. The recently published European CDI Treatment Guidelines (23) endorses FMT as first line therapy for patients who have had three or more CDI recurrences. The IDSA/SHEA 2010 guidelines (24) are currently being revised and updated, and recommendations for the use of FMT will likely mirror the European recommendations. The potential for long-term infectious and non-infectious unintended adverse effects from FMT are currently unknown. A US stool biorepository bank, which will make it possible to oversee the efficacy and safety of FMT, is currently in the planning stages with the FDA, National Institute of Health (NIH) and the Centers for Disease Control and Prevention (CDC) as the major stakeholders.

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