Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eMethods 1. Stool Microbial Composition Analysis

Whole metagenome sequencing was chosen because it is more amenable for taxonomic classification, enabling in some cases classification to the strain or species level. Shotgun whole genome libraries were constructed using the Nextera XT kit (Illumina) according to manufacturer instructions, and sequenced on a MiSeq instrument (Illumina) using a paired-end 300 cycles protocol. Libraries were sequenced at an average depth of ~ 293,000 paired-ends reads per library. Taxonomic classification of sequences was conducted with Kraken against a customized database that included all full-length genome sequences of bacteria, archaea, viruses, fungi, protozoa from NCBI RefSeq and the human genome assembly GRCh38. Kraken reports the proportion of each library assigned to each taxa, so that quantification remains independent of library size. Sequences generated in this study are publicly available at the SRA portal of NCBI under the accession number SRP117355. Principal coordinate analysis (PCoA), Shannon diversity indices, the Kolmogorov-Smirnov test applied on them and PERMANOVA analysis were computed using Scikit-bio 0.5.1, on a subsample of 5000 bacterial reads from each sample, both for capsule and colonoscopy samples pre- and post-FMT. PERMANOVA analysis was performed using Bray-Curtis distances and 999 permutations.
eMethods 2. Questionnaire of Patient Perspectives Before FMT

1. From what has been explained to you, why are physicians conducting a trial that randomly assigns patients to receive fecal transplant by pill or by colonoscopy? (Check all that apply)
   □ To find out if one option leads to a more effective cure than the other
   □ To find out if one option is safer than the other
   □ To find out if patients prefer one option over the other
   □ Other reasons; please specify: _______________________________________
   □ For reasons that are not clear

2. Do the reasons for conducting this trial make sense to you?
   □ Yes
   □ No; please specify why not: __________________________________________

3. Which of the following words reflect your views or feelings about the idea of getting a fecal transplant? (Check all that apply)
   □ Neutral
   □ Natural remedy
   □ Innovative treatment
   □ Disgusting
   □ Unpleasant
   □ Gross
   □ Unsanitary
   □ Risky or unsafe
   □ Other; specify _______________________________________________________

   For Questions 3-5, please circle the number that represents your response.

4. How unpleasant, disgusting or gross do you find the idea of getting a fecal transplant by any delivery method?
   1. Not at all unpleasant  2. Moderately unpleasant  3. Extremely unpleasant

5. How unpleasant, disgusting or gross do you find the idea of getting a fecal transplant by taking a pill?
   1. Not at all unpleasant  2. Moderately unpleasant  3. Extremely unpleasant

6. How unpleasant, disgusting or gross do you find the idea of getting a fecal transplant by colonoscopy?
   1. Not at all unpleasant  2. Moderately unpleasant  3. Extremely unpleasant

7. If you had to choose which way to get a fecal transplant, what would influence your choice? (Check all that apply)
   ___ Effectiveness (which option is more likely to make me healthier)
   ___ Safety (which option is safer)
   ___ Aesthetics (which option is least unpleasant)
   ___ Cost of the procedure to health care system
   ___ My doctor’s recommendation
   ___ Other; please specify _______________________________________________________

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8. Have you ever had a colonoscopy before?
   □ No
   □ Yes; please circle the highest level of discomfort you experienced during colonoscopy:
   \[1\quad 2\quad 3\quad 4\quad 5\quad 6\quad 7\quad 8\quad 9\quad 10\]
   No discomfort Moderate discomfort Severe discomfort

9. Which fecal transplant method was randomly assigned to you?  ____ pills  ____ colonoscopy
   Do you have concerns about the method you were assigned to?
   □ No
   □ Yes; please specify: ______________________________________________________
eMethods 3. Patient Satisfaction and Preference Questionnaire Before FMT

1. Do you understand the purpose for randomly assigning patients to receiving fecal transplant by pill or by colonoscopy?
   □ No   □ Yes

2. How do you feel about the idea of fecal transplant, no matter how it is delivered into a person?
   
   1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10
   Not bad       Moderately gross       Extremely gross

3. How do you feel about fecal transplant offered by pills?
   
   1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10
   Not bad       Moderately gross       Extremely gross

4. How do you feel about fecal transplant offered by colonoscopy?
   
   1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10
   Not bad       Moderately gross       Extremely gross

5. If you can choose which way to receive fecal transplant, what factors would influence your choice?
   ____ effectiveness (ie. how well one option works compared to the other)
   ____ safety (ie. if one option is safer compared to the other)
   ____ asthetics (yuk factor)
   ____ cost of the procedure to health care system
   ____ your doctor’s recommendation (either for or against)
   ____ other; please specify ______________________________________________________

6. Have you ever had a colonoscopy before?
   □ No   □ Yes
   If you answer yes to question 6, please skip question 7.

7. What was your experience with your previous colonoscopy?
   
   1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10
   No discomfort       Moderate discomfort       Severe discomfort

   You have been randomly assigned to fecal transplant by:  ____ pills         ____ colonoscopy

8. How do you feel about being randomly assigned to the group you are in?
   
   1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10
   I wish I could be in the other group       It does not matter at all

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eMethods 4. Patient Satisfaction and Preference Questionnaire Post FMT

You were randomly assigned to fecal transplant by: ____ pills  ____ colonoscopy

If you were in the pill group, answer questions 1-3.

1. Did you experience trouble swallowing the pills?
   1 2 3 4 5 6 7 8 9 10
   No trouble  Moderate trouble  Significant trouble

2. Did you experience nausea with the pills?
   1 2 3 4 5 6 7 8 9 10
   No nausea  Moderate nausea  Significant nausea

3. Did you experience unpleasant taste or smell with the pills?
   1 2 3 4 5 6 7 8 9 10
   Not at all  Moderately unpleasant  Extremely unpleasant

If you were in the colonoscopy group, answer questions 4-6.

4. Did you experience side effects from sedation during colonoscopy?
   1 2 3 4 5 6 7 8 9 10
   No problem  Moderate problem  Significant problem

5. Did you experience discomfort during colonoscopy?
   1 2 3 4 5 6 7 8 9 10
   No discomfort  Moderate discomfort  Severe discomfort

6. Did you experience discomfort when you were supposed to retain fecal transplant?
   1 2 3 4 5 6 7 8 9 10
   No discomfort  Moderate discomfort  Severe discomfort

Everyone answers questions 7-8.

7. How would you rate your overall fecal transplant procedure?
   1 2 3 4 5 6 7 8 9 10
   Not unpleasant  Moderately unpleasant  Extremely unpleasant

8. If you can go back and choose, would you have fecal transplant the same way?
   □ No
   □ Yes
**eTable 1.** Details of Immunosuppressed Patients and Medications Used

<table>
<thead>
<tr>
<th>Category</th>
<th>Disease</th>
<th>Number of patients</th>
<th>Steroid</th>
<th>Immuno-suppressant</th>
<th>Biologic</th>
<th>Group assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory bowel disease</td>
<td>Ulcerative colitis</td>
<td>4</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>Capsules</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Crohn’s</td>
<td></td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>Liver transplant</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td></td>
<td>Renal transplant</td>
<td>2</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td></td>
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<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td>Capsules</td>
</tr>
<tr>
<td>Rheumatologic disorder</td>
<td>Rheumatoid arthritis</td>
<td>3</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Capsules</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td></td>
<td>Lupus</td>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Capsules</td>
</tr>
<tr>
<td></td>
<td>Dermatomyositis, vasculitis</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td>Other</td>
<td>Nephrotic syndrome</td>
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<td>+</td>
<td>+</td>
<td></td>
<td>Capsules</td>
</tr>
<tr>
<td></td>
<td>Bone marrow transplant</td>
<td>1</td>
<td>-</td>
<td>+</td>
<td></td>
<td>Capsules</td>
</tr>
</tbody>
</table>
**eTable 2. Comparison of Baseline Characteristics Between Participants With Complete and Incomplete Primary Outcome**

<table>
<thead>
<tr>
<th>Variable</th>
<th>In the Primary Per Protocol Analysis</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (N = 11)</td>
<td>Yes (N = 105)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>54.3 (18.3)</td>
<td>58.5 (18.7)</td>
</tr>
<tr>
<td>Females, No. (%)</td>
<td>7 (63.6%)</td>
<td>72 (68.6%)</td>
</tr>
<tr>
<td>Charlson comorbidity index&lt;sup&gt;a&lt;/sup&gt;, median (Q1-Q3)</td>
<td>4 (1 - 5)</td>
<td>3 (1 - 5)</td>
</tr>
<tr>
<td>Immunosuppressed patients, No. (%)</td>
<td>3 (27.3%)</td>
<td>14 (13.3%)</td>
</tr>
<tr>
<td>Use of immune modulator, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>· Corticosteroid</td>
<td>2 (18.2%)</td>
<td>7 (6.7%)</td>
</tr>
<tr>
<td>· Immunosuppressants</td>
<td>1 (9.1%)</td>
<td>10 (9.5%)</td>
</tr>
<tr>
<td>· Biologic</td>
<td>0 (0%)</td>
<td>5 (4.8%)</td>
</tr>
<tr>
<td>Body mass index (BMI), mean (SD)</td>
<td>24.9 (3.7)</td>
<td>26.1 (5.4)</td>
</tr>
<tr>
<td>Inpatient status at screening, No. (%)</td>
<td>3 (27.3%)</td>
<td>11 (10.5%)</td>
</tr>
<tr>
<td>PPI use prior to FMT, No. (%)</td>
<td>4 (36.4%)</td>
<td>21 (20%)</td>
</tr>
<tr>
<td>Number of RCDI episodes prior to FMT, median (Q1-Q3)</td>
<td>4 (3 - 5)</td>
<td>4 (3 - 5)</td>
</tr>
<tr>
<td>Duration of RCDI prior to FMT (months), median (Q1-Q3)</td>
<td>5 (4.1 - 6.8)</td>
<td>4.2 (3.1 - 7)</td>
</tr>
<tr>
<td>Duration of CDI treatment prior to FMT (months), median (Q1-Q3)</td>
<td>3 (2.1 - 4.2)</td>
<td>2.4 (1.8 - 3.7)</td>
</tr>
<tr>
<td>Number of CDI related hospital admissions prior to FMT, median (Q1-Q3)</td>
<td>1 (0 - 3)</td>
<td>0 (0 - 1)</td>
</tr>
<tr>
<td>IBD, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>· Ulcerative colitis</td>
<td>3 (27.3%)</td>
<td>7 (6.7%)</td>
</tr>
<tr>
<td>· Crohn’s disease</td>
<td>0 (0%)</td>
<td>3 (2.9%)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), median (Q1-Q3)</td>
<td>13.2 (11.3 – 14.1)</td>
<td>13.7 (12.9 – 14.6)</td>
</tr>
<tr>
<td>WBC (/uL), median (Q1-Q3)</td>
<td>8,200 (6,600 – 8,600)</td>
<td>7,400 (6,100 – 8,600)</td>
</tr>
<tr>
<td>Albumin (g/dL), median (Q1-Q3)</td>
<td>3.7 (3.4 – 4.1)</td>
<td>4.0 (3.6 – 4.2)</td>
</tr>
<tr>
<td>CRP (mg/dL), median (Q1-Q3)</td>
<td>0.10 (0.07 – 0.99)</td>
<td>0.29 (0.12 – 0.83)</td>
</tr>
<tr>
<td>Creatinine (mg/dL), median (Q1-Q3)</td>
<td>0.92 (0.72 – 1.22)</td>
<td>0.80 (0.69 – 0.95)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Charlson comorbidity index is a method of categorizing comorbidities based on International Classification of Diseases (ICD) diagnosis codes, and assigns a weighted score for each condition from 1-6 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.
Abbreviations: SD, standard deviation; WBC, white blood cell; PPI, proton pump inhibitor; CDI, Clostridium difficile infection; IBD, inflammatory bowel disease; CRP, C-reactive protein; Q1, first quartile; Q3, third quartile.

**eTable 3. Site Differences in FMT Efficacy by Capsule or Colonoscopy at the Level of City: Calgary vs Edmonton**

<table>
<thead>
<tr>
<th></th>
<th>Per protocol analysis</th>
<th>Worst case scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>No CDI Recurrence at week 12</td>
</tr>
<tr>
<td><strong>Calgary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule</td>
<td>26</td>
<td>24 (92.3%)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>22</td>
<td>20 (90.9%)</td>
</tr>
<tr>
<td>Rate Difference</td>
<td>1.4%</td>
<td>-1.9% to ∞</td>
</tr>
<tr>
<td><strong>Edmonton</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule</td>
<td>27</td>
<td>27 (100%)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>30</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>Rate Difference</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

To examine site differences in efficacy, analyses were performed separately for each city, recognizing that this study was not powered for the non-inferiority of capsules compared to colonoscopy in each city. In Calgary, the per protocol analysis revealed 92.3% success rate (24 out of 26) for capsule and 90.9% (20 out of 22) for colonoscopy, leading to a rate difference of 1.4% (95% 1-sided confidence interval of -11.9% to ∞, p=0.021). In Edmonton, the per protocol analysis revealed 100% success for both capsule (29 out of 29) and colonoscopy (35 out of 35) groups.

When assuming the worst-case scenario, the success rate for Calgary was 85.7% (24 out of 28) for capsule group and 91.7% (22 out of 24) for colonoscopy, leading to a rate difference of -6% (95% 1-sided confidence interval of -23% to ∞, p=0.084). In Edmonton, the success rate was 93.1% (27 out of 29) for capsule group and 100% (35 out of 35) for colonoscopy, leading to a rate difference of -6.9% (95% 1-sided confidence interval of -14.6% to ∞, p=0.043). Therefore only results for the entire cohort were presented in the manuscript.

**eTable 4. Minor Adverse Events**

<table>
<thead>
<tr>
<th>Minor adverse event</th>
<th>Capsule group</th>
<th>Colonoscopy group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Minor AEs were experienced by 3/56 patients (5.4%) in the capsule arm and 7/56 patients (12.5%) in the colonoscopy arm (some patients reported multiple minor AEs).
eResults 1. Cost Estimate of FMT by Colonoscopy and Oral Capsules

Cost of FMT by colonoscopy
The cost of a colonoscopy is an aggregate value taken from a previously published literature estimate of $913 and increased to 2015 CAD dollar using the consumer price index to a cost of $950.\(^1\),\(^2\) This cost is all inclusive, and covers facility fees, physician billing, nursing time and drugs. The estimated aggregate cost of manufacturing slurry is CAD $170 which includes the cost of technician time and all consumables. Cost per person is assumed to be the same for those receiving FMT by colonoscopy. Below is the calculation to attain the overall cost of FMT by colonoscopy.

\[
\text{Adjusted cost of colonoscopy to 2015 } + \text{ cost of slurry manufacturing} = \text{CAD } 950 + \text{CAD } 170 = \text{CAD } 1120
\]

Cost of FMT by oral capsules
The cost of FMT by oral capsule is an aggregate cost based on the costs of the capsule manufacturing (estimated at CAD $347) and the nurse wage for an hour of intervention time for administering treatment (CAD $48.37/hr).\(^3\) Cost per person is assumed to be the same for those receiving FMT by capsules. The calculation for FMT by capsules covers the cost of technician time and all consumables and is shown below.

\[
\text{Hourly wage of Registered Nurse} \times \text{ 1 hour of intervention time} + \text{oral capsule manufacturing cost} = \text{CAD } 48.37 + \text{CAD } 347 = \text{CAD } 395.37
\]

eReferences


eResults 2. Details of 2 Patients With IBD Flares Post FMT in Colonoscopy Group

Patient 1: This patient was a 61 year-old male with a 10-year history of mild ulcerative pancolitis maintained on mesalamine. When he was assessed for FMT, he had pancolitis (Mayo score of 2) and was started on a tapering course of prednisone in addition to vancomycin, which put him into clinical remission. At the time of FMT by colonoscopy 4 months later, he had mild pancolitis (Mayo score of 1), and developed a flare 2 weeks after FMT, shortly after steroid taper. His therapy was escalated to vedolizumab and clinical remission was achieved.

Patient 2: This patient was a 24 year-old woman with a 1-year history of ulcerative pancolitis (UC), maintained on adalimumab. At the time of FMT assessment she was in clinical remission while on suppressive vancomycin therapy, but had mild inflammation in the proximal colon endoscopically at the time of her FMT delivered by colonoscopy. She developed a UC flare 4 weeks after FMT, and remission was achieved with switching therapy to infliximab.

Both of these patients had done well without CDI recurrence following adjustment in their therapies.

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**eFigure.** Taxonomic Classification of the Most Abundant Taxa of Bacteria Found in Stool Samples. The histogram bars show the average abundance for each taxa in each group of patients. Only taxa that were present at abundance of 1% or greater are shown. Only the names of the 30 most abundant taxa are depicted. Top gray bar labelled “others” represents all taxa that individually represent less than 1% of the total bacteria population classified. The number of patients at each time point is shown in parentheses (capsule group, colonoscopy group): BFMT (23, 23), 1WAFMT (22, 23), 4WFMT (14, 14) and 12WFMT (23, 23).

Abbreviations: BFMT, before FMT; 1WAFMT, 1 week after FMT; 4WAFMT, 4 weeks after FMT; 12WAFMT, 12 weeks after FMT; s, species; u, strain; p, phylum; g, genus; f, family; o, order.