Editorial

Microbiota replacement for *Clostridium difficile* by capsule is as effective as via colonoscopy

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Since its discovery in the late 1970s, the incidence of both primary and recurrent *Clostridium difficile* infection (CDI) has been increasing. For instance, from 2001 to 2012, the annual incidence of primary CDI and multiply recurrent CDI increased by 42.7% and 188.8%, respectively (1). *Clostridium difficile* (*C. Difficile*) is now the most commonly isolated health-care associated pathogen (2). There has been an increase in available treatment options for CDI. However, despite the advances made, it remains notoriously difficult to treat. The most challenging aspect is the high recurrence rate (despite lack of ongoing systemic antibiotic exposure) around 20% after the first successfully treated episode, and up to 60% after multiple previous episodes (3,4).

The treatment of recurrent CDI is based on the number of prior episodes and the treatment regimen used. According to the updated guidelines from the Infectious Diseases Society of America, a first recurrence is treated with oral vancomycin for 10 days if the first episode was treated with metronidazole. If a standard vancomycin regime was used for the first episode, a tapered and pulsed vancomycin or fidaxomicin is recommended. For subsequent recurrences (three or more episodes), tapering course of vancomycin, vancomycin with rifaximin chaser, fidaxomicin, or fecal microbiota transplantation (FMT) are recommended (5).

The initial evidence for FMT for CDI was based on case series and case reports. The first randomized controlled trial of FMT for CDI compared a standard 14-day course of vancomycin, vancomycin with bowel lavage, and vancomycin for 4 days followed by bowel lavage and FMT via nasoduodenal tube. It was terminated early after recruiting 43 patients due to a significant difference in remission rates in FMT (81% after one infusion) compared to vancomycin (27%) with resolution of diarrhea (P<0.001) (6). Another study compared FMT via colonoscopy with vancomycin tapered regimen. It was terminated after interim analysis owing to higher efficacy of FMT (90% *vs.* 26%, P<0.0001) (7). Meta-analyses of randomized trials have demonstrated FMT to be superior to vancomycin or placebo (RR =0.41; 95% CI, 0.22–0.74; number needed to treat, 3; 95% CI, 2–7) to treat CDI (8).

Owing to paucity of data, there is a lack of consensus on the best mode of delivery, dose, form or composition of the stool to be used for FMT. The various modes of delivery may have different efficacy due to the effect of gastric acid, bowel preparation, and the number of live microbes in a particular preparation. Importantly, there is a significant variability in costs and procedures for different delivery modalities with implications for healthcare providers as well as patients.

A meta-analysis of studies in patients with recurrent and refractory CDI found a significant difference between lower and upper gastrointestinal (GI) delivery of FMT [95% (95% CI, 92–97%) *vs.* 88% (95% CI, 82–94%), respectively (P=0.02)] (9). However, when cure rates were compared for a single infusion, there was no difference in efficacy. This included various modalities of delivery including nasogastric, naso-jejunal, upper GI endoscopy, colonoscopy

and retention enema. There were no studies that included oral capsules. Multiple courses of FMT resulted in incremental benefit, and FMT was superior to vancomycin. Furthermore, fresh *vs.* frozen preparations were similar in efficacy. An observational study conducted on 50 patients undergoing FMT for recurrent or severe refractory CDI compared nasogastric tube *vs.* lower GI endoscopy for FMT. They found that overall, nasogastric tube was inferior to colonoscopy for efficacy of the initial FMT (71.9% *vs.* 100%; RR =0.72; 95% CI, 0.58–0.89; P=0.002). This difference remained significant when adjusted for age, body mass index (BMI), sex, immunosuppression and CDI classification. However, the association was stronger for sicker patients (Charlson Comorbidity Index ≥5) than for those with fewer comorbidities (10). Another meta-analysis of recurrent/refractory CDI concluded that the upper GI route of delivery was inferior to the lower GI route of delivery with a 3-fold risk of failure in the first 30 days (11).

FMT by oral route is an attractive option for CDI treatment (12). The advantages include no significant procedure related complications and higher patient acceptability. Overall, it may also be economically more feasible. The efficacy of oral capsules in treating recurrent CDI is comparable to other routes of delivery, with cure rates of around 90% (13,14). These capsules are generally designed to be delayed release to avoid issues with gastric acid.

A recent study done by Kao *et al.* (15) is the first randomized controlled trial that compares the efficacy of FMT by oral capsule to colonoscopy in patients with recurrent CDI. It was an unblinded non-inferiority trial conducted in three centers in Canada. Overall, 116 patients were randomized to capsule or colonoscopy at a 1:1 ratio and 105 (91%) patients completed the trial. The primary outcome was proportion of patients without recurrent CDI at 12 weeks; secondary outcomes included adverse events, quality of life, patient perception and satisfaction. The primary outcome was achieved in 96.2% in both the groups after a single treatment (difference, 0%; 1-sided 95% CI, –6.1% to infinity; P<0.001), thus meeting the non-inferiority criterion. Minor adverse events were higher in the colonoscopy (12.5%) *vs.* the capsule (5.4%) group, but there was no difference in improvement in quality of life between groups. A greater proportion of patients found their experience 'not at all unpleasant' in the capsule vis-à-vis the colonoscopy group.

This study excluded patients undergoing radiation or chemotherapy for cancer, those requiring antibiotics for other indications, severe and complicated CDI. These patients tend to be sicker, and more predisposed to develop recurrent CDI. While colonoscopy can be challenging in such patients, it has been done. A previous study indicated that the lower GI route may be more useful in sicker patients compared to the upper GI route, though this study did not include oral capsules as a delivery mode (10). Exclusion of this group of patients may have led to an underestimation of the efficacy of the lower GI route.

An important difference in the procedure for FMT was that the investigators used a higher dose of stool than previous studies [100 *vs.* 48 g stool in Youngster *et al.* (13)], which could have led to a higher response rate. Patients were instructed to stop gastric acid suppressing medications. Use of these medications has been a general practice till date, owing to the theoretical risk of microbiota changes by gastric acid. However, they tend to increase the risk of recurrent CDI (16). The capsules used were not gastric acid resistant, and a higher amount of stool used was thought to counteract the effect of gastric acid on the oral study product. This study estimated that the cost of oral capsules was significantly lower than FMT via colonoscopy ($308 *vs.* $874). Though this does not include the cost of donor screening and FMT infrastructure, it nevertheless underlines the fact that oral capsules, if effective, may be a more feasible option than colonoscopy.

The study demonstrates the comparable efficacy of FMT by oral capsules and colonoscopy in treating recurrent CDI, with lower adverse event rates and a lower cost. Efficacy, feasibility and acceptability may differ by mode of delivery in such patients and affect treatment decisions. The study also raises important questions regarding the dose-response effect for FMT, and the use of acid suppression prior to the procedure. Further studies are required to explore these.

Overall, FMT is a highly effective cure for recurrent CDI. The mode of delivery may not significantly affect cure rates, and should be guided by patient profile, along with an active discussion between patients and their physicians regarding various options.

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Footnote

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