Clinical Primer:
Position Statement for Fecal Microbiota Transplantation Administration for Recurrent Clostridium difficile Infection

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Disclaimer
Fecal microbiota transplantation (FMT) for Clostridium difficile infection (CDI) is an emerging field and research is rapidly evolving, although significant heterogeneity in the current body of evidence still exists. This document is intended as a practical discussion of clinical considerations to take into account when preparing for the administration of FMT, but does not constitute a formal recommendation of best practice. Clinicians are responsible for examining the risks, benefits and alternatives in the context of each patient for which FMT may be a therapeutic option.

1. Lower or Upper Gastrointestinal Delivery?
A systematic review and meta-analysis of FMT for recurrent Clostridium difficile infection (n = 273) has suggested that lower gastrointestinal delivery (colonoscopy or enema) has higher rates of clinical resolution compared to upper gastrointestinal delivery. Specifically, in a priori subgroup analysis, lower gastrointestinal delivery had a 91.4% clinical cure rate compared to 82.3% for upper gastrointestinal delivery (unweighted proportion difference 9.1%, p < 0.05). This is consistent with randomized controlled evidence where nasoduodenal delivery was utilized with an 81% clinical cure rate after a single FMT. Only one small pilot study (n = 20) has compared FMT modalities. Although this study was underpowered to offer a meaningful conclusion on the ideal delivery modality, after a single FMT, they found a clinical cure rate of 80% (8/10) in the colonoscopy arm versus 60% (6/10) in a nasogastric tube (NGT) group arm.

Each delivery route carries its own set of potential procedure-related adverse events. NGT administration carries a risk of aspiration, thus the rationale for lower volume infusions; however, aspiration risks are theoretically minimized with nasoduodenal, nasojejunal or endoscopic delivery with infusion beyond the pyloric sphincter. Additionally, anecdotal observations suggest that upper gastrointestinal delivery may carry a risk of small bowel bacterial overgrowth, although this is not well described. Broadly, upper gastrointestinal delivery should be avoided if there is evidence of an ileus, which may be part of the severe-complicated CDI spectrum (Section 10), or if patients are experiencing nausea/vomiting, as the risk of aspiration is likely elevated.

Colonoscopy has rare but recognized procedure-related adverse events including perforation, bleeding, sedation-related aspiration or cardiopulmonary events. However, colonoscopy also has added utility in its diagnostic value. There are anecdotal reports of previously undiagnosed inflammatory bowel disease and colon cancer detected at the time of FMT by colonoscopy. It is
worth noting that a full colonoscopy in some CDI patient populations (e.g., toxic megacolon, severe pancolitis) may carry increased risk of perforation, and a flexible sigmoidoscopy or an alternate less invasive delivery modality is likely preferable, although there is limited data.

Lastly, retention enema is likely low-risk but may be less effective in some patients with poor sphincter tone. Regardless, in patients with advanced age, multiple comorbidities or limited life expectancy, this less invasive mode may be preferable.

Overall, clinicians should use their clinical judgment on the ideal delivery modality based on the risks, benefits and alternatives directly related to an individual patient’s clinical situation.

2. Patient Preparation

Broadly, there is heterogeneity in current practices due to a paucity of comparative evidence. However, below are common clinical points for consideration:

**Antibiotic**: In recurrent CDI, anecdotal experience suggests discontinuing anti-CDI antibiotics (e.g. vancomycin, fidaxomicin) **2 days** before FMT, although the literature reports between 1-3 days.\(^3,7,8\) The aim of discontinuing antimicrobial therapy pre-FMT is to ensure antibiotics do not impact the newly transferred microbiota.

**Bowel Preparation**: The FMT Workgroup recommends a standard large volume bowel preparation for both upper and lower gastrointestinal delivery, if the patient is able to tolerate based on the severity of their illness.\(^9\) This is consistent with a randomized controlled trial of FMT in CDI which used 4L of a standard polyethylene glycol – electrolyte preparation the day prior to nasoduodenal delivery.\(^3\) Anecdotal evidence suggest a limited bowel prep (1 bottle of magnesium citrate with 2 dulcolax) or no preparation may be equally effective; however, there is an absence of evidence examining the role of bowel preparation in upper gastrointestinal delivery. Broadly, if a patient is intolerant to bowel preparation, FMT by upper gastrointestinal delivery can still be employed in absence of bowel preparation.

**Loperamide**: The use of loperamide for FMT by lower gastrointestinal delivery is optional. The rationale for its use is to prolong fecal material retention; however, the rates of clinical success appear similar with or without, so most FMT tend not to use loperamide.\(^9\)

**Proton Pump Inhibitors**: For upper gastrointestinal delivery, the FMT Workgroup suggests a proton pump inhibitor the evening before FMT and the morning of the procedure to minimize the impact of gastric acid on the donor microbiota during a FMT.

3. Loading FMT Material

**Approach 1**:

1) Pour material ideally into a sterile container, although a clean K-basin or equivalent container is commonly used.

2) Using universal precautions, pre-load material with standard syringes that have a tip
compatible with the endoscope port for direct delivery of material through channel. A similar approach can be employed for naso-enteric or enema loading of material.

Approach 2:
1) Using universal precautions, pre-load syringes directly from OpenBiome container using standard syringes that have a tip compatible with the endoscope port for direct delivery of material through channel. Some syringes are too large to enter container opening directly, in which case, Approach 1 should be employed. A similar approach can be employed for naso-enteric or enema loading of material.

Endoscopic channel or naso-enteric tube blockage:
OpenBiome material is passed through a 330-micron filter to exclude particulate matter. Accordingly, channel blockage is highly unlikely and material does not require dilution to mediate. To our knowledge, our partners have not had any concerns regarding channel or tubing blockage.

4. Administration via Colonoscopy/Sigmoidoscopy
Standard guidelines apply on the best practices to conduct a colonoscopy. Infusion techniques vary at many institutions, however, anecdotal recommendations suggest infusion of all 250mL of fecal material in the cecum or most proximal aspect safely reached by colonoscopy. CDI tends have enrichment in the cecum, and the material will flow downstream from the cecum to rectum, so interval bolus dosing is likely not necessary although comparative studies are lacking. In patients who are unable to tolerate a full colonoscopy, FMT by sigmoidoscopy has been anecdotally employed with delivery in the most proximal aspect safely reached. One or two standard endoscope-compatible flushes can be utilized to clear the channel of fecal material.

5. Administration via Retention Enema
Practices related to FMT by enema are heterogeneous and head-to-head studies are absent. However, transfer of the all 250mL of fecal material using universal precautions to a standard retention enema bag is recommended. Some groups have empirically suggested administration of 8 ounces (~250mL) over 1 hour with material retained for at least 1 hour, although data is limited on the timing parameters. In terms of position, patients should be positioned in the left lateral decubitus position, and if patients are mobile, asked periodically to rotate 180 degrees to a right lateral position and back to the left lateral position, to theoretically promote movement of the FMT material throughout the colon.

6. Administration via Upper Gastrointestinal Delivery
Standard nasogastric, nasoduodenal and nasojejunal FMT delivery have all been reported with variable techniques. Broad safety principles include positioning the patient to sit upright at 45 to 90 degree angle to reduce the risk of aspiration or regurgitation. Additionally, confirmation of appropriate naso-enteric tube placement by radiograph or fluoroscopy before fecal instillation should minimize procedure-related risk. There is limited data on a recommended rate...
of infusion protocol, however, data from a randomized trial using nasoduodenal delivery infused material over 2-3 minutes, removed the tube 30 minutes after infusion, and monitored patients post-procedure for 2 hours. FMP30 have been specially formulated to ensure maximal concentration of fecal material, and accordingly, only a single FMP30 is required. FMP250 material is not recommended for use in the upper gastrointestinal tract. Appropriate caution should be employed for FMT delivery by a gastrojejunostomy tube placed through a G-tube given a recent case report of this technique leading to sepsis. Endoscopic delivery should be performed under direct visualization, with delivery of material in the most distal portion of the small bowel, at least beyond the second portion of the duodenum, to minimize aspiration risk. Routine post-endoscopic care and monitoring should be employed.

7. Follow-Up
Standard clinical practice suggests a clinic visit at 8-weeks post-FMT to assess for clinical symptoms suggestive of recurrence. Repeat stool testing for CDI is of limited utility as CDI positive status may persist for months. It is recommended that FMT clinicians conduct telephone follow-up assessments in the short (Week 1 post-FMT) and intermediate (Week 4 post-FMT) time points. Additionally, patients should be counseled by clinicians to monitor for potential adverse events and when to seek clinical care. Lastly, patients should receive OpenBiome Patient Education material in order to provide guidance on antibiotic stewardship and household cleaning techniques to reduce the risk of CDI re-infection.

8. Non-Response Regimen
Given the high rates of clinical success with a single FMT, particularly by colonoscopy, non-responsive patients must be carefully evaluated to rule out other etiologies. Recurrence is often reinfection either driven by a failure to clean high-touch surface areas/bathroom at home, or possible re-exposure after repeat antibiotics. Accordingly, patient education and post-FMT counseling is vital in relation to household cleaning and antibiotic stewardship. Post-infectious irritable bowel syndrome (IBS) or pre-existing IBS are challenging to delineate from recurrent CDI given the absence of a ‘test of cure’, but must be considered clinically. A course of vancomycin or fidaxomicin in preparation for a repeat FMT may empirically help, as those with IBS are unlikely to respond to anti-CDI therapy but those with recurrent CDI typically will. If the clinical context suggests a non-response to FMT secondary to CDI, a repeat FMT is suggested from a difference donor, and preferably by colonoscopy unless there are contraindications. It should be noted that enema delivery may require multiple treatments, especially in an elderly population with poor rectal sphincter tone, and some groups employ a protocol where a repeat FMT is conducted if diarrhea recurs within 7 days.

9. Immunocompromised Host
There is limited data for FMT in recurrent CDI among the immunocompromised population. The most robust data come from a multi-center retrospective review of 80 (75 adult and 5 pediatric) immunocompromised patients with CDI, predominantly outpatient, undergoing FMT. The reason for immunosuppression included: HIV/AIDS (3), solid organ transplant (19), oncologic condition (7), immunosuppressive therapy for inflammatory bowel disease (IBD; 36), and other
conditions/medications (15). The cure rate after a single FMT was 78% and the overall cure rate was 80%. Overall, 15% of patients had a serious adverse event within 12-weeks post-FMT, of which 10 were admitted to hospital. Two deaths occurred: a sedation-associated aspiration during FMT by colonoscopy; and the other unrelated to FMT. No patients developed infections definitely related to FMT; however 2 patients developed unrelated infections and 5 had self-limited diarrheal illness in which no causal organism was identified. One patient had a superficial mucosal tear at the time of colonoscopy.

Broadly speaking, immunocompromised patients appear to have approximately the same rates of clinical cure; however, serious adverse events must be monitored for closely, and more data is needed given the limitations of retrospective case series data.

10. Severe-complicated CDI

Severe and severe-complicated CDI defined by the 2012 American College of Gastroenterology Guidelines (Table 1) appears to be a different phenotype then recurrent CDI. Accordingly, a single FMT approach may be less likely to have clinical success in severe and severe-complicated CDI non-responsive to standard therapy. Recently, FMT has been proposed as an option utilizing an endoscopic response-guided approach, which may be particularly useful in non-surgical candidates. In an open-label cohort study (n = 17), after discontinuing antibiotics 12-24 hours before FMT, and undergoing split dose standard PEG prep if no evidence of ileus/obstruction, FMT was delivered by colonoscopy to the most proximal region safely reached. If pseudomembranes were identified, patients reinitiated oral vancomycin 24 hour after FMT and continued for 5 days. A repeat FMT by colonoscopy was given on day 7. If pseudomembranes persisted, vancomycin was restarted the following day for a 5 days course and a third FMT was offered on day 13. If pseudomembranes were absent during any colonoscopy, no further therapy was initiated. The results were promising with a combined clinical cure rate of 88%. Further research is required to confirm this protocol; however, in absence of alternatives, this approach appears optimal compared to a single FMT technique.
Table 1 – modified from Surawicz et al. American Journal of Gastroenterology 2012

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<th>CDI Severity</th>
<th>Criteria</th>
<th>Treatment</th>
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<td>Severe CDI</td>
<td>Serum albumin &lt;3g/dL plus ONE of the following:&lt;br&gt;WBC ≥ 15,000 cells/mm³&lt;br&gt;Abdominal tenderness</td>
<td>Vancomycin 125mg PO QID x 10 days</td>
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<td>Severe-Complicated CDI</td>
<td>Any of the following attributable to CDI:&lt;br&gt;Admission to ICU for CDI&lt;br&gt;Hypotension with or without vasopressors&lt;br&gt;Fever ≥ 38.5°C&lt;br&gt;Ileus or significant abdominal distension&lt;br&gt;Mental status changes&lt;br&gt;WBC ≥ 15,000 cells/mm³ or &lt;2,000 cells/mm³&lt;br&gt;Serum lactate level &gt;2.2mmol/L&lt;br&gt;End organ failure (e.g., mechanical ventilation, renal failure)</td>
<td>Vancomycin 500mg PO QID and metronidazole 500mg IV q8h, and vancomycin per PR (vancomycin 500mg in 500mL saline as enema) QID AND Surgical consultation</td>
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References


