Pilot study of autologous fecal microbiota transplants in nursing home residents: Feasibility and safety☆

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ARTICLE INFO

ABSTRACT

Introduction: Antibiotic resistant bacterial infections (ARBIs) are extremely common in nursing home residents. These infections typically occur after a course of antibiotics, which eradicate both pathological and beneficial organisms. The eradication of beneficial organisms likely facilitates subsequent ARBIs. Autologous fecal microbiota transplant (aFMT) has been proposed as a potential treatment to reduce ARBIs in nursing home residents. Our objective was to determine the feasibility and safety of aFMT in a nursing home population.
Methods: Pilot clinical trial. We evaluated feasibility as total number of stool samples collected for aFMT production and safety as the number and relatedness of serious (SAE) and non-serious adverse events (AE).
Results: We screened 468 nursing home residents aged ≥18 years for eligibility; 67 enrolled, distributed among three nursing homes. Participants were 62.7% female and 35.8% Black. Mean age was 82.2 ± 8.5 years. Thirty-three participants underwent successful stool collection. Seven participants received antibiotics; four participants underwent aFMT. There were 40 SAEs (17 deaths) and 11 AEs. In the aFMT group, there were 3 SAEs (2 deaths) and 10 AEs. All SAEs and AEs were judged unrelated to the study intervention.
Conclusions: In this pilot study of aFMT in nursing home residents, less than half were able to provide adequate stool samples for aFMT. There were no related SAEs or AEs during the study. In sum, we conclude aFMT has limited feasibility in a nursing home population due to logistic and technical challenges but is likely safe.
Trial registration: ClinicalTrials.gov Identifier: NCT03061097.

1. Introduction

Fecal microbiota transplants (FMT), in which the microbial community of a donor(s) is administered to restore the microbiome of another individual, have emerged as a highly effective treatment for recurrent Clostridioides difficile (previously named *Clostridium difficile*) infections [1,2]. *C. difficile* is an example of an antibiotic resistant bacterial infection (ARBI), which typically occurs after antibiotic treatment.

Within the body, there exists an innate microbial community that creates an inhospitable environment for *C. difficile* and other ARBI pathogens. Evidence suggests that the commensal microbiome suppresses infectious pathogens through various mechanisms, including depletion of nutrients and production of metabolites that suppress germination of spore-forming pathogens (e.g. *C. difficile*) [1]. A course of antibiotic treatment destroys this innate microbiome [3], thus enabling organisms such as *C. difficile* to flourish. As evidence, prior work has demonstrated that the loss of innate microbiome due to antibiotic treatment reduces the amount of bacteria needed to cause a pathological infection [4–7].

Most FMT treatments are formulated using microbiomes reconstituted from stool from another individual(s). Thus, there is always a small risk of unintentional transmission of pathogens from one individual to another. Recently, autologous FMT (aFMT) has been proposed as a solution. Much like autologous blood banking prior to a surgical procedure, a person "banks" their own microbiome from stool samples collected during a period of health, which are used later when needed. The risk of transmission of pathogens from another individual is greatly reduced, as individuals would receive back their "own" microbiome [8].

Prior studies have evaluated the benefits of aFMT in persons undergoing bone marrow transplant [9]. However to our knowledge, no studies have evaluated the benefits of aFMT in nursing home residents. Nursing home residents are extremely vulnerable to ARBI, as antibiotic overuse is common in this setting [10]. For this high-risk population, we hypothesized that aFMT may be a means to prevent ARBI that occur post-antibiotic treatment. As nursing home residents are medically complex with frail health, the feasibility and safety of aFMT must be examined before fully pursing aFMT as a therapy. In this study, our primary objective was to determine the feasibility and safety of aFMT in nursing home residents.

2. Materials and methods

2.1. Study design and participants

The study duration was from June 2017 to December 2019. From June 2017 to June 2018, we recruited participants from four local nursing homes located in an urban setting in the United States, determining eligibility through chart review. Inclusion criteria were age $\geq$18 years and permanent residence in the nursing home. Persons were excluded if they were enrolled in hospice, had a colostomy, or had an allergy to glycerol or sodium chloride, which were components of the aFMT. Our initial recruitment goal was 180 participants.

As many nursing home residents are cognitively impaired, we utilized two strategies for recruitment. For those who had severe cognitive impairment as determined by chart review, we sent a letter to their health care proxy introducing the study and followed up with phone calls. For those who were not cognitively impaired, we approached individuals directly in the nursing home to determine interest. All participants (or their health care proxies when appropriate) provided written informed consent. The Boston University Medical Campus Institutional Review Board approved the study (H-35722) and the study was registered at ClinicalTrials.gov (NCT03061097).

2.2. Demographics and medical history

We obtained demographic, comorbidity and medication data from the medical record. Each participant also underwent a baseline physical examination after informed consent.

2.3. Stool collection

Initial stool collections occurred between 7 a.m. and 3 p.m. for three consecutive days (Tuesday-Wednesday-Thursday) at each nursing home, and each nursing home underwent at least 6 days of stool collections. We chose this strategy to permit multiple attempts of stool collection for each participant. Prior to each collection, participants were screened for any gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting or diarrhea) in the prior 30 days, or antibiotic medications in the prior 42 days. On the day of collection participants were checked for fever (temperature of $\geq$100.4 °F). On a collection day, study staff checked in periodically with a participant about the need to defecate. If continent, we asked participants to defecate directly into a collection receptacle. If incontinent, we collected the stool sample from their disposable brief, and transferred the sample into the collection receptacle. We removed any visible debris from the disposable brief. After stool collection, we also obtained three rectal swabs from the participant. Stool samples and swabs were immediately refrigerated after collection. Stool samples were shipped to the manufacturing facility (OpenBiome, Cambridge, MA) within 12 h. Swabs were shipped either directly to the processing laboratory (see section 2.4 for details), or to the manufacturing facility (OpenBiome, Cambridge, MA) and then to the processing laboratory (see section 2.4 for details).

2.4. Screening of stool samples and processing into autologous FMT

Only stool samples that weighed at least 40 g and met a consistency criteria (Bristol Stool Scale 1 to 6) were permitted. We tested the stool samples for Clostridioides difficile (previously known as *Clostridium difficile*; Toxin Gene PCR assay, LabCorp, Burlington, NC or Toxin B PCR assay, Quest Diagnostics, Secaucus, NJ) carbapenem-resistant *Enterobacteriaceae* (culture-based assay, Massachusetts Host-Microbiome Center at Brigham and Women's Hospital, Boston MA), and extended spectrum beta-lactamase producing organisms (culture-based assay, Massachusetts Host-Microbiome Center at Brigham and Women's Hospital, Boston MA), and vancomycin-resistant *Enterococcus* (culture-based assay, Massachusetts Host-Microbiome Center at Brigham and Women's Hospital, Boston MA).

If the stool sample was negative for all tested pathogens, the sample was processed into aFMT at the manufacturing facilities, the details of which have been described previously [11]. Placebo FMTs consisted of a mixture of sodium chloride, glycerol, and brown food coloring for masking agent.

2.5. Randomization

Participants became eligible to receive the aFMT or placebo FMT if they received antibiotics. Participants were randomized within seven days of verification of antibiotic treatment on a 2:1 basis with a random permuted block sizes of three for either aFMT or placebo FMT. We anticipated that 20 participants would be eligible for the intervention, based on historical data of prior antibiotic use at the nursing home sites.

2.6. FMT intervention

The aFMT or placebo FMT was administered within eight weeks of antibiotic treatment. On day of procedure, the aFMT or placebo FMT was thawed between 30 and 60 min in a water bath at approximately 30 °C. The aFMT or placebo FMT was then transferred to two enema squeeze bottles. The participant was placed in the recumbent position. The bottle nozzle was placed at least 3–4 cm into the anus and aFMT or placebo FMT administered over approximately a 10-min period. A study clinician or nurse monitored the participant for 30 min post-procedure.

2.7. Feasibility and safety

The primary outcomes were feasibility and safety of aFMT. Feasibility was determined by the number of participants from whom we were able to successfully collect an adequate stool sample for aFMT. Safety was determined by the occurrence of SAEs and AEs. During the study, the study team periodically reviewed all participants' medical records for SAEs and AEs. If the medical record was insufficient, study staff communicated with participant's clinician about the participant

either in person, phone, or via secure e-mail. We also obtained relevant medical records from outside facilities (e.g. hospital or emergency room) if care was sought outside the nursing home for a possible SAE or AE. In addition, participants who had the aFMT intervention also underwent assessments, which included a physical exam by clinical staff, at days 3 (±1 day), 7 (±2 days), 28 (±5 days), as well as 6 months (±14 days) after the intervention. A study clinician reviewed each event to determine relatedness to the study procedures and the study intervention. An external data and safety monitoring board also reviewed all events.

2.8. Microbiome composition

Samples were prepared and sequenced at the University of Michigan DNA Sequencing Core (Ann Arbor, MI; brcf.medicine.umich.edu/cores/advanced-genomics/) on an Illumina MiSeq (2 × 250 bp paired-end). 16S rRNA reads were processed using QIIME 2 (version 2019.10) [12]. Reads were joined (plugin *vsearch* and method *join-pairs*, default parameters), primer trimmed (*cutadapt trim-paired*, discarding untrimmed reads), quality filtered (*quality-filter q-score-joined*, default parameters), and denoised (*deblur denoise-16S*, trim length, 253 nt; minimum reads per feature, 1) with Deblur [13]. Taxonomies were assigned to amplicon sequence variants using a naïve Bayesian classifier (*feature-classifier classify-sklearn*, trained on Greengenes 13_8 99% OTUs) [14,15].

3. Results

3.1. Characteristics of study sample

We screened 468 nursing home residents at four nursing homes for eligibility, as shown in Fig. 1. Informed consent was completed by 78 individuals and/or their proxies. Due to staffing limitations, we removed one nursing home from the study and thus withdrew 11 participants. Our final sample size was 67 participants. As shown in Table 1, 62.7% of the participants were female with a mean age of 82.2 years (range 63.6–96.4 years). The majority of participants were identified as white. One nursing home housed 46% of the participants. Dementia was present in 57% of the participants. Hypertension was diagnosed in 45% of the participants, while 30% had diabetes.

3.2. Feasibility

As shown in the Figure, we attempted to collect stool samples for aFMT from 67 participants. Adequate stool samples of appropriate volume and consistency were collected from 33 participants (49%). Eleven participants withdrew after their successful stool collection. Of the remaining 22 participants, eight participants received antibiotics, making them eligible for the intervention. One participant died prior to randomization. Four participants were randomized to aFMT and three to the placebo FMT. In the placebo group, one participant did not receive the intervention due to being out of intervention window following antibiotic exposure, and two withdrew prior to the placebo intervention.

3.3. Safety

Table 2 describes the serious (SAEs) and non-serious adverse events (AEs) that occurred. During the study, 17 (25%) of the participants died, and 21 hospitalizations occurred. A total of 27 participants experienced at least one SAE. Eight participants experienced two or more SAEs, including one participant who underwent five hospitalizations. In the aFMT group, there were two deaths and one hospitalization. Ten AEs occurred in the aFMT group, including one participant who experienced diarrhea, which self-resolved. All serious and non-serious adverse events were deemed unrelated to the study intervention.
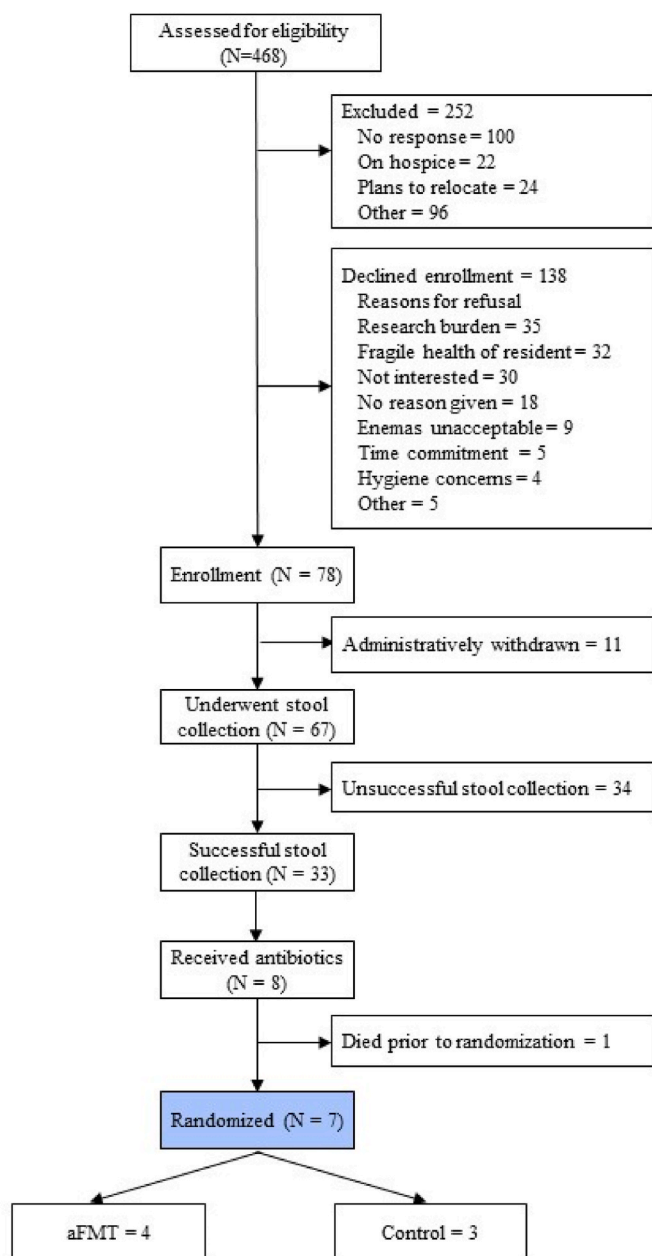

Fig. 1. CONSORT diagram of study.

3.4. Microbiome composition at baseline

Out of the 33 stool samples collected, we analyzed 32 samples for microbiome composition. One sample was discarded due to contamination. Overall, organisms from the *Firmicutes* phylum were the most predominant. On 16S rRNA sequencing, organisms from *Firmicutes* phylum were the most predominant. We found increased abundance of *Proteobacteria* compared to younger populations (Supplemental Figure), consistent with prior studies of older adults [16–18].

4. Discussion

In this pilot study, we explored the feasibility and safety of aFMT in nursing home residents. In terms of feasibility, we successfully collected adequate stool samples for aFMT from about half of the participants (49%). Three participants subsequently underwent the aFMT intervention. While a total of 40 SAEs and 11 AEs occurred, including 17 deaths,

Table 1
Demographics of study sample.

Characteristic Mean ± SD or no. (%)	All participants (N = 67)	aFMT (N = 4)	Placebo (N = 3)
Female	42 (62.7)	1 (25.0)	2 (66.7)
Age in years	82.2 ± 8.5	79.2 ± 8.4	80.8 ± 15.2
White	39 (58.2)	2 (50.0)	1 (33.3)
Black	24 (35.8)	2 (50.0)	2 (66.7)
Asian	1 (1.5)	0	0
Other/unknown	4 (6.0)	0	0
Education – some college or higher	2 (3.0)	1 (25.0)	0
Sites			
Site 1	15 (22.4)	2 (50.0)	1 (33.3)
Site 2	21 (31.3)	2 (50.0)	0
Site 3	31 (46.3)	0	2 (66.7)
Dementia	38 (56.7)	2 (50.0)	0
Cerebral vascular disease	8 (11.9)	3 (75.0)	0
Depression	6 (9.0)	3 (75.0)	1 (33.3)
Atrial fibrillation	9 (13.4)	1 (25.0)	1 (33.3)
Heart failure	13 (19.4)	0	1 (33.3)
Hypertension	42 (62.7)	3 (75.0)	3 (100)
Asthma	4 (6.0)	1 (25.0)	0
COPD	23 (34.3)	0	1 (33.3)
Diabetes mellitus	30 (44.8)	2 (50.0)	1 (33.3)
Inflammatory bowel disease	1 (1.5)	0	0
GERD	8 (11.9)	1 (25.0)	0
Chronic kidney disease	16 (43.2)	0	1 (33.3)
Malignancy/cancer	9 (13.4)	0	0

none were assessed to be related to the study intervention. In sum, this pilot study demonstrated that in a nursing home population, aFMT has limited feasibility due to logistical and technical challenges but is likely safe.

To our knowledge, this is the first placebo-controlled study to examine the feasibility of aFMT in a nursing home population. Past studies of aFMT, either as a therapeutic or sham intervention, have focused primarily on community-dwelling populations [8,9,19,20]. In contrast, nursing home residents are under constant medical supervision, and we theorized this environment would facilitate the logistics associated with stool collection. Yet despite multiple attempts, successful collection of adequate stool samples from participants was low. It is possible that constipation and dementia contributed to the situation. In constipation, defecation is infrequent and can be irregular and difficult to accomplish [21]. In nursing homes, the prevalence of constipation has been shown to be as high as 71.5% [22]. Dementia, which was present in 57% of the participants, also likely impacted our ability to collect stool. In dementia, the individual has reduced cognitive capacity, hindering their ability to respond appropriately to sensory signals for defecation, especially in the later stages of dementia [23]. Our study sample aligns with national data that 48% of nursing home residents have dementia [24]. Given this evidence regarding constipation and

Table 2
Number of serious and non-serious adverse events.

	All participants (N = 67)	aFMT (N = 4)	Placebo (N = 3)
Serious adverse events - total[a]	40	3	2
Deaths	17	2	0
Hospitalizations	21	1	2
Life-threatening/ disabling	10	0	0
Non-serious adverse events - total	11	10	0
Gastrointestinal disorders	1	1	0

[a] Eight participants had ≥2 SAEs; number of participants experiencing SAEs=27. Ten of the hospitalizations were also judged to be life-threatening/disabling and are thus also included in that catagory.

dementia, we doubt that aFMT is feasible in the nursing home setting.

In terms of safety, our results suggest that aFMT is likely safe in a nursing home population. Overall, 25% of the participants died with 2 of the 17 deaths in randomized participants. In terms of SAEs, 40.3% of all participants and most of those randomized experienced at least one SAE. None of the SAEs, including the deaths, were judged to be related to the study intervention. For comparison, a systematic review of FMT studies published between 2000 and 2020 found the overall rate of SAEs was 1.4% when the FMT was delivered via the lower gastrointestinal tract [25]. It should be noted these studies were primarily conducted with younger and community-dwelling persons. In fact, there are only two published studies in the literature studying FMT exclusively in older adults [26,27]. While the proportion of deaths and SAEs were greater in our study, we suspect these results are driven by the baseline high mortality and hospitalization rates of nursing home residents. Prior studies have demonstrated that between 25 and 35% of U.S. nursing home residents die annually [28,29], and up to 48% of this population is hospitalized every year [30].

While our results suggest that aFMT is likely safe, we found the feasibility of autologous FMT to be quite limited in this group. Obtaining adequate stool samples from nursing home residents for aFMT was very challenging, despite multiple attempts with each participant. As this approach had never been tested in this population and stooling is a routine bodily function, whether this challenge could have been foreseen is unclear. In addition, we originally designed our study to address the feasibility and safety of aFMT in nursing home residents. While the intent was to target a population that could highly benefit, in retrospect our goal might have been better achieved with two separate studies, with one focused on just feasibility and the other on safety. Such study designs might have enabled us to better address the recruitment and technical challenges that occurred.

Overall given the study results, we suspect aFMT is unlikely to become a routine and widespread treatment for nursing home residents. Alternative options which avoid the issue of stool collection from the nursing home resident should be explored. One pragmatic option may be using FMTs from stool banks, which create and supply FMTs from pre-screened donors. Another strategy is stool-derived microbe mixtures. In this approach, a prespecified mix of beneficial organisms are isolated from donor stool, cultured in vivo, and then administered [31]. More recently, there is growing interest in donor-independent approaches, in which the prespecified organisms are cultured in vivo from the very start, but these studies are still in the early stages [32].

4.1. Limitations and strengths of study

Our study had several limitations that should be noted. Only seven participants were randomized, and all of those in the placebo group withdrew, reducing our ability to detect adverse events related to the study procedures. Our sample size was much smaller than we anticipated. Intervention eligibility required antibiotic treatment, and in recent years there have been efforts to limit antibiotic use in nursing home residents to reduce the emergence of multi-drug resistant organisms [33]. As this was a pilot study, participants were concentrated in one geographic area, limiting the generalizability of the findings. Finally, due to workforce limitations, collection of stool samples for aFMT was restricted to daytime hours, and therefore did not occur outside of this period. There were multiple strengths to our investigation. The study design was a randomized clinical trial, which is the gold standard for evaluating a new treatment [34]. Our sample was racially diverse, with Black participants making up 35.8% of the participants. Finally, given that individuals of advanced age and high co-morbidity burden are more likely to experience dysbiosis [35], the study sample was a population that would likely gain notable clinical benefit if aFMT is effective.

4.2. Conclusions

In sum, we examined the feasibility and safety of aFMT in a nursing home population. While aFMT appears to cause no harm in nursing home residents, the feasibility of aFMT in this population is limited. Other therapeutic options should be explored as alternative to aFMT treatments for this population.

Author contributions

CKL: Data curation; formal analysis; investigation; methodology; project administration; resources; supervision; validation; visualization; roles/writing - original draft, review & editing.

JS: Data curation; investigation; methodology; project administration; resources; supervision; validation; roles/writing - review & editing.

VP: Data curation; investigation; roles/writing - review & editing.

SF: Data curation; investigation; roles/writing - review & editing.

MG: Data curation; investigation; roles/writing - review & editing.

KC: Data curation; investigation; roles/writing - review & editing.

RL: Data curation; investigation; resources; roles/writing - review & editing.

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JV: Project administration; roles/writing – review & editing.

MN: Data curation; investigation; methodology; project administration; resources; supervision; roles/writing - review & editing.

SO: Formal analysis; visualization; roles/writing - review & editing.

SB: Investigation; methodology; project administration; resources; roles/writing - review & editing.

ZK: Conceptualization; funding acquisition, roles/writing-review & editing.

MO: Formal analysis; investigation; project administration; resources; validation; visualization; roles/writing - review & editing.

Funding

Study highlights

- Autologous fecal microbiota transplants could mitigate the dysbiosis caused by antibiotics.
- In nursing home residents, autologous fecal microbiota transplants are likely safe but have limited feasibility.

Data sharing

Proposals should be directed to chliu1@stanford.edu. To gain access, data requestors will need to provide a methodologically sound proposal of the planned research, sign a data use agreement, and obtain Institutional Review Board approval from their organization.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Shrish Budree is a shareholder and employee of Finch Therapeutics. Zain Kassam is a shareholder of Finch Therapeutics.

Data availability

Data will be made available on request.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2022.100906.

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