Faecal microbiota transplantation for *Clostridium difficile* infection: a multicentre study of non-responders

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Faecal microbiota transplantation (FMT) has emerged as an effective therapy for recurrent *Clostridium difficile* infection (rCDI), but 10–30% of patients do not respond to treatment.[1,2] Data on this patient phenotype are scarce; in this article we describe a cohort of 135 patients in the United States who did not respond to FMT.

We assessed consecutively collected prospective case report forms for patients who did not respond to FMT for rCDI, completed by physicians during August 2014 – November 2015 and submitted to a not-for-profit stool bank (OpenBiome, http://www.openbiome.org/).[3] Demographic, clinical, and treatment characteristics were evaluated. Non-response to FMT was defined by clinical symptoms and laboratory confirmation or endoscopic evaluation, according to standard of care. Clinicians who reported non-response were asked to complete a detailed non-response form.

Outcomes for 1845 FMT treatments during the study period were reported; the efficacy rate was 84.0%. Among the 295 non-responders, 135 non-response forms (46% response rate) were received from 74 health care facilities in 27 US states and the Netherlands. Most of these 135 non-responders were women (70%) and Caucasian (79%); the mean age was 65.9 years; 23 patients (17%) had previously undergone FMT. Of ten patients who received FMT by nasogastric tube, two had not received pre-procedure proton pump inhibitors (PPI). At least 19% of patients did not clean high-touch surface areas at home, such as toilets; only 30% of non-responders were clinically assessed for post-infectious irritable bowel syndrome (IBS) (Box).

Three novel observations are particularly important for practice. First, some physicians who performed FMT by nasogastric tube did not provide pre-therapy PPIs. Acid suppression is recommended for protecting the microbiota from gastric acid when delivered above the pre-pyloric sphincter; not doing so may significantly affect the efficacy of treatment.[1,4]

Second, 19% of non-responders did not decontaminate toilets from CDI spores after FMT. As molecular typing studies indicate that 10–50% of rCDIs are caused by re-infection,[2] our results suggest that counselling patients about cleaning high-touch surfaces may be useful; however, more evidence about the benefits of home decontamination is required.

Finally, only 30% of patients were assessed for post-infectious IBS, a common aetiology of loose stool after CDI. Concerns about the accuracy of rCDI diagnosis in patients referred for FMT have been reported.[5] There is no gold standard test for distinguishing these entities; differentiating rCDI from post-infectious IBS with underlying colonisation detected by polymerase chain reaction is particularly challenging.

Our study included the largest cohort of FMT treatment non-responders reported to date. We publish our findings with caution, given the uncontrolled design of our study and the potential for selection bias. However, this large multicentre study

Demographic and clinical characteristics of 135 United States patients who did not respond to faecal microbiota transplantation (FMT) for *Clostridium difficile* infection (CDI)

Characteristic	
Age at time of FMT (years), mean (SD)	65.9 (17.9)
Sex (men)	41 (30%)
Ethnic background	
Caucasian	107 (79%)
Black or African American	11 (8%)
Hispanic or Latino	6 (4%)
Other	3 (2%)
Not reported	8 (6%)
Long term care resident	19 (14%)
History of inflammatory bowel disease	17 (13%)
History of irritable bowel syndrome	18 (13%)
Medications at time of FMT	
Proton pump inhibitors	53 (39%)
Immunosuppressive agents	33 (24%)
Laxatives	3 (2%)
Anti-motility agents	26 (19%)
Horn index (of disease severity)	
1 (mild)	7 (5%)
2 (moderate)	62 (46%)
3 (severe)	45 (33%)
4 (extremely severe)	7 (5%)
Not reported	14 (10%)
Received antibiotics prior to CDI diagnosis	81 (60%)
Health care-associated CDI	34 (25%)
Initial CDI diagnosis method*	
Toxin A or B	42 (31%)
Polymerase chain reaction	89 (66%)
Anaerobic culture/other	2 (2%)
Not reported	12 (9%)
CDI treatment prior to FMT*	
Vancomycin	84 (62%)
Metronidazole	59 (44%)
Fidaxomicin	2 (2%)
CDI type*	
Refractory CDI	48 (37%)
Recurrent CDI	101 (77%)
Average number of recurrences, mean (SD)	3.0 (1.9)
Inpatient admission to hospital	79 (61%)
NAP-1 strain of *C. difficile*	9 (7%)
FMT delivery modality	
Colonoscopy	81 (60%)
Enema	10 (7%)
Flexible sigmoidoscopy	2 (2%)
Oesophagogastroduodenoscopy	15 (11%)
Nasogastric tube	10 (7%)
Nasoduodenal tube	2 (2%)
Other	11 (8%)
Not reported	4 (3%)
Colonoscopy preparation†	95 (74%)
Proton pump inhibitor prior to nasogastric tube	8 (80%)
Frozen FMT thaw methods	
Water bath	73 (56%)
Room temperature	40 (30%)
Time between FMT and non-response (days), mean (SD)	15.3 (12.8)
Patient decontaminated toilets at home	
Yes	51 (38%)
No	26 (19%)
Not reported	58 (43%)
Assessed for post-infectious irritable bowel syndrome	41 (30%)

NAP-1 = North American pulsed-field gel electrophoresis type 1; SD = standard deviation.
* Physicians could select more than one option. † Colonoscopy preparation is applied outside colonoscopy because of its potential role in spore clearance. ◆

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offers insights into the heterogeneity of the current state of FMT practice. Given the broad adoption of FMT, guidelines are required for improving education, developing criteria for assessing non-response to FMT, and guiding the informed consent process, so that clear advice about risks, benefits and alternatives can be provided, including the risk of non-response.

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Competing interests: Majdi Osman, Alexandra Lieberman and Zain Kassam are employed at OpenBiome, a not-for-profit stool bank that provides clinicians with preparations for faecal microbiota transplantation and supports research into the human microbiome and its role in medicine. Zain Kassam is a research consultant and shareholder at Finch Therapeutics; Jessica Allegretti is a special advisor to OpenBiome and research consultant at Finch Therapeutics. ■

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