

Upper Versus Lower Gastrointestinal Route of Fecal Microbiota Transplantation in the Treatment of *Clostridium Difficile* Infection

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Increasing incidence of *Clostridium difficile* infection (CDI) and emergence of new and more virulent, antibiotic resistant strains such as 027 ribotype (NAP1/B1/027) [1] has been associated with an increased incidence of recurrences and primary treatment failure with standard antibiotic therapy [2]. Fecal microbiota transplantation (FMT) has shown promise in the treatment of recurrent or refractory CDI [3,4]. FMT involves instillation of stools obtained from a healthy donor into the recipient gut either by upper gastrointestinal (GI) route through naso-gastric tube or through lower GI route administered during colonoscopy or rectal enemas. There are no controlled studies comparing the efficacy and safety of upper and lower GI routes of FMT delivery in the treatment of CDI. In the absence of such studies, the preferable method of FMT administration is unknown.

Earlier in 2012, we published a pooled-data analysis of studies on FMT in the treatment of CDI (289 patients) [3]. In this analysis, we showed that the rate of treatment failure was 15.4% with upper GI route compared to 6.6% with lower GI route of FMT delivery. This difference in the treatment outcome between the two routes of FMT delivery was statistically significant in univariate analysis ($p=0.027$), however no significance was noted in multivariate analysis ($p=0.569$). Similar results were later obtained from a meta-analysis by Kassam et al. with an observed trend towards higher clinical resolution rates by lower GI route compared to upper GI route of delivery of FMT [4]. Although, pooled-data analysis by Postigo and Kim did not show any difference in the treatment efficacy by upper or lower GI routes of FMT delivery [5], the number of cases analyzed in this analysis was smaller (182 patients) compared to former two reviews.

The potential superiority of lower over upper GI route of delivery of FMT is not well understood. Survival of colonic microflora in upper GI tract, including beneficial (obligate) anaerobic bacteria, is uncongenial, although these bacteria are present in terminal ileum [6]. This antagonistic environment for colonic microflora in upper GI tract is thought to be due to factors like intestinal peristalsis, pH, redox potential, bacterial adhesion, bacterial cooperation and antagonism, mucin secretion, diet, and nutrient availability [7]. Additionally, enzymatic activity of intestinal, pancreatic, and biliary secretions helps destroy bacteria in the small intestine [8]. Therefore, an unreceptive milieu for donor fecal microflora in the recipient's small intestine could potentially result in insufficient number of viable bacteria reaching the colon which may perhaps contribute to lower response rate in patients with upper GI route of FMT. Interestingly, in a study by Polak et al. [9], treatment failure with FMT was much higher (50%) when they used 20 grams of donor stool administered by upper GI route for the first six patients in their cohort. The success rate improved to 80% after transplant use of 40 grams of fecal matter in the remainder of the cohort. Similar results were obtained from a recently published study by van Nood et al. who achieved 81% cure rate with 50 gram dose of feces administered by upper GI route [10]. Hence, the size of 'viable' inoculums of the donor bacterial flora reaching colon may be an important factor to determine successful outcome of FMT.

Based on current available (albeit limited) evidence, delivery of FMT through colonoscopy seems more efficacious than upper GI route for FMT. However, administration of FMT by colonoscopy is more invasive and expensive method in comparison to upper GI delivery

using naso-gastric tube. Future trials are needed to identify safer, efficacious and economical mode of FMT delivery. Additionally, well conducted studies comparing the safety and efficacy of FMT based on upper or lower GI route of administration are eagerly awaited. These studies will also help in better understanding of its mechanism of action

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