Fecal Microbiota Transplant for Relapsing Clostridium difficile Infection Using a Frozen Inoculum from Unrelated Donors – a Randomized, Open Label, Controlled Pilot Study.

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BACKGROUND

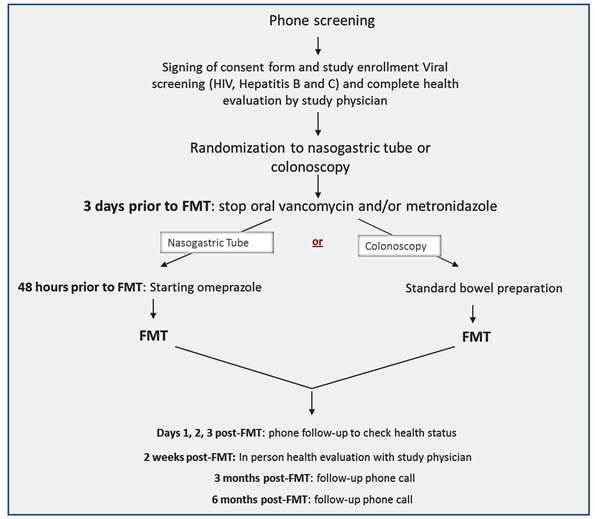
- Recurrent and refractory Clostridium difficile infection (CDI) is a growing medical concern with a recent dramatic increase in the number of pediatric and adult patients globally.
- Response to standard antimicrobial therapy with oral vancomycin or metronidazole is suboptimal, with CDI recurring in up to 30% of individuals treated for a first episode.
- After two or more episodes of CDI the estimated risk for subsequent recurrence exceeds 60% with antimicrobial therapy.
- Though the illness is toxin-mediated, overgrowth of the organism in the setting of dysbiosis is thought to be a key inciting event. Failure to reconstitute normal flora was shown to be a factor in severe, recurrent, and prolonged illness.
- Fecal microbiota transplantation (FMT) has been a successful therapeutic approach to recurrent/refractory CDI in animal studies, numerous case series and a single randomized clinical trial.
- Practical and aesthetic barriers have hindered the widespread use of FMT to date.
- Furthermore, recruitment and screening of donors is a lengthy process associated with significant costs, thus preventing the use of FMT in acute situations.

OBJECTIVES

- To establish a repository of prescreened frozen donor stools.
- To investigate the clinical outcomes of FMT for refractory or relapsing CDI using a frozen suspension from unrelated donors while comparing between colonoscopic and nasogastric tube (NGT) administration.

METHODS

Figure 1. Study flow-chart



An open-label, randomized, controlled trial.

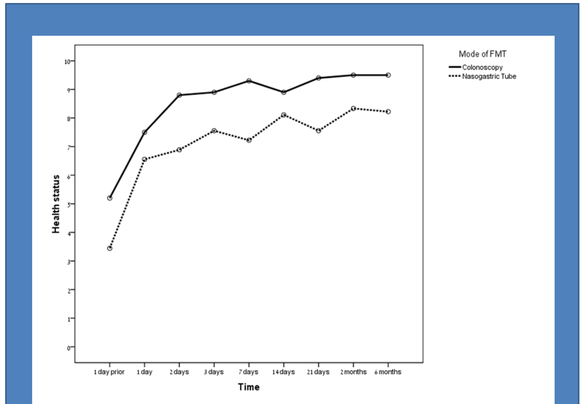
Study participants
- Ages 2-90.
- Refractory or recurrent CDI.
- Exclusion criteria included presence of anatomic contraindication to NGT or colonoscopy, delayed gastric emptying syndrome, recurrent aspirations, pregnancy, significantly compromised immunity and having a history of significant allergy to foods not excluded from the donor diet.

Donors
- Healthy, non-pregnant adults 18-50 years of age, on no medications, with a normal Body Mass Index (BMI 18.5-25).
- Screened for: CBC, renal function and electrolytes, complete liver function tests, lipid profile, CRP, ANA, and RF. Donor feces were screened for occult blood, enteric bacterial pathogens, ova and parasites, *C. difficile* and H. pylori antigen. Blood was screened for antibodies to hepatitis A, B and C; HIV and Treponema pallidum.

RESULTS

Donors

- 12 candidates passed the initial screening (of 37 responders) and underwent a full donor work-up.
- Seven were excluded from donating based on abnormal screening labs: 4 with positive anti-nuclear titers, 1 with elevated bilirubin, 1 with mild neutropenia and 1 with eosinophilia. The remaining 5 donors provided 3 stool samples each, that were used for 25 infusions in 20 study patients.The median number of cultures obtained per patient was 16 with a range of 1-72. 232 patients (64.4%) had at least one positive FSC.



Mean scores of subjective well-being over time as reported using standardized questionnaire scale 1-10, with 1 being the lowest. The colonoscopy group had consistently higher scores, accounted for by a higher reported score at day -1. When analyzing the absolute increment in health scores, the groups do not differ (p=0.51).

Clinical cure
- 14 patients were cured after the first infusion of donor feces (70%); 8 in the colonoscopy group (80%) and 6 in the NGT group (60%).
- 5 patients were given a second infusion, all via NGT, using feces from the same donor.
- 4/5 relapsed patients obtained cure, resulting in an overall cure rate of 90% (80% in the NGT group and 100% in the colonoscopy group, p=0.53).

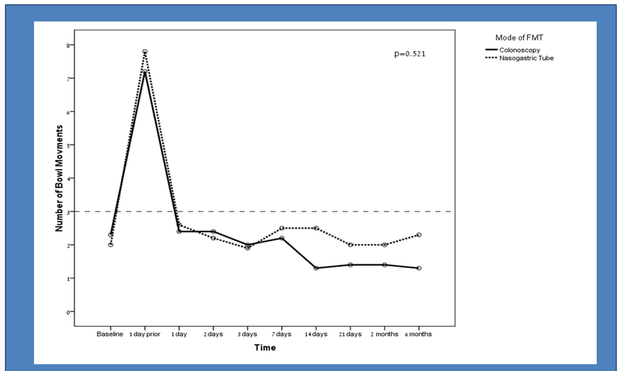
FUTURE DIRECTIONS

We have now generated frozen, encapsulated concentrated stool suspension for easy oral delivery.

Table 1. Select baseline characteristics of study population stratified by treatment group.

	Colonoscopy	Nasogastric Tube	p-value
[a]Age (years)	50.4±28.8	58.6±19.6	0.739
[b]Female gender	6 (60)	5 (50)	1.00
[b]Time since initial CDI (months)	7 (3-34)	12 (3-66)	1.00
[b]Hospital-acquired CDI	2 (20)	3 (30)	1.00
[c]Number of CDI recurrences prior to FMT	4 (2-7)	5 (3-14)	0.42
[b]Previous vancomycin taper	9 (90)	10 (100)	1.00
[b]Previous use of fidaxomycin	5 (50)	7 (70)	0.64
[b]Hospital admissions in the past due to CDI	6 (60)	7 (70)	1.00
[b]Inpatient at time of FMT	2 (20)	3 (30)	1.00
[c]Number of BM 1 day prior to FMT	6 (4-13)	7 (5-13)	0.43
[c]Health status 1 day prior to FMT	5 (2-7)	4 (1-10)	0.21

[a]mean±SD, [b]n(%), [c]median (range). CDI – *Clostridium difficile* infection; FMT-fecal microbiota transplant.



Mean number of daily bowel movements in both study arms. Baseline represents reported BM prior to contracting C.diff..

CONCLUSIONS

- In our initial feasibility study FMT using a frozen inoculum from unrelated donors is effective in treating relapsing CDI.
- NGT administration appears to be as effective as colonoscopic administration.
- Relapsed recipients appear to benefit from a second dose.