Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection
A Randomized Clinical Trial

Dina Kao, MD, FRCPC; Brandi Roach, RN; Marisela Silva, MD; Paul Beck, MD, PhD, FRCP; Kevin Rioux, MD, PhD, FRCP; Gilaad G. Kaplan, MD, FRCP; Hsiu-Ju Chang, MSc; Stephanie Coward, MSc; Karen J. Goodman, PhD; Huiping Xu, PhD; Karen Madsen, PhD; Andrew Mason, MBBS; Gane Ka-Shu Wong, PhD; Juan Jovel, PhD; Jordan Patterson, MSc; Thomas Louie, MD, FRCP

**IMPORTANCE** Fecal microbiota transplantation (FMT) is effective in preventing recurrent *Clostridium difficile* infection (RCDI). However, it is not known whether clinical efficacy differs by route of delivery.

**OBJECTIVE** To determine whether FMT by oral capsule is noninferior to colonoscopy delivery in efficacy.

**DESIGN, SETTING, AND PARTICIPANTS** Noninferiority, unblinded, randomized trial conducted in 3 academic centers in Alberta, Canada. A total of 116 adult patients with RCDI were enrolled between October 2014 and September 2016, with follow-up to December 2016. The noninferiority margin was 15%.

**INTERVENTIONS** Participants were randomly assigned to FMT by capsule or by colonoscopy at a 1:1 ratio.

**MAIN OUTCOMES AND MEASURES** The primary outcome was the proportion of patients without RCDI 12 weeks after FMT. Secondary outcomes included (1) serious and minor adverse events, (2) changes in quality of life by the 36-Item Short Form Survey on a scale of 0 (worst possible quality of life) to 100 (best quality of life), and (3) patient perception on a scale of 1 (not at all unpleasant) to 10 (extremely unpleasant) and satisfaction on a scale of 1 (best) to 10 (worst).

**RESULTS** Among 116 patients randomized (mean [SD] age, 58 [19] years; 79 women [68%]), 105 (91%) completed the trial, with 57 patients randomized to the capsule group and 59 to the colonoscopy group. In per-protocol analysis, prevention of RCDI after a single treatment was achieved in 96.2% in both the capsule group (51/53) and the colonoscopy group (50/52) (difference, 0%; 1-sided 95% CI, −6.1% to infinity; *P* < .001), meeting the criterion for noninferiority. One patient in each group died of underlying cardiopulmonary illness unrelated to FMT. Rates of minor adverse events were 5.4% for the capsule group vs 12.5% for the colonoscopy group. There was no significant between-group difference in improvement in quality of life. A significantly greater proportion of participants receiving capsules rated their experience as “not at all unpleasant” (66% vs 44%; difference, 22% [95% CI, 3%–40%]; *P* = .01).

**CONCLUSIONS AND RELEVANCE** Among adults with RCDI, FMT via oral capsules was not inferior to delivery by colonoscopy for preventing recurrent infection over 12 weeks. Treatment with oral capsules may be an effective approach to treating RCDI.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT02254811


© 2017 American Medical Association. All rights reserved.
F.M. (FMT) by oral capsules is noninferior to delivery by colonoscopy. The hypothesis that given the same amount of donor stool, FMT by oral capsule with colonoscopy may be an effective approach to treating RCDI.

Key Points

Question Does the clinical efficacy of fecal microbiota transplantation (FMT) in treating recurrent Clostridium difficile infection (RCDI) depend on the route of delivery?

Findings In this noninferiority randomized clinical trial that included 116 adults with RCDI, the proportion without recurrence over 12 weeks was 96.2% after a single treatment in a group treated with oral capsules and in a group treated via colonoscopy, meeting the noninferiority margin of 15%.

Meaning FMT by oral capsules may be an effective approach to treating RCDI.

Methods

Study Population

Adult inpatients and outpatients, aged 18 to 90 years, with at least 3 documented episodes of CDI were recruited. In the absence of an alternative cause of diarrhea, each episode was defined as recurrence of diarrhea (>3 unformed bowel movements every 24 hours) within 8 weeks of completing a prior course of treatment, with either a positive C. difficile toxin by glutamate dehydrogenase and C. difficile toxins A/B (C. diff QuikChek Complete; Techlab) or by detection of glutamate dehydrogenase and C. difficile cytotoxin B gene (Cepheid), plus resolution of diarrhea for the current episode. Exclusion criteria included complicated CDI as defined by Surawicz and colleagues; chronic diarrheal illness; inflammatory bowel disease (IBD), unless in clinical remission 3 or more months prior to enrollment; cancer undergoing therapy; subtotal colectomy, colostomy, or ileostomy; dysphagia; life expectancy of less than 3 months; pregnancy; breastfeeding; and conditions requiring antibiotic therapy. Written informed consent was obtained before screening. This study was approved by Health Canada (control No. 176567) and the ethics board of each participating center. The full trial protocol is available in Supplement 1.

Study Design and Treatment

This randomized, noninferiority trial compared FMT delivered by capsule with colonoscopy. Potential participants were enrolled between October 2014 and September 2016, with follow-up to December 2016 at 3 academic centers in Edmonton and Calgary, Alberta, Canada. Eligible patients were randomized to FMT by capsule or colonoscopy at a 1:1 ratio by computer-generated random numbers in blocks of 4, stratified by age (≥65 vs <65 years) and immunosuppression. This study was not blinded owing to the practical barriers to masking. A data and safety monitoring board monitored the trial to completion.

Following 10 or more days of vancomycin at 125 mg by mouth 4 times a day until symptom resolution, patients were treated with vancomycin, 125 mg, by mouth twice a day until 24 hours prior to FMT. No proton pump inhibitor (PPI) was given prior to FMT; patients taking a PPI discontinued it after screening. All patients received 4 L of Golytely (polyethylene glycol) the night before FMT and remained fasting until the scheduled treatment. Patients randomized to the colonoscopy group received 360 mL of fecal slurry in the cecum. Those randomized to the capsule group swallowed 40 capsules under direct observation. All patients had clinic visits at weeks 1, 4, and 12 after FMT, with a telephone follow-up at week 2. In the event of diarrhea recurrence, C. difficile testing was repeated. If test results were positive, patients were treated with vancomycin prior to the second FMT by the same delivery modality, with identical follow-up.

Serial stool samples were collected and frozen at −80°C prior to FMT and at 1, 4, and 12 weeks after FMT. A subset of 23 capsule and 23 colonoscopy recipients was randomly chosen to proportionally represent the study cohort for microbiome profiles. Stool microbial DNA was extracted using the FastDNA Spin kit for Feces (MP Biomedicals) for whole-genome shotgun sequencing. Metagenome libraries were constructed using the Nextera XT (Illumina) protocol. Libraries were sequenced in an Illumina MiSeq using a paired-end 300-cycle protocol. Taxonomic classification of sequences was conducted with Kraken against a customized database that included full-genome sequences of bacteria, archaea, viruses, fungi, protozoa, and the human genome assembly GRCh38.15 Re-estimation of bacterial abundance was carried out with Bracken (eMethods 1 in Supplement 2). Participants filled in the 36-Item Short Form Survey (SF-36) questionnaire at the screening visit and 4 weeks after FMT. Responses were used to score the quality of life in 8 health domains on a scale of 0 (worst possible) to 100 (best possible), including physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Participants
also filled in at screening and 1 week after FMT a patient satisfaction and perception questionnaire (eMethods 2-4 in Supplement 2) the investigators developed. The questionnaire involved rating participants’ perceptions of FMT before the procedure and their experience with the procedure on a scale of 1 (not at all unpleasant) to 10 (extremely unpleasant).

Stool Donor and FMT Manufacturing

Seven healthy volunteer stool donors provided stool for all participants. Donor inclusion/exclusion criteria, screening, and testing followed recommendations proposed by Kelly and colleagues. Each fresh stool donation, weighing 80 g to 100 g, was received by laboratories within 12 hours of collection. Each collection was processed separately without pooling, by mixing in 200 cc of 0.9% normal saline and filtered using a stomacher bag to produce 180 cc of fecal slurry. The slurry was mixed with 20 cc of 100% glycerol and kept frozen at −70°C for up to 2 months. When required, the frozen slurry was thawed at 4°C overnight and reconstituted with 160 cc of 0.9% normal saline. For capsule manufacturing, the fecal slurry (approximately 200 cc) was mixed with 40 cc of 100% glycero and centrifuged (Sorvall Legend RT+; Thermo Scientific) at room temperature at 4000 g for 30 minutes.

After decanting the supernatant, it was centrifuged at 10000 g for 30 minutes at 4°C to 8°C using a high-speed centrifuge (Avanti J-30 I; Beckman Coulter). The supernatant was discarded and the final sediment (approximately 12 cc, estimated to contain 10^{13} microbes) was mixed to incorporate residual liquid to allow pipetting into capsules. Using either a microtiter template or by individual handheld half capsules, No.1 gelatin capsules (1889-02; Medisca) were filled, then over encapsulated twice with No.0 (2009-02; Medisca) and No. 00 (1109-02; Medisca) capsules, flash frozen at −55°C on dry ice and stored at −70°C for up to 2 months. Forty capsules were manufactured from 1 donation.

Study End Points

The primary outcome was the proportion of patients without RCDI 12 weeks after FMT in each group. Secondary outcomes included (1) serious adverse events (infections and mortality related to FMT, colonic perforation) and minor adverse events (nausea, vomiting, abdominal pain, and fevers), (2) changes in quality of life assessed by SF-36 on a scale of 0 (worst possible quality of life) to 100 (best possible quality of life), (3) patient perception on a scale of 1 (not at all unpleasant) to 10 (extremely unpleasant) and satisfaction on a scale of 1 (best) to 10 (worst) in each group. Cost of intervention, microbrial composition changes, and IBD flares after FMT were exploratory outcomes.

Statistical Analysis

To determine noninferiority of FMT administered by capsule compared with by colonoscopy, a sample size of 49 in each group was required to achieve 80% power to detect a noninferiority margin of −15% in success rates between the 2 groups at 5% significance level, assuming a 90% success rate for the colonscopy group, as reported in the literature, and no difference in success rates between the capsule and colonoscopy groups. Data comparing upper gastrointestinal vs colonoscopy administration of FMT were limited. For example, one study reported a success rate of 74% (28/38) following FMT administration by duodenal instillation compared with a 92% success rate with 1 FMT delivered by colonoscopy by Kelly and colleagues. The proposed −15% noninferiority margin was chosen based on investigators’ judgment that FMT administration by capsule was noninvasive and relatively inexpensive compared with colonoscopy, an invasive and costly procedure. Assuming a 15% attrition rate, a sample size of 58 patients in each group was needed.

The per-protocol population consisted of all patients who strictly adhered to the study protocol and had completed the planned 12-week follow-up. The primary outcome was analyzed using the per-protocol approach based on the 2-sample binomial noninferiority test at the 5% significance level. The noninferiority was established when the 1-sided 95% CI for the difference in 12-week success rate was −15% or greater. Sensitivity analysis was performed to examine the noninferiority of the capsules considering the worst-case scenario, where all patients excluded from the primary analysis were assumed to have CDI recurrence if they were in the capsule group and no recurrence if they were in the colonoscopy group. For secondary outcome comparisons, between-group differences and 95% CIs were reported, along with 2-sided P values from the Wilcoxon rank sum test for changes in SF-36 scores between screening and week 4 and Fisher exact test for patient satisfaction using a 2-sided significance level of 5%. Because secondary end points were not adjusted for multiple comparisons, these findings should be considered exploratory. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

Cost estimation of colonoscopy was based on an aggregate value previously reported, which accounted for all direct costs. The costs of FMT manufacturing and delivery were based on aggregate costs during the conduct of this study. Microbial composition analyses and principal coordinates analysis (PCoA) were conducted with EMPeror. Shannon diversity indices, the Kolmogorov-Smirnoff test, PCoA, and the permutational multivariate analysis of variance were conducted with the Scikit-bio 0.5.1.

Results

Patients

Of 213 patients assessed for eligibility, 97 patients were excluded. The remaining 116 underwent randomization (mean [SD] age, 58 [19] years; 79 women [68%]; 105 [91%] completed the trial): 57 in the capsule group and 59 in the colonoscopy group (Figure 1). Baseline characteristics were not significantly different between the groups (Table 1). Seventeen patients, 10 randomized to the colonoscopy and 7 to the capsule group, were immunosuppressed (Table 1 in Supplement 2). In the end, 53 in the capsule group and 52 in the colonoscopy group were included in the per-protocol analysis for primary outcome; numbers of patients included for secondary analyses varied by outcomes (Figure 1).
Primary Efficacy End Point

The primary outcome was not assessed for 11 patients: 4 did not receive the assigned treatment, 2 died, 3 withdrew from the study owing to IBD flare, and 2 were lost to follow-up before 12 weeks (eTable 2 in Supplement 2). Among the remaining patients, absence of RCDI was achieved in 96.2% of patients, CDI indicates Clostridium difficile infection; QOL, quality of life; and UC, ulcerative colitis.
both in the capsule group (51/53) and the colonoscopy group (50/52) after a single treatment as per-protocol analysis, with a rate difference of 0% (1-sided 95% CI, −6.1% to infinity; P < .001), resulting in rejection of the null hypothesis that FMT by capsule was less effective than FMT by colonoscopy by at least −15%. Sensitivity analysis assuming the worst-case scenario had a similar finding. With a success rate of 89.5% (51/57) for the capsule group and 96.6% (57/59) for the colonoscopy group, the rate difference was −7.1% with a 1-sided 95% CI of −14.9% to infinity (P = .048), demonstrating the noninferiority of the capsule group. Site differences in efficacy are present in eTable 3 in Supplement 2. Two patients in each group developed RCDI and were successfully treated with a second FMT by the same modality.

Secondary End Points

Changes in Quality of Life

Quality of life before FMT and 4 weeks after FMT were not assessed for 13 patients: 4 did not receive the assigned treatment, 2 withdrew before 4 weeks, 1 died, and 6 did not complete the SF-36 questionnaire at 4 weeks. Among the remaining 103 patients, the domains of role limiting due to physical and emotional health problems scored lowest among all domains, both with a median of 0 before FMT. Four weeks after FMT, the domains of role physical and role emotional improved significantly, with an increase of 25 and 33 in the median, respectively. Other domains also had significantly higher scores at 4 weeks compared with baseline. However, these changes were not significantly different between the 2 groups (Table 2).

Patient Perception and Satisfaction

Post-FMT perception was not assessed in 6 patients, all of whom either did not receive the assigned treatment or withdrew early. Participants most frequently characterized FMT as “innovative treatment” (63% of patients), “natural remedy” (41%), and “unpleasant, gross, or disgusting” (30%). Factors reported most frequently to influence preference for FMT

Table 1. Patient Baseline Characteristics at Screening

<table>
<thead>
<tr>
<th>Variable</th>
<th>FMT by Oral Capsule (n = 57)</th>
<th>FMT by Colonoscopy (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>58.7 (18.5)</td>
<td>57.4 (19.1)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>43 (75.4)</td>
<td>36 (61)</td>
</tr>
<tr>
<td>Charlson Comorbidity Index score, median (Q1-Q3)</td>
<td>4 (2-5)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Immunosuppressed patients, No. (%)</td>
<td>7 (12.3)</td>
<td>10 (16.9)</td>
</tr>
<tr>
<td>Use of immune modulator, No. (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Corticosteroid</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td></td>
<td>Immunosuppressant</td>
<td>6 (10.5)</td>
</tr>
<tr>
<td></td>
<td>Biologic</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td></td>
<td>BMI, mean (SD)</td>
<td>25.4 (5.5)</td>
</tr>
<tr>
<td>Inpatient status at screening, No. (%)</td>
<td>8 (14)</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>PPI use prior to FMT, No. (%)</td>
<td>14 (24.6)</td>
<td>11 (18.6)</td>
</tr>
<tr>
<td>No. of RCDI episodes prior to FMT, median (Q1-Q3)</td>
<td>4 (3-5)</td>
<td>4 (3-4)</td>
</tr>
<tr>
<td>Duration of RCDI prior to FMT, median (Q1-Q3), mo</td>
<td>3.9 (2.9-7.1)</td>
<td>4.6 (3.5-6.6)</td>
</tr>
<tr>
<td>Duration of RCDI treatment prior to FMT, median (Q1-Q3), mo</td>
<td>2.3 (1.9-3.8)</td>
<td>2.4 (1.7-3.5)</td>
</tr>
<tr>
<td>No. of RCDI-related hospital admissions prior to FMT, median (Q1-Q3)</td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>IBD, No. (%)</td>
<td>Ulcerative colitis</td>
<td>4 (7)</td>
</tr>
<tr>
<td></td>
<td>Crohn disease</td>
<td>2 (3.5)</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin, median (Q1-Q3), g/dL</td>
<td>13.6 (12.8-14.4)</td>
</tr>
<tr>
<td></td>
<td>White blood cell count, median (Q1-Q3), /μL</td>
<td>7700 (6400-8600)</td>
</tr>
<tr>
<td></td>
<td>Albumin, median (Q1-Q3), g/dL</td>
<td>4.0 (3.6-4.3)</td>
</tr>
<tr>
<td></td>
<td>C-reactive protein, median (Q1-Q3), mg/dL</td>
<td>0.21 (0.10-0.43)</td>
</tr>
<tr>
<td></td>
<td>Creatinine, median (Q1-Q3), mg/dL</td>
<td>0.81 (0.70-0.98)</td>
</tr>
<tr>
<td>Quality of life, SF-36 subscales, median (IQR)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Physical functioning</td>
<td>45 (20-70)</td>
</tr>
<tr>
<td></td>
<td>Role physical</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Role emotional</td>
<td>0 (0-67)</td>
</tr>
<tr>
<td></td>
<td>Vitality</td>
<td>30 (10-45)</td>
</tr>
<tr>
<td></td>
<td>Mental health</td>
<td>60 (44-72)</td>
</tr>
<tr>
<td></td>
<td>Social functioning</td>
<td>25 (13-50)</td>
</tr>
<tr>
<td></td>
<td>Bodily pain</td>
<td>45 (33-68)</td>
</tr>
<tr>
<td></td>
<td>General health</td>
<td>50 (35-60)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CDI, Clostridium difficile infection; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; PPI, proton pump inhibitor; Q1, first quartile; Q3, third quartile; RCDI, recurrent Clostridium difficile infection; SF-36, 36-Item Short Form Survey.

SI conversion factors: to convert albumin and hemoglobin to grams per liter, multiply by 0.001; C-reactive protein to nanomoles per liter, multiply by 9.524; creatinine to micromoles per liter, multiply by 88.4; and white blood cell count to ×10⁹ per liter, multiply by 0.001.

<sup>a</sup> Charlson Comorbidity Index is a method of categorizing comorbidities based on International Classification of Diseases diagnosis codes and assigns a weighted score for each condition from 1 to 6 based on the adjusted risk of mortality. A score of 0 indicates no comorbidities. The higher the total score, the higher the risk of mortality.

<sup>b</sup> Some of these patients were taking more than 1 class of immune modulators.

<sup>c</sup> SF-36 scores range from 0 (worst possible quality of life) to 100 (best possible quality of life).
Cost of Intervention

The cost of administering FMT via colonoscopy was CAD $1120 (US $874) per patient. In comparison, the cost of administering FMT by capsule was CAD $395 (US $308) per patient (eResults 1 in Supplement 2).

Exacerbation of Underlying Inflammatory Bowel Disease

During follow-up, 2 patients with IBD in the colonoscopy group developed exacerbation of their underlying disease, requiring adjustment in treatment regimens (eResults 2 in Supplement 2).

Microbial Composition Analysis

Prior to FMT, patients with RCDI had decreased diversity as measured by the Shannon diversity index compared with donors (Figure 2). Following FMT, diversity increased significantly in both the capsule and colonoscopy groups to values not significantly different from donors. This increased diversity was maintained in both groups up to 12 weeks following the FMT. PCoA of the patients with RCDI showed a significantly different microbial community structure before and after FMT (permutational multivariate analysis of variance \( P = .001 \) (Figure 2). Patients with RCDI clustered apart from donors prior to FMT and moved toward the donor profiles and persisted to week 12 after FMT. Taxonomic composition of the patient and donor microbiota is shown in the eFigure in Supplement 2.

Discussion

Among adults with RCDI, FMT via oral capsules was not inferior to delivery by colonoscopy for preventing recurrent infection over 12 weeks.

The success rate with FMT capsules in this study was higher compared with other studies. Most studies administering FMT by the upper route provided a relatively small fecal inoculum derived from a mean of 25 g of donor stool to the stomach compared with a mean of 93 g delivered by colonoscopy.20 Following a 48-hour vancomycin washout period and without bowel lavage, Youngster and colleagues6 reported a response rate of 70% when 15 capsules were administered per day for 2 consecutive days. A randomized clinical trial comparing frozen-and-thawed or fresh FMT by enema, derived from 17 g of donor stool, showed efficacy at approximately 60% following a single treatment in both
A small randomized clinical trial showed that FMT by colonoscopy vs vancomycin prevented recurrent infection in 90% of patients using a mean of 152 g of donor stool. The higher efficacy observed in this study suggests a dose-dependent response to FMT, and a benefit of bowel lavage prior to FMT, because residual vancomycin was detected up to 8 days despite its discontinuation.

Currently, most patients with RCDI are referred to gastroenterology or infectious diseases, and the method and route in which FMT is administered are specialty dependent.

Figure 2. Shannon Diversity of Taxonomic Data From Patients With Recurrent *Clostridium difficile* Infection and Donors

Figure 3. Principal Coordinates Analysis (PCoA) of Taxonomic Data From Patients With Recurrent *Clostridium difficile* Infection and Donors

PCoA is a method to visualize similarities or dissimilarities in high-dimensional data. In this case, it assigns each patient’s microbial composition to a location in a 2-dimensional graph indicated by principal coordinate 1 (30.9%; x-axis) and principal coordinate 2 (8.4%; y-axis) where the distance between any 2 samples is a measure of their similarity (smaller distance for higher similarity). The microbial composition of patients with recurrent *C difficile* infection (red circles and triangles) was significantly different from donors (black squares) before fecal microbiota transplantation (FMT) (*P* < .001) and between each group of patients before and after FMT at 1, 4, and 12 weeks (*P* < .01). There was no difference between the capsule and colonoscopy groups at any point. Some donors had provided 2 samples for the microbial composition analysis. Each patient is represented by a single point. The lines within boxes represent medians, while the edges of the boxes represent lower and upper quartiles. The whiskers represent the range of the data set.

The Shannon diversity index is a measure of the relative abundance and evenness of bacterial species in a community. The index is highest in communities with large numbers of species with near equal representation, and lowest in communities with low numbers of species with skewed distribution. Shannon diversity index was significantly different between patients with recurrent *C difficile* infection in the capsule or colonoscopy groups and the donors before fecal microbiota transplantation (FMT) (*P* < .001) and between each group of patients before and after FMT at 1, 4, and 12 weeks (*P* < .01). There was no difference between the capsule and colonoscopy groups at any point. Some donors had provided 2 samples for the microbial composition analysis. Each patient is represented by a single point. The lines within boxes represent medians, while the edges of the boxes represent lower and upper quartiles. The whiskers represent the range of the data set.
Although colonoscopy delivery is more invasive, resource intensive, costly, and inconvenient for patients, it has the advantage of identifying alternative diagnoses. Conversely, when FMT is given by oral capsules, it can be administered in an office setting, which could substantially reduce cost and wait time. Complete economic evaluations are needed to understand the value and efficiency of FMT by oral capsule.

In this study, 15% (2/13) experienced an IBD flare following FMT delivered by colonoscopy. Although this association has been previously reported at 13% (9/67) and 25% (11/43), it remains unknown whether IBD exacerbation in this setting is caused by FMT, RCDI, or natural progression of IBD.

The theoretical need to prevent gastric acid from destroying the transferred microbes during FMT has led to the practice of using PPIs and/or acid-resistant capsules. However, in this study, PPIs or histamine antagonists were not used prior to FMT. If a patient was taking a PPI at the screening visit, PPI was discontinued because it is a known risk factor for CDI. Furthermore, the gelatin capsules used were not acid resistant. To counteract the lack of acid suppression, the microbial inoculum used in this study may have been sufficient to overcome the potential microbial loss in the stomach. Observing similar microbial composition in colonoscopy- and capsule-administered FMT supports the position that microbes alone can restore integrity to the intestinal ecosystem.

Strengths
This study has several strengths. First, only patients with a propensity for RCDI within a short period of treatment completion were included in this study (median of 4 CDI episodes over a 4-month period and median anti-CDI treatment duration of 2.4 months). Second, patient-reported outcomes were captured by SF-36 and satisfaction/preference questionnaires before and after FMT. Third, IBD and immunosuppressed patients were included, although the numbers were too small to determine the safety profile. Fourth, using a small number of stool donors minimized the risk of potential disease transmission, screening costs, and wait time.

Limitations
This study has several limitations. First, by not including a placebo group in this study, it was not possible to measure the magnitude of effect of FMT administered by each route. In a recent FMT vs placebo trial in the treatment of RCDI, the placebo response rate was 45%. In this study, patients knew that they received FMT regardless of randomization and this knowledge may have inflated the response rate. At the same time, the placebo effect would have existed in both groups. Assuming similar placebo effect, the result of this study still provides a valid comparison of the efficacy between the 2 treatment modalities. Second, there was no blinding. Although technically possible, blinding would have required patients randomized to the capsule group to undergo an invasive and expensive procedure. Furthermore, blinding would not have allowed for assessing a potential difference in patient preference or adverse events based on method of FMT delivery. Third, the generalizability of these findings was limited by the enrollment criteria as patients with severe and complicated CDI were excluded. Fourth, the cost comparison did not include donor screening, cost from a societal perspective, or FMT program infrastructure or liability. Additionally, the cost of colonoscopy is lower in Canada than in the United States. Therefore, the cost difference between FMT by capsule compared with colonoscopy may be larger in the United States. Fifth, strain typing was not performed in this study cohort, although the NAP1/ribotype 027 strain is estimated to be 20% in Calgary and 30% in Edmonton based on recent provincial surveillance data.

Conclusions
Among adults with RCDI, FMT via oral capsules was not inferior to delivery by colonoscopy for preventing recurrent infection over 12 weeks. Treatment with oral capsules may be an effective approach to treating RCDI.
Oral Capsule vs Colonoscopy-Delivered Fecal Microbiota Transplantation on C difficile Infection

ORAL CAPSULE VS COLONOSCOPY-DELIVERED FECAL MICROBIOTA TRANSPLANTATION ON C difficile INFECTION: SYSTEMATIC REVIEW AND META-ANALYSIS


