

Fecal Microbiota Transplantation for the Treatment of Recurrent Pseudomembranous (*C. difficile*) Colitis



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Objectives



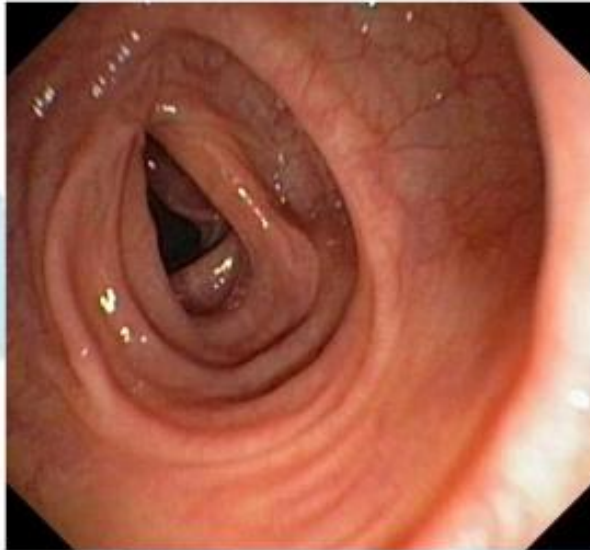
- 1. To review the concept of fecal microbiota transplantation (FMT) and its origins.
- 2. To discuss the indications and logistics of the process.
- 3. To review the outcome data.

Defining the enemy...



Wirral Community **NHS**
NHS Trust

Pseudomembranous Colitis



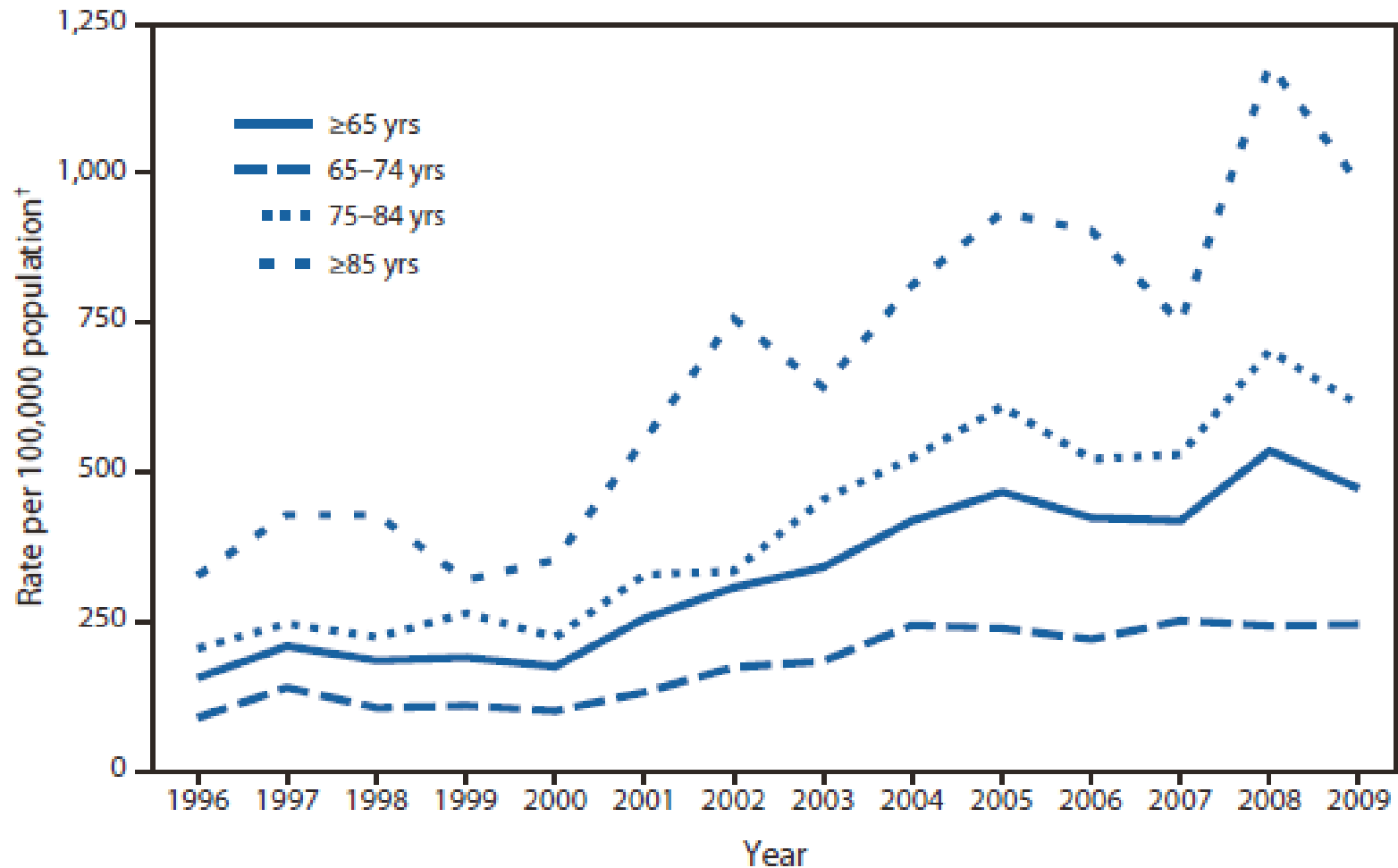
♥ for you,
with you

Background: the nature of the beast



- 500,000 cases per year
- \$5 billion in excess costs
- Approximately 30,000 deaths annually

Rate of CDI Among Hospitalized Patients Aged 65 and Over



Background



- *C. difficile* frequently recurs despite treatment:
 - 15-20% relapse after first infection
 - 30-45% will have second recurrence
 - 45-60% will have third recurrence

ACG Pharmacological Treatment Guidelines for Recurrent CDI



- 1st: can use same treatment as for initial episode; use vancomycin if severe
- 2nd: Pulsed vancomycin regimen
- 3rd: Pulsed-tapered dose vancomycin regimen

Background



- Human gut microbiota consists of as many as 1200 bacterial species and 10^{14} bacteria, most of which are in the colon
 - Synthesis of vitamins
 - Fermentation of dietary carbohydrates
 - Bile metabolism

Background



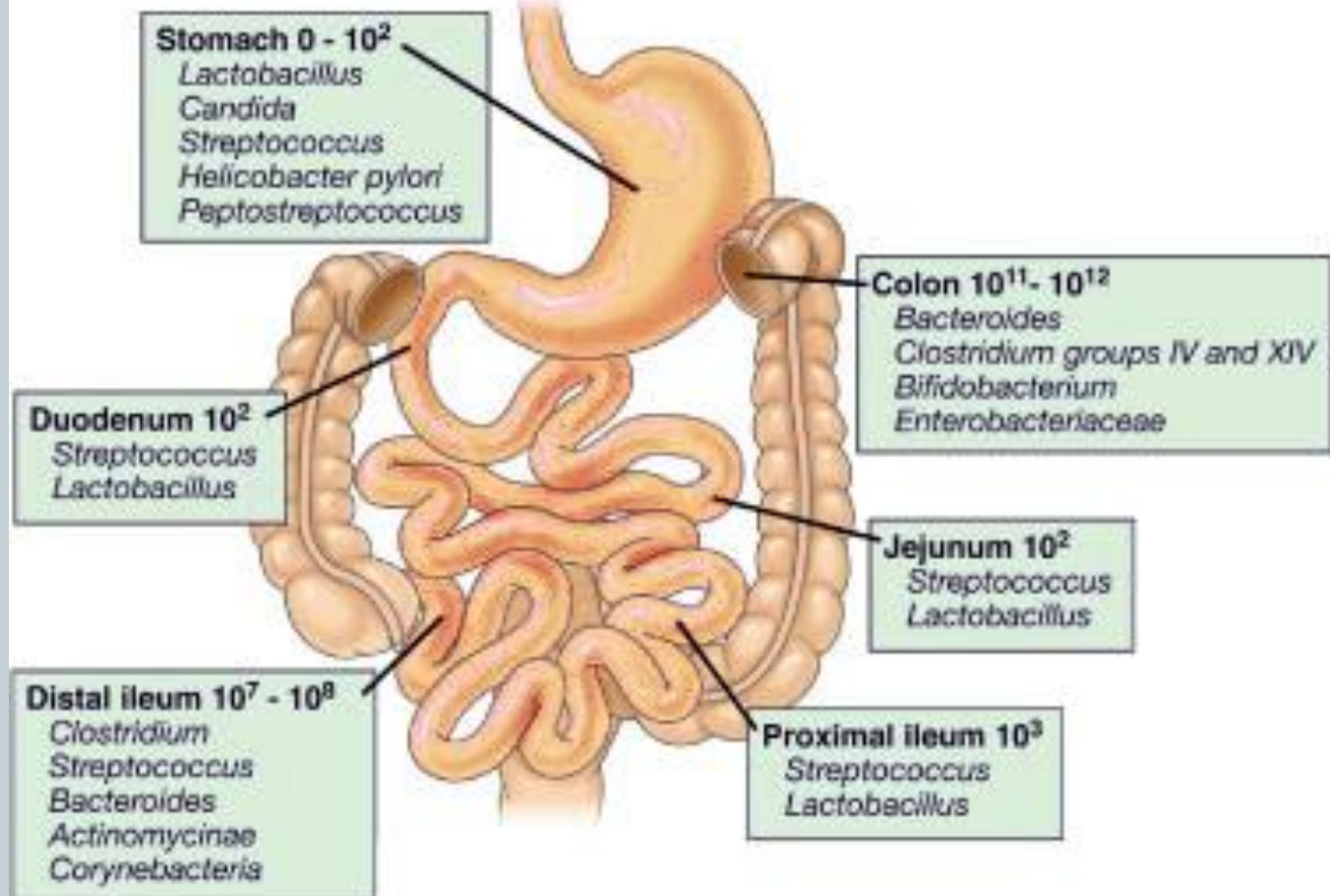
- **Additional roles of the microbiota:**
 - Resist colonization of pathogens “taking residence” in the gut

Background



- Composition of microbiota is affected by extensive use of antibiotics → selective removal of a bacterial species that serve as colonization barrier
- Recurrent *C. diff.*: associated with decrease in fecal microbial diversity deficient in *Bacteroides* and *Firmicutes*, both of which generally dominate

Background



FMT: how does it work?



- *C. difficile* becomes “overwhelmed” by the introduction of good bacteria into the colon and can no longer thrive.

Origins of FMT



- First documented in 4th century China
- Has been used for over 100 years in veterinary medicine
- Used in many countries as first line defense, or treatment of choice, for *C. diff*.
 - Customary for newborn infants in many parts of the world to receive a tiny amount of mother's stool by mouth

FMT in the United States



- Has been used since the 1950's sporadically
- Late spring, 2013: FDA announced it was classifying FMT as an Investigational New Drug (IND) and Biologic
 - Only physicians in possession of an approved IND application would be able to continue performing the transplants.
 - ✦ This resulted in less than 20 physicians throughout the United States being able to perform FMT.

FMT in the United States



- June 17th, 2013 – FDA reversed their position & announced that qualified physicians could continue to perform FMT for recurrent *C. difficile* only, with signed consents from patients and tested donor stool.

Candidate selection



- Relapsing CDI (3 or more episodes)

OR

- Two episodes that require hospitalization

OR

- Refractory disease that is unresponsive to traditional antibiotics

Donor Selection



- Must be screened for transmissible blood borne diseases, such as hepatitis, HIV-1, HIV-2 and syphilis.
- Not eligible if received antibiotics within the past 6 months
 - Can change the intestinal microflora and increase infection risk
- Stools must be screened for infectious pathogens

Donor Selection



- Donors must be generally healthy and have daily, normal stools
- Donors cannot have inflammatory bowel disease

Where does Winchester Hospital get the donor stool?

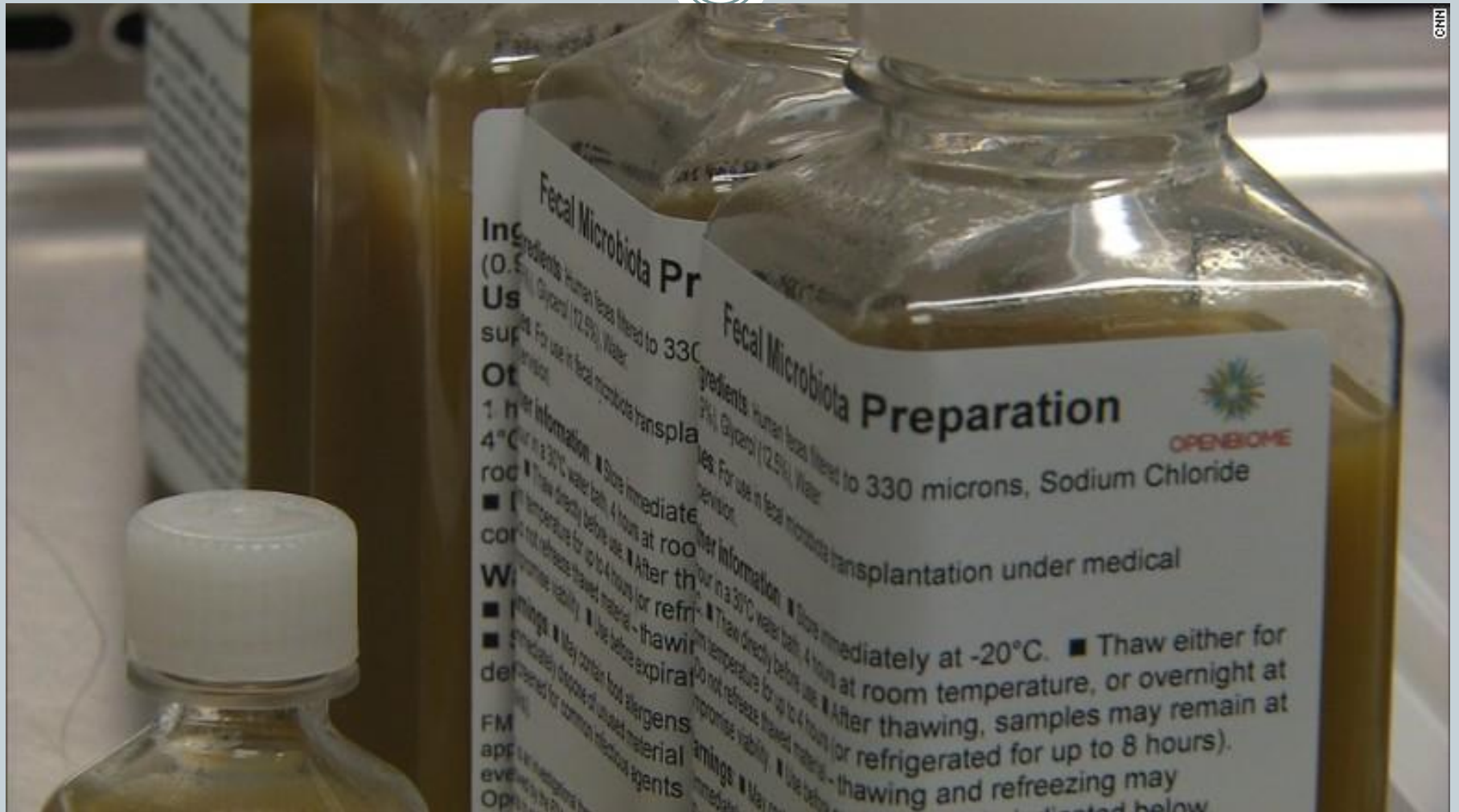


- OpenBiome, a nonprofit stool bank
- Donors undergo rigorous 109 question Clinical Evaluation with an internist and a battery of serological and stool screens
- Less than 3% of prospective donors pass the clinical evaluation

Open Biome



Open Biome



Efficacy of FMT



- Several routes have been used to administer fecal microbiota with cure rates ranging from 81-94% in patients with recurrent disease.
- In studies where time to response has been specified, it has been observed within 24 hours to 12 days.

Efficacy based on route of administration



- **Enema**

- Series of 16 patients with severe, refractory disease treated during an 18 year period, 13 patients responded dramatically with decrease in diarrhea, temperature and leukocytosis¹
- In another report of 9 patients, a single administration of a fecal enema was effective in 7 of 9 patients but the response was delayed for up to 5 days. No relapses occurred during 18 months of follow-up.²

Efficacy based on route of administration



- Case series of 27 patients with refractory or recurrent *C. difficile* underwent FMT via retention enema.
 - After FMT, 25/27 (93%) experienced clinical resolution.
 - ✦ Of these 22 resolved within 24 hours of FMT.
- Of the five patients who underwent a repeat FMT for recurrence of diarrhea, three had symptom resolution and two continued to experience diarrhea despite two FMTs³.

Efficacy based on route of administration



- **Colonoscopy**

- Allows for administration of bacteria throughout colon and possibly the distal small bowel where *C. difficile* can reside.
- Easy to administer in both inpatient and outpatient settings & introduces flora to the site where most *C. difficile* is located
 - ✦ For these reasons, colonoscopy is preferential route of delivery of fecal microbiota.

Efficacy Based on Route of Administration



- **Colonoscopy**
 - In patients who are healthy enough to prep, a 4 L Golytely prep should be administered.
 - Vancomycin pretreatment (500 mg twice daily for 7 days)
 - Imodium post FMT?

Colonoscopy data



- 19 patients with recurrent *C. difficile* infections who failed standard therapy achieved cure with infusion of donor stool
 - One patient required second infusion
 - Three patients developed recurrent infection after taking prescribed antibiotics for unrelated infections⁴

Colonoscopy data



- Study of 12 patients with recurrent/refractory infection
 - Cure rate of 100%
 - Durable clinical response (follow-up range of three weeks to 8 years)⁵

Colonoscopy data



- 26 patients with relapsing infection underwent FMT over a 28-month period
- Followed for an average of 10.7 months
- 24 (92%) remained symptom-free, with most patients reporting immediate improvement within hours or days following FMT⁶

Efficacy Based on Route of Administration



- **Nasogastric/jejunal tube**
 - Permits delivery of bacteria to small bowel and then throughout colon
 - Open label, randomized controlled trial
 - ✦ 43 patients with recurrent CDI after at least one course of Abx were randomized to:
 - Duodenal infusion of donor stool preceded by an abbreviated regimen of vancomycin and bowel cleansing
 - Standard vancomycin regimen for 14 days
 - Standard vancomycin regimen with bowel lavage

Efficacy based on route of administration



- **Nasogastric / jejunal tube**
 - Single infusion of donor feces associated with significantly higher rates of resolution of CDI associated diarrhea without relapse at 10 weeks as compared with standard vancomycin regimen with or without bowel lavage⁷

Data summary



Table 2. Summary Results for Reported Resolution of Symptoms After Initial FMT for Recurrent CDI, Overall and by FMT Method

FMT Method	Patients With Resolution of Symptoms Without Recurrence, %*	Studies/Total Studies Analyzed, n/N
Upper GI tract	77	7/187†
Colonoscopy	90	11/257†
Enema	78	5/45
Upper GI tract and colonoscopy	100	1/27
All methods	85	23/516‡

CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; GI = gastrointestinal.

* Because of small sample sizes and the abundance of data from case-series studies, 95% CIs were considered to be unreliable and were not calculated.

† Includes 10 patients from reference 18.

‡ Total number of studies is 1 less than the sum of individual rows.

Patients with underlying inflammatory bowel disease



- Review of 6 patients (four with ulcerative colitis (UC) and two with Crohn's disease) who were positive for *C. diff.* and failed to respond to antibiotic therapies:
 - FMT led to eradication of CDI with marked symptom reduction in all 6 patients⁸

Patients with underlying inflammatory bowel disease



- In a study of 14 IBD patients (6 with Crohn's, four with UC and four with lymphocytic colitis) with recurrent *C. difficile*, FMT was effective in treating the infection
 - Two Crohn's patients required a second infusion to clear the infection⁹

Patients who have undergone subtotal/total colectomy



- Anecdotal evidence suggests that FMT may be less effective in these populations.
- Fecal bacteriotherapy may lose its effectiveness when patients have had a subtotal colectomy.
- Randomized trials have not been performed.

Safety data



- FMT appears to be safe
- Risks include those associated with use of NG tubes and colonoscopy
- Major risk is transmission of infectious agents contained in the stool.

Our experience at Winchester Hospital



- To date, a total of 7 FMTs have been performed.
- 2 of the patients recurred
 - One of these patients was re-transplanted and cured.
- The other 5 patients did well.
- 3 of the 7 total patients had concomitant inflammatory bowel disease.

How can we foster this program to grow?



- It is up to us!
- Our patients with recurrent *C. difficile* should be offered FMT because it is an effective and safe treatment modality.

Sources



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Sources



- 9. Hamilton, MJ, et. al. Standardized frozen preparation for transplantation of fecal microbiota for recurrent CDI. *Am J Gastroenterology* 2012; 107:761.

Questions?

