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PERSPECTIVES

Is a Single Fecal Microbiota Transplant a Promising Treatment for Recurrent *Clostridium difficile* Infection?

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Clostridium difficile infection, a common hospital-associated infection, is a gastrointestinal illness that becomes recurrent in about 25% of infected patients. Fecal microbiota transplantation (FMT) is increasingly supported by clinical trials as an effective treatment for recurrent *Clostridium difficile* infection, but a number of questions remain about how it can be optimally performed. In this Perspective, we discuss controversies in FMT methodologies and reporting within randomized controlled trials, all of which may influence clinical outcomes in treated patients. Finally, we focus on the question of whether single vs multiple FMTs are necessary to achieve favorable outcomes for the treatment of recurrent *Clostridium difficile* infection, postulating on why there may be an association between number of FMTs and clinical effectiveness.

Keywords. fecal microbiota transplantation methodologies; recurrent *Clostridium difficile* infection; single fecal microbiota transplant.

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Clostridium difficile infection (CDI) is one of the most common hospital-associated infections in developed countries, causing an estimated 450 000 infections and 29 000 deaths annually in the United States [1]. Approximately 25% of CDI cases result in recurrent CDI (RCDI), a condition primarily driven by disruption of the intestinal microbiota from antibiotic exposures and other medical interventions. Fecal microbiota transplantation (FMT), which aims to restore the intestinal microbial flora through instillation of stool from a healthy, screened donor, has an undeniable conceptual appeal as a treatment for this disease.

Over the past decade, FMT has gone from medical urban myth to a well-accepted treatment for RCDI. Early observational studies often reported very high cure rates but were viewed with caution due to lack of controls. Since 2013, 10 randomized trials using various forms of FMT (fresh, frozen, and encapsulated formulations) and routes of administration have been reported, each comparing FMT against different interventions, with only a handful comparing it against vancomycin treatment or placebo [2, 3]. Although effectiveness estimates from these studies range from 44% to 96%, the cumulative evidence suggests that FMT offers a safe, viable, and durable treatment for RCDI [2, 3].

Last year, our group published a trial comparing 14 days of oral vancomycin followed by a single FMT by enema with a 6-week taper-pulse regimen of oral vancomycin, the current standard of care, in patients experiencing an acute episode of RCDI [4]. Our main finding, that a single FMT by enema had comparable effectiveness to vancomycin taper in resolving RCDI (44% resolution of FMT vs 56% of vancomycin taper) was surprising to the FMT community, ourselves included. The use of single vs multiple FMT, the lack of patient bowel preparation, the donor stool mass, FMT volume, and retention time in our study were all raised as possible contributors to our lower FMT response rate. Indeed, these plus other variables that we brought forward, such as the design of the trial, selection of comparators, timing of FMT relative to the patient's most recent RCDI episode (provision of FMT during an acute episode vs in patients on suppressive vancomycin), vancomycin washout period, donor selection, FMT manufacturing, route of administration, and duration of patient follow-up, are variables that may influence outcomes. In effect, what has for years been referred to as a single procedure, "FMT," more accurately represents an array of interventions, given the lack of standardization of these variables.

An unfortunate challenge is that the specific details on FMT trial design and conduct are not easy to locate within publications. A systematic review into the methods and reporting of studies assessing FMT concluded that key components of FMT interventions—those necessary to replicate and interpret study

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findings on efficacy and safety—are poorly reported [5]. Of 85 studies reviewed, methodologic components that were commonly not reported included eligibility criteria for donors (47%); materials used for collecting stools and the period of collection (96%); methods for conservation of stools (76%); the amount and type of stools used and duration of stool conservation (67%). When reported, the methods used for selecting donors, preparing stools, and administering FMT were heterogeneous.

One of the factors we hypothesize was a major contributor to the seemingly low effectiveness of FMT in our study was the use of a single FMT. A growing body of literature supports that multiple FMT administrations may be required to overcome RCDI, and the effect does not appear to be dependent on route of administration [2, 6]. In the largest randomized controlled trial evaluating FMT for RCDI, a single fresh or frozen FMT administered by enema was successful in resolving RCDI in 53% and 51% of patients [7]. The proportions of successful treatment increased to 75% and 70% after 2 FMTs and to 91% and 86% with more than 2 administrations. In a pilot randomized trial comparing FMT by nasogastric (NG) tube with colonoscopy administration, only 60% of the patients in the NG tube arm achieved RCDI resolution after a single administration, while a second administration raised success to 80% [8]. Finally, in another randomized controlled trial using colonoscopy administration of FMT for RCDI, success after single FMT was 65% while a repeat administration resulted in a 90% cure [9]. Importantly, this trial included a high proportion of patients with severe CDI, a specific population in which additional evidence suggests that multiple FMTs may be necessary [10].

Contrasting these studies, three randomized trials have demonstrated high success of FMT after a single administration. In 1 trial, a single FMT by nasoduodenal administration was successful at curing RCDI in 81% [11]. A recent trial comparing FMT given by oral capsules with colonoscopy administration showed resolution of RCDI in 96% after single FMT in both groups [3]. In a study comparing FMT from screened donors with autologous FMT, effectiveness of a single donor FMT was 91% [12]. However, in this study, a high placebo effect was noted in the autologous FMT group, suggesting that RCDI may not have been active in many enrolled patients. Indeed, with the use of molecular testing for diagnosis of CDI, there is a risk of misdiagnosing colonized patients with alternative reasons for diarrhea as having active CDI; this presents a significant challenge in interpreting all trials evaluating FMT for RCDI to date.

Why would a single FMT be insufficient to cure a patient from RCDI? A number of postulates exist, although empiric evidence to support any one over the other is as yet lacking. It could be that a lasting or effective change in intestinal microbiota is not achieved in all individuals after a single administration, regardless of other variables. Depending on the timing of the FMT relative to the patient's most recent RCDI episode, it could also be that colonic inflammation persists at the time of the first FMT in some patients, particularly in those with severe disease, limiting microbiota uptake. Depending on the dose of vancomycin, the washout period, and whether a bowel preparation is used, it may be that vancomycin remaining in the colon reduces the effectiveness of a single FMT. Oral vancomycin has been shown to remain in the stool at inhibitory concentrations 4–5 days after discontinuation of medication, potentially impacting the instilled FMT [13]. Alternatively, it may be that a single FMT simply does not have enough mass, volume, or retention time to result in a positive effect in all patients. None of these variables is independent of the others, making it challenging to study and determine which are most important.

So, is a single FMT a promising treatment for RCDI? The clinical trials data are mixed, with some trials suggesting that administering multiple FMTs results in better patient outcomes. However, the mechanism by which this effect is achieved—and whether it is truly a matter of number of administrations vs other factors that may be altered to achieve better success with a single FMT—is not clear.

As the field moves toward developing more palatable methods of delivery of FMT, such as encapsulated products, the issue of appropriate FMT dosing may be clarified through well-designed phase 2 clinical trials. In the meantime, a continued emphasis on comparative methodologic research in FMT should be maintained to answer this and other emerging procedure-related questions.

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