Fecal microbiota transplantation for treatment recurrent Clostridium difficile

Contents

- Overview: Epidemiology, Microbiology, Pathogenesis, Risk factors, Clinical spectrum, Treatment
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Epidemiology

- Among children hospitalized at 22 United States children's hospitals, the incidence of *C.difficile* infection increased by 53% from 2001 – 2006 (2.6 to 4.0 cases per 1000 admissions)
- In 2011, incidence of *C.difficile* infection in children < 18 years was 24.2 cases per 100,000 population
- Recurrence rates: 20 – 24%

Microbiology

- *C.difficile*
  - *Anaerobic*
  - *Gram positive*
  - *Spore – forming*
  - *Toxin – producing bacillus*
- Exist in spore form in the environment
- Resistant to heat, acid, antibiotics and most disinfectants
- Germinate to vegetative form and produce toxins

Pathogenesis

- Alteration of the colonic microflora
- Ingestion, colonization, and overgrowth of *C. difficile*
- Production of *C. difficile* toxin(s)
- Injury to and inflammation of intestinal epithelium, resulting in diarrhea

Risk factors

- Antibiotic exposure: penicillins, cephalosporins, clindamycin and flouroquinolones most frequently implicated
- Proton pump inhibitors
- Gastrointestinal feeding devices (gastrostomy, jejunostomy tubes)

Predisposing conditions

- Immune compromise
- Inflammatory bowel disease
- Cystic fibrosis
- Hirschsprung disease
- Structural or postoperative intestinal disorders

Clinical spectrum

- Diarrhea
- Pseudomembranous colitis
  - Fever
  - Prolonged watery diarrhea
  - Abdominal pain and distention
  - Blood or mucus in stool
- Fulminant colitis
  - Toxic megacolon
  - Bowel perforation

Treatment

- Antibiotics
  - Metronidazole
  - Vancomycin
- Fecal microbiota transplantation

Evidence – based Medicine

Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

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Clostridium difficile **infection (CDI) is a gastrointestinal disease believed to be causally related to perturbations to the intestinal microbiota. When standard treatment has failed, intestinal microbiota transplantation (IMT) is an alternative therapy for patients with CDI. IMT involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of a sick patient to restore the microbiota. However, protocols and reported efficacy for IMT vary. We conducted a systematic literature review of IMT treatment for recurrent CDI and pseudomembranous colitis. In 317 patients treated across 27 case series and reports, IMT was highly effective, showing disease resolution in 92% of cases. Effectiveness varied by route of instillation, relationship to stool donor, volume of IMT given, and treatment before infusion. Death and adverse events were uncommon. These findings can guide physicians interested in implementing the procedure until better designed studies are conducted to confirm best practices.**

Table 2. Outcomes Achieved in Patients Treated With Intestinal Microbiota Transplantation for *Clostridium difficile* Infection and Related Conditions, Excluding Retreatments After Treatment Failure, by Characteristics of the Procedure

Procedure characteristics	Studies, no.	Patients with outcome/patients in sample (%)			
		Resolution[a]	Relapse[b]	Deaths due to treated condition	Deaths due to any cause
All procedures	28	284/317 (89.0)	11/284 (3.9)	4/317 (1.3)	13/317 (4.1)
Infusions, no.					
1	12	147/168 (87.5)	7/147 (4.8)	3/168 (1.8)	8/168 (4.8)
≤3	5	67/70 (95.7)	3/67 (4.5)	0/70 (0.0)	0/70 (0.0)
>3	5	36/40 (90.0)	1/36 (2.8)	1/40 (2.5)	5/40 (12.5)
NR	6	34/39 (87.2)	0/34 (0.0)	0/39 (0.0)	0/39 (0.0)
Instillation method[c]					
Colonoscope	9	55/62 (88.7)	3/55 (5.4)	0/62 (0.0)	0/62 (0.0)
Enema	11	105/110 (95.4)	5/105 (4.8)	1/110 (0.9)	5/110 (4.5)
Gastroscope or NJ tube	4	55/72 (76.4)	2/55 (3.6)	3/72 (4.2)	7/72 (9.7)
Rectal catheter	2	44/46 (95.6)	0/44 (0.0)	0/46 (0.0)	1/46 (2.2)
>1 method	2	19/21 (90.5)	1/19 (5.3)	0/21 (0.0)	0/21 (0.0)
NR	1	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)
Donor[c]					
Related	19	195/209 (93.3)	7/195 (3.6)	0/209 (0.0)	3/209 (1.4)
Unrelated	4	21/25 (84.0)	0/21 (0.0)	0/25 (0.0)	1/25 (4.0)
Mixed[d]	3	57/72 (79.2)	4/57 (7.0)	4/72 (5.6)	9/72 (12.5)
NR	3	11/11 (100.0)	0/11 (0.0)	0/11 (0.0)	0/11 (0.0)
Diluent					
Normal saline	20	169/196 (86.2)	5/169 (3.0)	4/196 (2.0)	11/196 (5.6)
Water	1	64/65 (98.5)	5/64 (7.8)	0/65 (0.0)	1/65 (1.5)
Other[e]	3	31/35 (88.6)	1/31 (3.2)	0/35 (0.0)	1/35 (2.9)
NR	4	20/21 (95.2)	0/20 (0.0)	0/21 (0.0)	0/21 (0.0)
Pre-IMT treatment					
Vancomycin or metronidazole[f]	6	150/164 (91.5)	5/150 (3.3)	3/164 (1.8)	6/164 (3.7)
Antibiotics[g] and bowel lavage	2	33/35 (94.3)	4/33 (12.1)	0/35 (0.0)	0/35 (0.0)
Other[h]	8	43/50 (86.0)	2/43 (4.6)	0/50 (0.0)	3/50 (6.0)
NR	12	58/68 (85.3)	0/58 (0.0)	1/68 (1.5)	4/68 (5.9)
IMT suspension volume, mL					
<200	5	32/40 (80.0)	2/32 (6.2)	0/40 (0.0)	3/40 (7.5)
200–500	13	98/114 (86.0)	4/98 (4.1)	3/114 (2.6)	5/114 (4.4)
>500	2	107/110 (97.3)	5/107 (4.7)	0/110 (0.0)	1/110 (0.9)
NR	8	47/53 (88.7)	0/47 (0.0)	1/53 (1.9)	4/53 (7.5)
Stool weight, g					
<50	9	53/64 (82.8)	2/53 (3.8)	0/64 (0.0)	2/64 (3.1)
≥50	7	100/116 (86.2)	1/100 (1.0)	3/116 (2.6)	6/116 (5.2)
NR	12	131/137 (95.6)	8/131 (6.1)	1/137 (0.7)	5/137 (3.6)

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Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

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ABSTRACT

BACKGROUND

Recurrent *Clostridium difficile* infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile* infection.

METHODS

We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

RESULTS

The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of *C. difficile*–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of *C. difficile* infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%)

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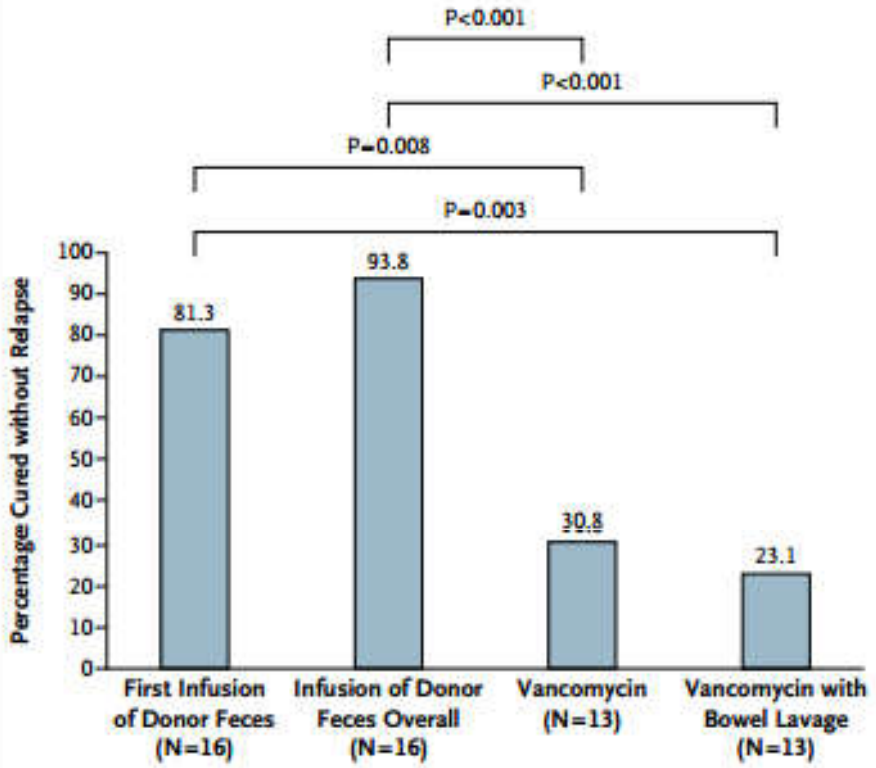

Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

* Adverse events that were reported on the day of donor-feces infusion and those that were reported during follow-up are listed separately. NA denotes not applicable.

† During follow-up, one patient with recurrent urinary tract infections had a urinary tract infection for which antibiotics were prescribed. Another patient had fever during hemodialysis for which antibiotics were prescribed; cultures remained negative.

‡ On day 56, one patient was hospitalized for symptomatic choledocholithiasis, for which endoscopic retrograde

Fecal Microbiota Transplantation for the Treatment of *Clostridium difficile* Infection

A Systematic Review

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Results: Twenty full-text case series, 15 case reports, and 1 randomized controlled study were included for the final analysis. Almost all patients treated with donors' fecal infusion experienced recurrent episodes of CD-associated diarrhea despite standard antibiotic treatment. Of a total of 536 patients treated, 467 (87%) experienced resolution of diarrhea. Diarrhea resolution rates varied according to the site of infusion: 81% in the stomach; 86% in the duodenum/jejunum; 93% in the cecum/ascending colon; and 84% in the distal colon. No severe adverse events were reported with the procedure.

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2 cases report

- Patient 1:
  - 20 months
  - Refractory RCDI of 8 months' duration
  - Received cefdinir at 10 month for ear infection
  - Developed bloody diarrhea, feces test (+) for *C.difficile*
  - 10 day course of metronidazole → second course → 2 week oral vancomycin course
  - Weight less than 5th and length less than 3rd
  - 3 months after FMT, weight increased to 50th and length reach 3rd
  - No CDI recurrence during 2 years follow up

2 cases report

- Patient 2:

  30 months

  Developed upper respiratory infection requiring amoxicillin – clavulanate and ciprofloxacin

  Diarrhea (+) *C.difficile*

  10 day course of metronidazole

  3 courses of oral vancomycin

  5 – month – pulse tapered vancomycin with probiotics

  4 months after FMT, increase in weight to 84th

Fecal Microbiota Transplantation Via Nasogastric Tube for Recurrent *Clostridium difficile* Infection in Pediatric Patients

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Results

- Donors included 9 parents and 1 sibling
- Median duration of follow up was 44 days
- Median age was 5.4 years
- 9 patients (90%) remained asymptomatic during follow up

FMT procedures

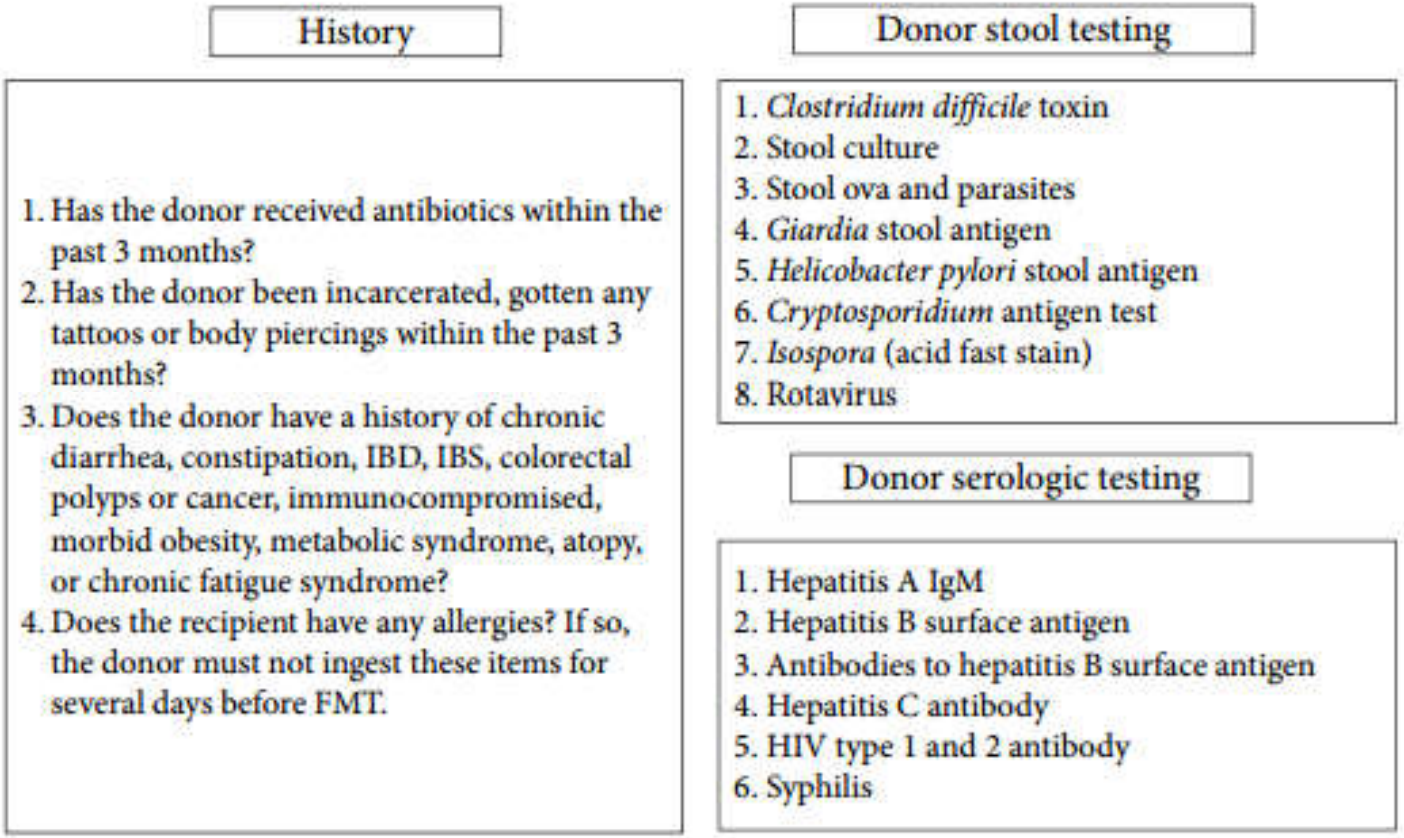

Fig. 1. Donor and recipient screening for fecal microbiota transplantation. IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IgM, immunoglobulin M; FMT, fecal microbiota transplantation; HIV, human immunodeficiency virus.

Administration of donor feces

- Lower GI route:
  - Colonoscopy
  - Flexible sigmoidoscopy
  - Rectal tube
  - Retention enema
- Upper GI route:
  - Nasogastric tube
  - Nasointestinal tube
  - Gastroduodenoscopy

Table 2. Short-Term or Potential Long-Term Adverse Events of Fecal Microbiota Transplantation

Short-term adverse events		Potential long-term adverse events
Minor events	**Serious events**	
Abdominal discomfort	Complications of endoscopy (perforation, bleeding)	Transmission of unrecognized infectious agents that cause illness years later (e.g., hepatitis C, HIV)
Bloating	Adverse effects related to sedation (aspiration)	Induction of chronic diseases based on alterations in the gut microbiota (e.g., obesity, diabetes, atherosclerosis, IBD, colon cancer, nonalcoholic fatty liver disease, IBS, asthma, autism)
Flatulence	Transmission of enteric pathogens	
Diarrhea	Peritonitis in a patient undergoing peritoneal dialysis	
Constipation	Pneumonia	
Borborygmus	IBD flares	
Vomiting		
Transient fever		

HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

Conclusions

- Recurrent C.difficile infection remains high (30%)
- Efficacy of fecal microbiota transplantation was high than antibiotics (metronidazole, vancomycin) 80% - 90% compared to 30%
- More RCTs are needed in pediatric patients

Thank you for your attention