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M E D I C I N E

The What, When, Why, and How of Fecal Transplantation

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Disclosure

- I have no financial disclosures.

Case presentation

- 75 yo woman was prescribed ciprofloxacin for treatment of a symptomatic urinary tract infection
- Developed abdominal cramping and > 5 loose bowel movements each day
- Presented to an outside hospital where she was admitted to the step-down intensive care unit with severe dehydration

Case presentation

- Stool was positive stool for *C. difficile*
- Was treated and eventually discharged with oral vancomycin to complete a 10 day course
- Within 2 weeks of finishing therapy, her symptoms relapsed and she was readmitted
- Stools were again positive for *C. difficile*
- Received another course of vancomycin
- Eventually received an additional 2 courses with taper

The Epidemic

- In 2010, the US incidence of *C. difficile* infection (CDI) was estimated at 500,000
- In 2009, 92 percent of deaths from CDI occurred in those > 65
- The cost of managing CDI in the US was estimated to be at least \$1 billion per year



Antibiotics most commonly implicated

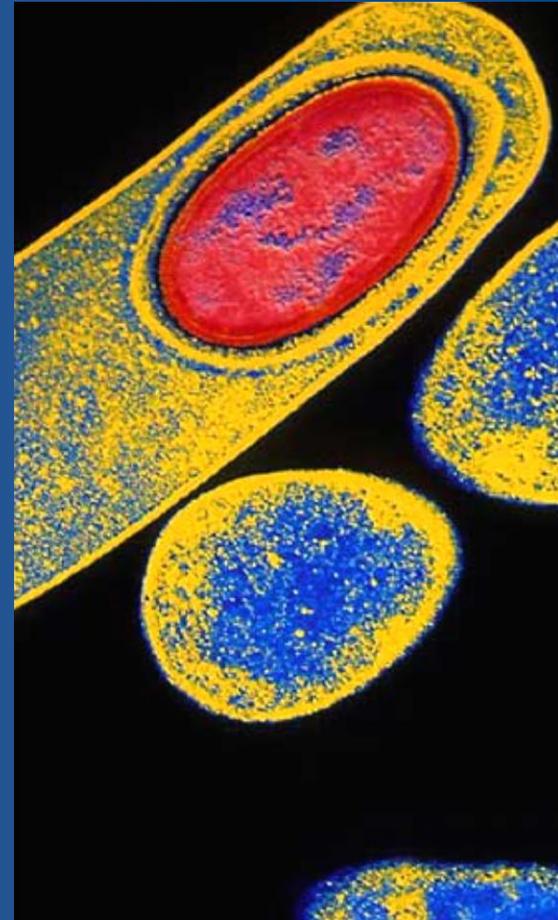
- Clindamycin
- Cephalosporins
- Fluoroquinolones

Community Acquired CDI

- In a population-based US study in Olmsted County, 41% of the CDI cases were not associated with hospitalization
- 26% reported no prior antibiotic exposure
- Community acquired cases were younger (mean age 50 vs. 72) and had less severe disease

A more virulent strain since 2004

- North American pulsed-field type 1 (NAP1), ribotype 027, and group BI
- Characteristics of the NAP1 strain
 - Fluoroquinolone resistance
 - Production of binary toxin in addition to toxins A and B
 - Possesses a deletion in the *tcdc* gene, which normally represses toxin A and B production



CDI Relapse

- Initial CDI is followed by a relapse within 30 days in up to 30% of cases
- Relapse is in part attributed to spores formed by *C. difficile* that are not susceptible to antibiotic therapy
- Host risk factors for relapse:
 - Older age
 - Intercurrent antibiotic use for non-*C. difficile* indications
 - Renal insufficiency
 - Immunodeficiency
 - Antacid use
 - IBD

The presence of these 3 factors is associated with >90% relapse rate:

- Age >65
- Severe disease
- Continued use of antibiotics

CDI is associated with decreased diversity in the gut microbiome



- A study of the microbiota of seven patients with initial and recurrent CDI demonstrated the bacterial species diversity was reduced¹
- Dysbiosis may in part be due to the ability of *C. difficile* to convert tyrosine to *para*-cresol, a phenolic compound that is toxic to other anaerobes²

1. Chang JY , Antonopoulos DA , Kalra A et al. Decreased diversity of the fecal microbiome in recurrent Clostridium difficile-associated diarrhea . J Infect Dis 2008;197:435 – 8

2. Dawson, LF, et al. J Med Microbiol 2008; 57:745-749

PCR detects the toxigenic strain

- Rapid and highly sensitive (88-96%)
- Detects the DNA of the toxigenic strain of *C. difficile* and not the toxin itself
- Test only those individuals with symptoms and diarrhea
 - 3% asymptomatic carrier rate

Treatment recommendations are based on severity

Table 1. Guideline Recommendations for Treatment of CDI¹

Episode	Severity	Clinical Definition	Treatment
Initial	Mild or moderate ^a	WBC \leq 15,000 cells/ μ L and SCr $<$ 1.5 times baseline	Metronidazole 500 mg po 3 times a day for 10-14 days
	Severe ^a	WBC \geq 15,000 cells/ μ L or SCr \geq 1.5 times baseline	Vancomycin 125 mg po 4 times a day for 10-14 days
	Severe, complicated ^a	Hypotension/shock, ileus, megacolon	Vancomycin 500 mg po 4 times a day plus metronidazole 500 mg iv every 8 hours ^a
First recurrence	Same as above		Same as first episode
Second recurrence	Same as above		Vancomycin pulse and/or tapering regimen

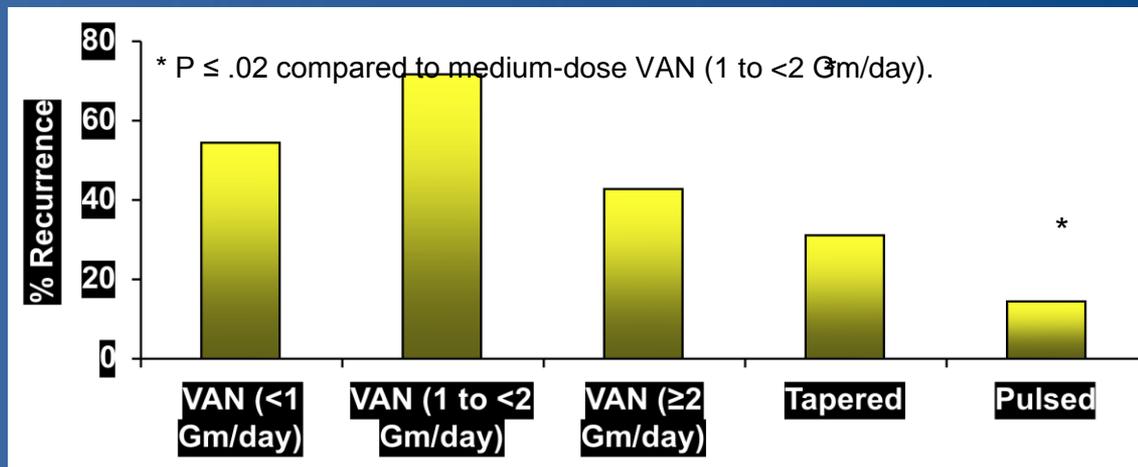
CDI = *Clostridium difficile* infection; SCr = serum creatinine; WBC = white blood cell.

^aVancomycin 500 mg per rectum is recommended in patients with ileus.

- Fidaxomicin now FDA approved for mild-mod *C. diff* colitis
- As effective as vancomycin po, but may have less negative impact on fecal flora so relapse rate is slightly less (15% vs 25%); not so with NAP1 strains
- Wholesale cost for 10 day course is \$2800

Tapered or Pulsed Dosing of Vancomycin

- Based on the rationale that *C difficile* spores may continue to germinate after symptoms resolve¹
- In a retrospective study of 163 patients with recurrent CDI, rates of additional recurrences were lowest in patients who had tapered or pulsed dosing of VAN²



1. Bauer MP, et al. Clin Microbiol Infect. 2009;15:1067-1079.

2. McFarland LV, et al. Am J Gastroenterol. 2002;97:1769-1775.



Approach to Recurrent CDI (courtesy of Dr. John Bartlett)



Vancomycin 125 qid x 10 d or
Metronidazole 250 tid x 10 d*



Relapse #1 → Repeat



Relapse #2 → Vancomycin 125 qid 10 d →
125 bid 7 d → 125 qd 7 d → 125 qod 4 wks
or Fidaxomicin 200 mg bid 7 d
or Vancomycin x 10 d, then Rifaximin x 10 d
or stool transplant

*metronidazole is not FDA approved for *C. difficile* infection

1958: Fecal Transplantation for Pseudomembranous colitis



- Three of 4 patients were suffering with life-threatening fulminant pseudomembranous colitis, which at that time carried a 75% mortality rate
- In desperation the physicians used fecal retention enemas
- Prompt recovery was achieved in all patients and they were discharged from the hospital within days

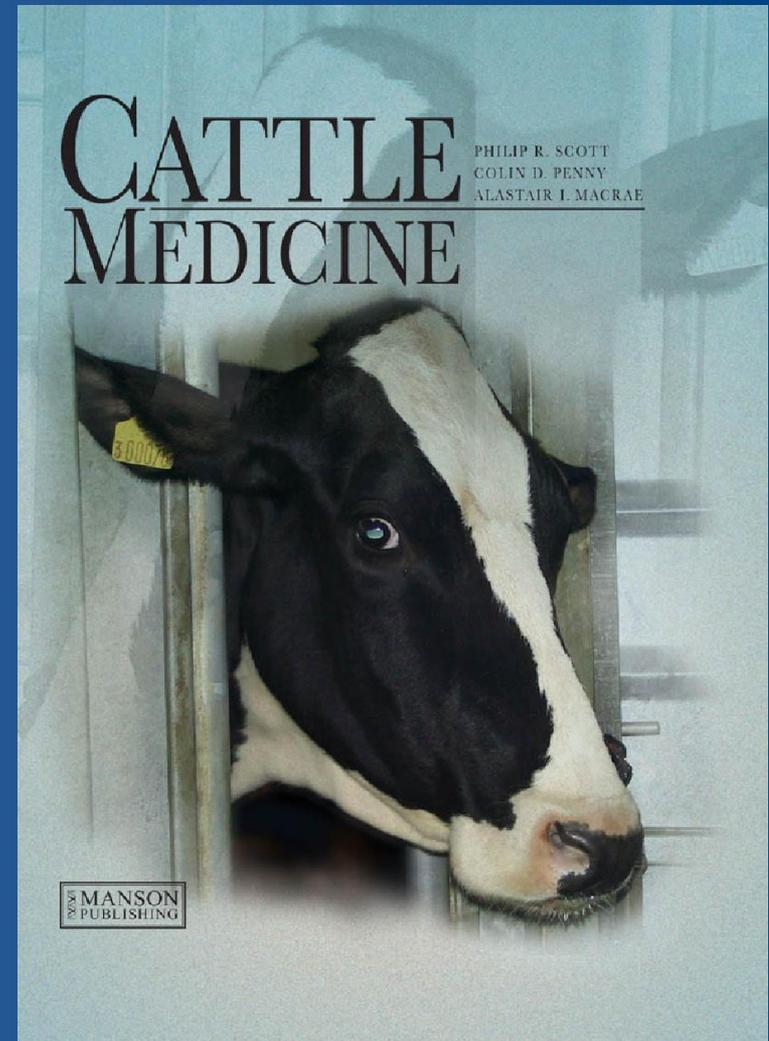
Historical fecal transplantaion



- 4th century in China, Ge Hong, a well-known traditional Chinese medicine doctor, described the use of human fecal suspension by mouth for patients who had food poisoning or severe diarrhea

Historical fecal transplantation JOHNS HOPKINS MEDICINE

- Common veterinary practice to administer “ruminatorics” to cattle and horses
 - “Fresh ruminal fluid is considered to be the best available ‘ruminotoric’ because it contains viable bacteria ” –Merck Vet Manual



Donors and method of administration



- Routes of administration described
 - NG tube
 - Colonoscope
 - Self-administered enemas at home
- Patient-identified individual donors (most common)
- Universal volunteer donors
 - Frozen samples stored for 1-8 weeks at -80 C^0 , thawed in an ice bath for 2-4 hours, reconstituted in 250 cc non-bacteriostatic saline

Donor Testing

- No recent antibiotic exposure; no immunosuppressive exposure
- Other “no’s”
 - Tattooing or body piercing in past 6 months
 - Drug use
 - High-risk sexual behavior
 - Incarceration
 - Travel to endemic areas
 - GI comorbidities
- Check HIV, hepatitis B, C, hepatitis A IgM, RPR
- Stool tests
 - C. diff PCR
 - Giardia antigen
 - Ova & parasites
 - Culture & sensitivity
 - Acid fast stain for cyclospora and isospora
 - Fecal cryptosporidium antigen

Protocol for administration

- Patient does routine colonoscopy prep
- Donor provides fresh sample (within 6 hours, at least 50 gms)
- Preparation
 - Blend in 250 cc non-bacteriostatic saline
 - Filter through gauze
 - Draw up into 60 cc syringes, administer through colonoscope during withdrawal



Afterwards

- Positive outcome defined as prompt resolution of diarrhea with no relapse within 8 weeks
- Symptomatic improvement may occur within a few days
- **Don't retest as colonization may occur without causing active disease**

Outcomes

- Recent review of 317 patients from 27 case series and reports
- FT resulted in resolution for 92% of patients (89% after a single treatment)
- When case data were summarized by the characteristics of the procedure, instillation by EGD or NJ tube seemed least effective, stool from a related donor was most effective

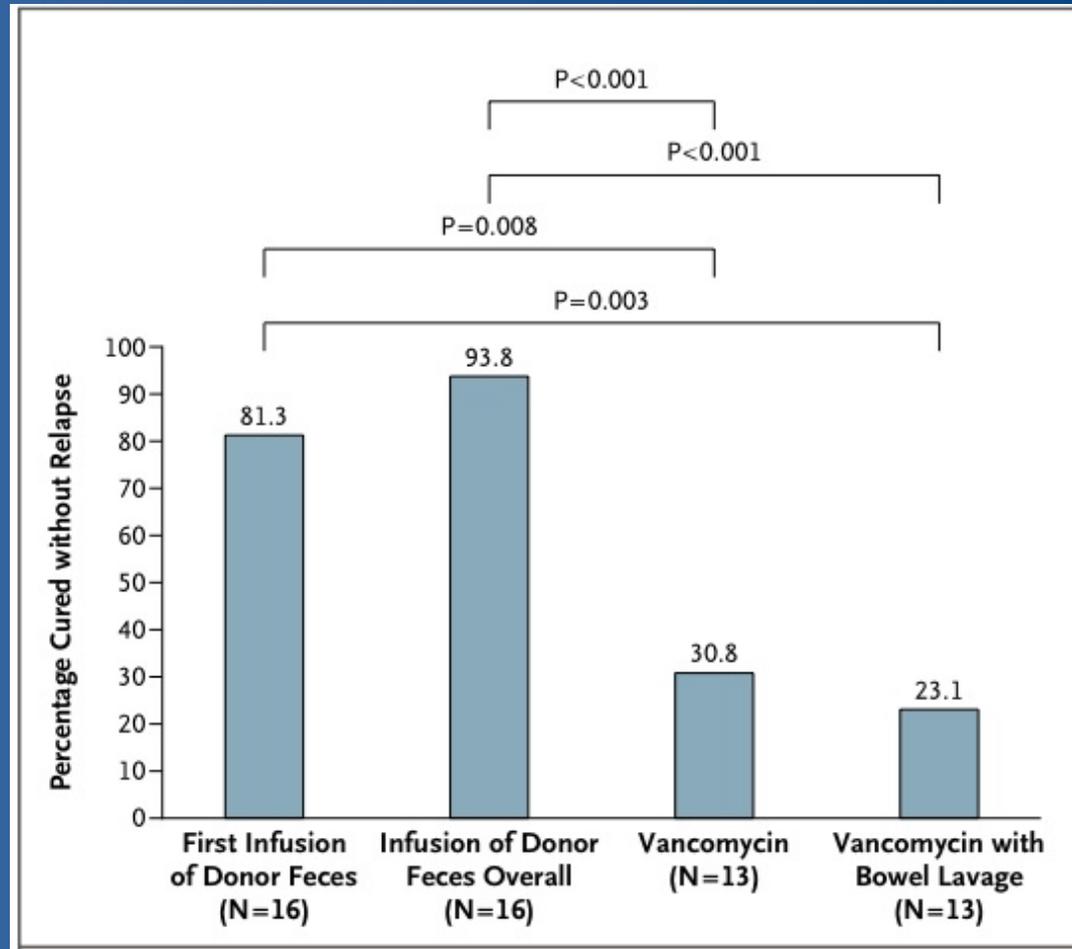
Fecal bacteriotherapy vs. vancomycin x 14 d for recurrent CDI



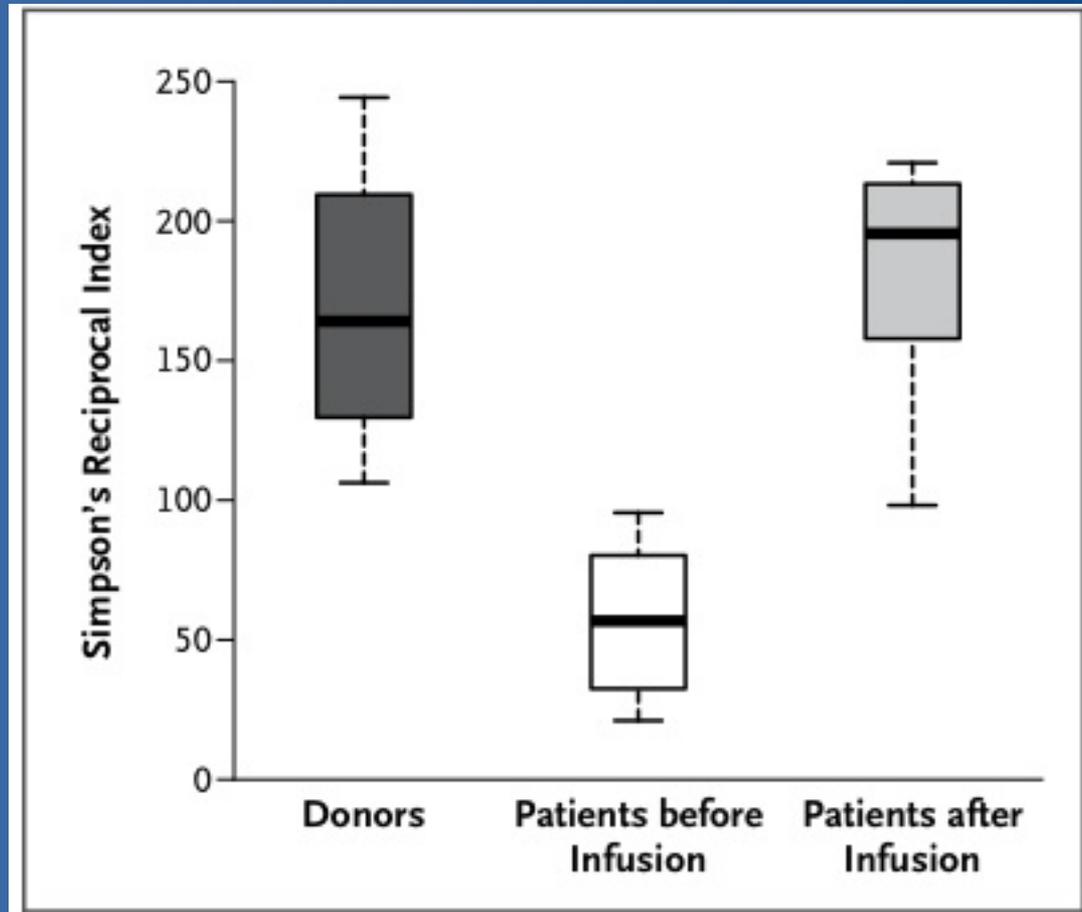
- Open-label, randomized, controlled trial comparing vancomycin (500mg qid x 14 d), vancomycin and bowel lavage, or vancomycin x 4 days followed by FMT
- Inclusion – adults with recurrent *C. difficile* and diarrhea, and history of adequate course of metronidazole or vancomycin
- Outcome – cure (no diarrhea, *C. diff* negative x 3) without relapse after 10 weeks

Fecal bacteriotherapy vs. vancomycin x 14 d for recurrent CDI

Proportions of patients who were cured by infusion of donor feces



Microbiota diversity before and 14 days later



“Long-term” Outcome?

- 77 of 94 eligible patients who had colonoscopic FT for recurrent CDI \geq 3 months before; mean follow-up was 17 months
- 73% were women; average age was 65 years
- Spouses and partners accounted for 60% of donors; 27% were either first-degree relatives or otherwise related to the patient

“Long-term” outcome (cont.)



- Average symptom duration before FT was 11 months and patients had failed an average of five conventional antimicrobial regimens
- 74% had resolution of diarrhea in < 3 days
- The primary cure rate was 91%
- All *C. difficile* recurrences occurred in the setting of antibiotic use

What patients thought

- 97% of patients stated that they would undergo another FT if they were to experience a recurrent bout of *C. difficile* colitis
- 53% of patients reported that they would choose FT as their first treatment option before a trial of antibiotics
- 4 patients reported a new medical condition after FT:
 - Peripheral neuropathy
 - Sjogren's disease
 - Idiopathic thrombocytopenic purpura
 - Rheumatoid arthritis

Donor fecal flora detectable months later

- Patient's fecal microbiota composition consisted predominantly of the bacteria derived from the healthy donor 1 month post-FT in one study
- Donor strains detectable up to 24 months in another study

Grehan MJ, Borody TJ, Leis SM, Campbell J, Mitchell H, Wettstein A. Durable alteration of the colonic microbiota by the administration of donor fecal flora. *J Clin Gastroenterol* 2010; 44:551–61

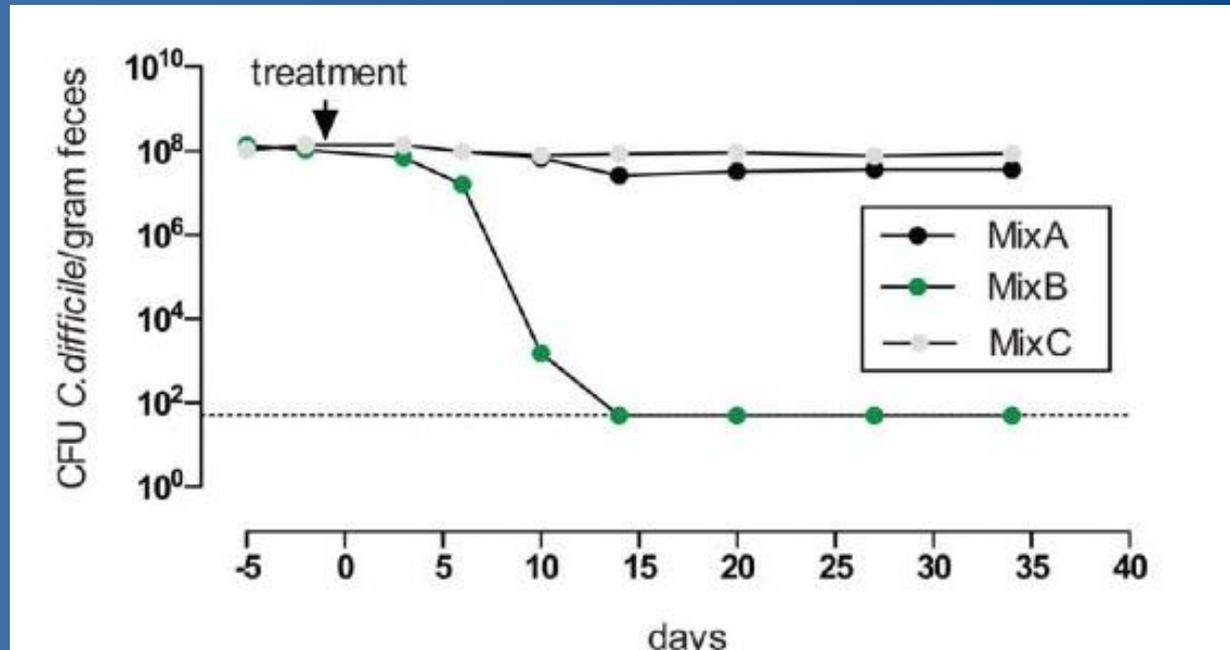
Khoruts, A., Dicksved, J., Jansson, J. K. & Sadowsky, M. J. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent *Clostridium difficile*-associated diarrhea. *J. Clin. Gastroenterol.* 1010, 44:354–360

Gustaffson, A., Berstad, A., Lund-Tønnesen, S., Midtvedt, T. & Norin, E. The effect of fecal enema on five microflora-associated characteristics in patients with antibiotic-associated diarrhea. *Scand. J. Gastroenterol.* 1999, 34:580–586

Future Stool Donor Options

- Institutional donor pool
 - Frozen
 - Pelleted
- Autologous donation?
- Defined bacteriotherapy using distinct strains

Defined bacteriotherapy prevents recurrent CDI in a mouse model



- Mix B contains *Staphylococcus warneri*, *Enterococcus hirae*, *Lactobacillus reuteri*, and three novel species, *Anaerostipes sp. nov.*, *Bacteroidetes sp. nov.* and *Enterorhabdus sp. nov.*

It's Official: 2013 Medicare CPT codes

- G0455: preparation with instillation of fecal microbiota by any method, including assessment of donor specimen
- 44705: preparation of fecal microbiota for instillation including assessment of donor specimen

Brief moratorium on FMT

- Summer 2013 – FDA declares transplanted stool a “biologic”
 - Required Investigational New Drug (IND) permit per patient
- 2 months later – restriction rescinded
 - Need to inform patients that FMT is investigational and could have risks

Back to our patient . . .

- Fecal bacteriotherapy proposed
- Patient said, “eewww” – but ok
- Daughter was her donor
- Bacteriotherapy delivered by colonoscopy
- 48 hours later –patient reports first formed bowel movement in months
- One year later, no recurrence

Fecal bacteriotherapy: other clinical scenarios?

- Fulminant CDI
- Ulcerative colitis
- IBS constipation
- Metabolic syndrome
- Depression, chronic fatigue syndrome, MS



Photo from Science, 2009, 324:5931, pp. 1136 – 1137

Fecal Bacteriotherapy for Refractory Ulcerative Colitis



- Patients with IBD have decrease microbial diversity
 - Decreased *Firmicutes* and *Bacteroidetes*, and increased *Actinobacteria* and *Proteobacteria*
- Nine patients with severe, active longstanding ulcerative colitis (mean, 8.6 years) refractory to treatment with corticosteroids, 5-aminosalicylates and azathioprine
- FT was administered as retention enemas x 5 days
- Complete resolution of all symptoms with cessation of medications within 6 weeks without relapse
- Remission was maintained for up to 13 years and follow-up colonoscopy in 8 patients showed no evidence of ulcerative colitis (n = 6) or only mild chronic inflammation (n = 2)
- Currently 6 registered trials of FMT in IBD ongoing

FMT as therapy for UC – not so fast

- Case series of 5 patients with moderate to severe UC, who were refractory to standard therapy (steroids, thiopurines, anti-TNFs)
- All patients developed fever and increase CRP immediately after FMT
- Only 1 patient had response at 12 weeks
 - Only patient to have stable donor derived bacterial phylotypes after 12 weeks

Treatment of metabolic syndrome? JOHNS HOPKINS MEDICINE

- Alteration in intestinal microbiota can increase intestinal permeability leading to metabolic endotoxemia
- Breakdown of diet-derived fibers into SCFAs dependant on intestinal bacteria
 - SCFA reduce intestinal permeability

Treatment of metabolic syndrome?

- Double-blind, randomized, controlled trial of FMT in 18 men with the metabolic syndrome
- Half of the patients received fecal material from lean male donors and half were implanted with their own feces as controls
- Post-transplantation of fecal flora from lean donors:
 - Fasting triglyceride levels in patients with the metabolic syndrome were markedly reduced; no effect was observed in the control group re-instilled with their own feces
 - peripheral and hepatic insulin sensitivity markedly improved after 6 weeks in the lean donor group

Summary

- Recurrent CDI is a major problem especially for those > 65 yo and is a significant cause of morbidity
- Fecal bacteriotherapy is an effective treatment for recurrent CDI whether administered by NG tube, enemas, or colonoscopy
- Potential donors may have to pay for their own screening tests
- Fecal bacteriotherapy may prove useful in the treatment of other disorders in which intestinal dysbiosis is implicated
- Remember, we are only 10% human!

