# Fecal Microbiota Transplantation

## What's in the Poop?

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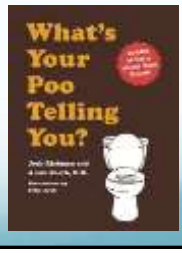
## Disclosures

- Speaker fees:
  - AbbVie, Janssen, Takeda, Pendopharm, AstraZeneca, Abbott, Shire
- Advisory Boards:
  - AbbVie, Janssen, Takeda
- Research:
  - AbbVie, Robarts




## TRIVIA

## When was the first documented to be completed?

- 4th century China
- Was known as the "yellow soup"
- Many areas give new born baby a small liquid sample of mothers stool→ leads to good bacteria populating the baby's colon and jump starting their immune system

- Used in the US sporadically since the 1950s
- 2013, FDA classified fecal matter as a new investigational drug (IND)
  - Resulted in < 20 Physicians that could perform FMT
- Later that year changed position to allow larger number of Physicians to before the procedure

## Clostridium Difficile

- 1978 C.diff was identified as causative agent in majority of Antibiotic assoc. Diarrhea
- 1989-92 "J strain" implicated in Lg outbreaks of outbreaks of diarrhea in 4 hospitals in U.S.
- 2003-06 infections were more frequent, severe, refractory to standard therapy and more likely to relapse
  - Attributed to new strain NAP1/BI/027

- C. Diff carriage occurs in 20-50% of adults in hospitals and long term care facilities
- Although asymptomatic, are capable of shedding pathogenic organisms and serve as a reservoir

## Transmission

- Patients with C.diff carriage are a reservoir for environmental contamination in the presence or absence of clinical infection
- Fecal-oral spread by ingestion of spores

## Risk Factors

- Antibiotics
  - 2 major roles
    - Disrupt normal colonic flora
    - Development of antibiotic resistance to clindamycin or Fluoroquinolones
  - Any antibiotic can predispose to colonization by C.Diff
  - Broad spectrum, multiple antibiotics and increased duration of use all contribute

- Initial cases were all attributed to Clindamycin (J strain)
- Increased use of Fluoroquinolones has been correlated with C.Diff ( NAP1/BI/027)

**Antimicrobial agents that may induce clostridium difficile diarrhea and colitis**

| Frequently associated | Occasionally associated | Rarely associated |
|---|---|---|
| Fluoroquinolones | Macrolides | Aminoglycosides |
| Clindamycin | Trimethoprim | Tetracyclines |
| Penicillins (broad spectrum) | Sulfonamides | Chloramphenicol |
| Cephalosporins (broad spectrum) | | Metronidazole |
| | | Vancomycin |

- Advanced Age
  - Outbreak in 2002 in Quebec frequency among patients > 65 was 10 fold higher than in younger
  - Diminished immune response and presence of other co-morbidities.

- Gastric acid suppression
  - Controversial
- Community-associated infection
  - Has been increasing
  - Previously thought to be low risk
  - Must be considered despite absence of antibiotic exposure

## Microbiology

- Anaerobic gram-positive, spore-forming, toxin-producing bacillus described in 1935
- "Difficult clostridium"
- Produces 2 potent exotoxins (A & B)
  - A causes inflammation leading to intestinal fluid secretion, mucosal injury.
  - B is essential for virulence, 10x more potent

## Hypervirulent Strain

- NAP1/BI/027 – named because of it's characterisitics by different straining methods
- 5 characteristics that contribute to virulence
  - Produces Binary toxin
  - Produces larger quantities of toxin A & B
  - Toxinotype III
  - Has a partial deletion of tcdC
  - Resistant to Fluoroquinolones

## Clinical Manifestations

- Watery Diarrhea main symptom
- Range from asymptomatic carrier to severe fulminant disease with toxic megacolon

## Carrier State

- 20% of hospitalized adults are C diff carriers
- Asymptomatic, but serve as reservoir.
- Treatment is not recommended

## Diarrhea with Colitis

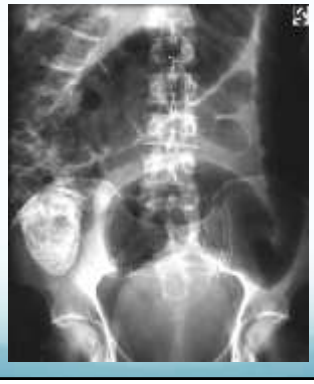
- Watery diarrhea 10-15 times a day
- Lower abdominal pain and cramping
- Low grade fever
- Leukocytosis
- Fever > 38.5 is a sign of sever CDAD
- Symptoms may occur during therapy or 5-10 days following Abx administration
- As late as 10 weeks after cessation

## Fulminant Colitis

- Typically includes severe lower quadrant/ diffuse abdominal pain, diarrhea, abdominal distension, fever, hypovolemia, lactic acidosis, and marked leukocytosis
- Diarrhea may be less prominent
- Complications include toxic megacolon and perforation

## Why to worry???

- Toxic megacolon
  - Clinical diagnosis (>7 cm in its greatest diameter)
  - With severe systemic toxicity
  - Abdominal plain films showed small bowel dilatation, air-fluid levels and " thumb-printing"
  - Needs surgical consultation



## Diagnosis

- 2 categories
  - Toxin assays
  - Organism detection assays
- Optimal approach is uncertain

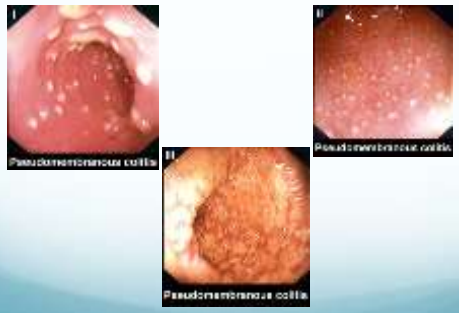
## Toxin Assays

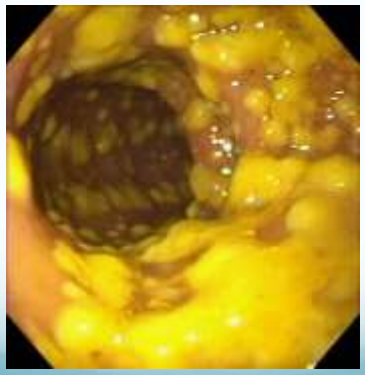
- Cytotoxicity Assay
  - Gold standard
  - Most sensitive (94-100%)
  - Can detect as little as 10 pg of toxin B
  - High specificity (99%)
  - Not routinely used as costly and long turnaround time

- Enzyme Immunoassay for toxins A&B
  - Simple and available in 24 hours
  - Specificity 99%, sensitivity 60-95% ( high false positive as 100-1000 pg required )
- Enzyme Immunoassay for GDH (glutamate dehydrogenase)
  - Essential enzyme produced by all C. diff
  - Cannot differentiate toxic from non-toxic
- PCR
  - Rapid and accurate
  - 97% sensitive and 93% specificity

## Endoscopy

- High clinical suspicion with neg. Lab assays
- Prompt diagnosis needed before lab tests can be obtained
- Failure of infection to respond to antibiotic therapy
- Atypical presentation with ileus or minimal diarrhea





## Recurrent C. Diff infection

- 20% of patients experience recurrence of Symptoms
- Rates of recurrence rise to 40-60% after one episode
- Similar after Metronidazole and Vanco.
- Can be same or different strain

## Treatment

- STOP ALL other antibiotics if possible
  - Increased risk of recurrence and need for prolonged therapy
- Contact measures
  - Hand washing with soap and water felt to be more effective than alcohol based sanitizers
- General treatment measures
  - Fluid replacement
  - Regular x-rays for sicker patients (?toxic megacolon)

## Non-severe disease

- Flagyl/metronidazole vs Vancomycin
  - Several older studies suggest that flagyl and vancomycin are similar in efficacy for treatment of initial infection
  - Some more recent data suggests that patients maybe more at risk of recurrence if initial treatment was with flagyl
  - CDC and Infectious Diseases Society of America still suggest flagyl as 1st line therapy for non-severe disease (2010 guidelines)…500mg PO TID for 10-14 days

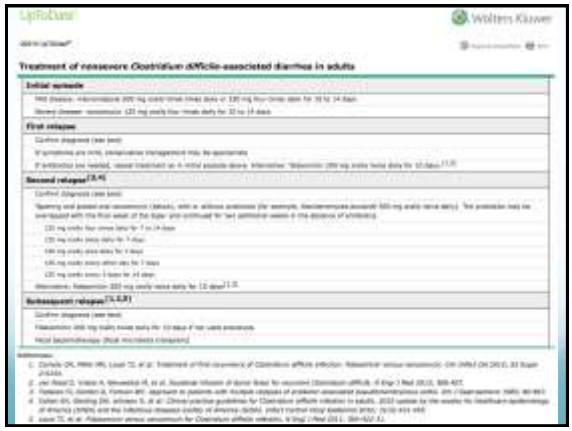
## Moderate to Severe Diseae

- WBC >15, fever, ileus
  - Vancomycin 125-250 mg PO QID for 10-14 days +/- Flagyl 500 mg IV TID
  - Can also consider the use of Vancomycin enemas, 250 mg in 750 cc of D5W

## Recurrence

- Consider alternative causes of diarrhea
  - Post infectious IBS, IBD, etc…
- If symptoms are no more severe than last presentation, could consider re-treatment with initial antibiotic choice
- Vancomycin taper
- Fidaxomicin
  - Bactericidal vs bacteriostatic (Vancomycin)
  - Phase III study of 629 patients, similar treatment results to Vanco but lower rates of recurrence (10 vs 28%), but in non-NAP1 strains

Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK, OPT-80-003 Clinical Study Group, N Engl J Med. 2011;364(5):422.


Treatment of nonsevere *Clostridium difficile*-associated diarrhea in adults

- Probiotics
  - Inconclusive results on benefit
  - Questionable benefit in prevention, but perhaps beneficial if concomitant use of antibiotics in hospital
  - For treatment of C. diff, **non-severe**, maybe useful…
    - L. acidophilus, L. casei, S. boulardii, or L.rhamnosus
    - >10 billion colony-forming units per day
- Monoclonal antibodies
  - Against toxin A&B
  - NEJM article, 200 patients, recurrence rates of 7 vs 25%
  - Not yet available for clinical use

Treatment with monoclonal antibodies against Clostridium difficile toxins. Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas WD Jr, Leney M, Sloan S, Hay CA, Ambrosino DM. N Engl J Med. 2010;362(3):197.

- Surgery – toxic megacolon
  - Subtotal colectomy – most experience with this approach
  - Diverting loop ileostomy and colonic lavage
    - Small study, 42 patients, preservation of colon in 93%

## And finally, the reason we are all here….

LETS TALK ABOUT THE POOP!!!


## Who qualifies for FMT???

- Any patient who has failed multiple attempts at antibiotic therapy for C. diff
- Multiple meta-analyses have demonstrated efficacy for FMT in patients with recurrent/refactory disease
  - Cure rates range from 81-94% depending on study looked at and route of administration
- However, a recent systematic review in the Annals of Internal Medicine suggests that the evidence is insufficient on FMT for refactory or initial CDI treatment and on whether effects vary by donor, preparation, or delivery method
  - 2 RCTs, 28 case series, 5 case reports
  - Drekonja, Dimitri, et al. Fecal microbiota transplantation for Clostridium difficile infection: A systemic review, Ann Intern Med. 2015; 162 (9): 630-638.
- Limited observational data in SEVERE disease
- Special populations???

## How do we give the poop?

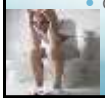
- Enema
- Nasogastric
- Colonoscopy
- Capsule

- A pooled analysis of 182 cases of recurrent CDI treated with FMT showed that colonoscopy has a slightly higher cure rate than nasogastric or enema (93 vs 85%), but not statistically significant difference
- The efficacy of FMT may depend partially on the technique used to cleanse the colon

Colonoscopic versus nasogastric fecal transplantation for the treatment of Clostridium difficile infection: a review and pooled analysis. Postigo R, Kim JH. Infection. 2012 Dec;40(6):643-8. Epub 2012 Jul 31.

## Donor/Recipient Screening

- Donor stool and blood tested prior to infusion
  - CBC, Hep A/B/C, HIV, syphilis
  - C&S, O&P, C diff, norovirus, rotavirus (some check H. pylori antigen if doing upper GI administration)
  - ? Should they be living in same house
- Recipient screened for
  - HIV, Hep A/B/C, syphilis
  - C&S, O&P, norovirus, rotavirus



## Enema

- Cleansing with PEG lavage prior to administration can reduce the density of C. diff organisms including the metabolically inactive spores
- My n of 7 has been 100% successful
- My recipe…

The standard barium enema bag and catheter with the inflatable balloon is used. Approximately 1500cc of the slurry placed inside the enema bag. The contents do not need to be warmed. Room temperature or enema temperature of 10-15 degrees C is acceptable. The bag is suspended 24 to 48 inches above the patient. The bed is covered with an impermeable sheet, then covered with sheets/cloths (impermeable one side) in layers, in the event that there is patient leakage.

Begin slow infusion with patient lying in the lateral Sims's position, facing away with the left colon down. Infuse about 3-400 cc slowly over 12-15 minutes. Reposition the patient on the back. Continue the infusion to 600-1000 ccs. Massage abdomen if there are cramps. Also stop the infusion if there are cramps, and wait for the cramps to pass off. Advise the patient beforehand that there will be slow infusion, and that cramps will dissipate over several minutes for each episode. Turn the patient to have the R. colon descendent, hoping that the fecal effluent will gravitate into the cecum. Turn patient on back again, complete the 1400 cc or high infused. Re-turn the patient onto the right side again to have effluent flow into the cecum. Total elapsed time is between 45 minutes and 90 minutes. If there are a lot of cramps, decompress the bowel by siphoning back the infusate, perhaps 400-600-cc, so that 80% if the inoculums remains in the colon at the time of removal of the catheter [after deflation of the balloon]. Siphoning is lowering the bag.

## Colonoscopy

- Presumed benefit is that can ensure full coverage of entire colon and distal small bowel (and yes, can live in the terminal ileum)
- Many experts feel this is the preferred method of administration, but caution must be considered to minimize risk of perforation
- Multiple studies and meta-analyses demonstrate that a single administration is extremely efficacious in eradicating C. diff in the inpatient and outpatient setting

Khoruts A, Dicksved J. Jansson JK, Sadowsky MJ. J Clin Gastroenterol. 2010;44(5):354.
Rohlke F, Surawicz CM, Stollman N. J Clin Gastroenterol. 2010;44(8):567.
Persky SE, Brandt LJ. Am J Gastroenterol. 2000;95(11):3283.
Yoon SS, Brandt LJ. J Clin Gastroenterol. 2010;44(8):562.

## Nasogastric tube

- Study in the ICU setting (NEJM)
- Study stopped early due to positive results…81% had resolution of diarrhea vs 31% receiving Vanco alone
- Received a bowel lavage first with PEG and related donor feces

Duodenal infusion of donor feces for recurrent Clostridium difficile. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JF, Tijssen JG, Speelman P, Dijkgraaf MG, Keller JJ. N Engl J Med. 2013;368(5):407.

## Nasogastric tube/capsule

- Patient and stool preparation similar to those who receive via lower GI tract
- Many experts suggest a dose of PPI the evening prior and the morning of to decrease gastric acid
- NJ preferred over NG
- Often use 25-30 g of stool diluted in 50 cc of saline

http://www.uptodate.com/contents/fecal-microbiota-transplantation-in-the-treatment-of-recurrent-clostridium-difficile-infection

## FMT Capsule

- Lots of discussion in the media regarding the "poop pill"
- Overall, 90% success rate in resolution of diarrhea and maintained at 8 weeks
  - 20 patient trial, pills at -80$^0$C, 15 capsules on 2 consecutive days
- Further studies ongoing designing a non-donor poop pill that may lead to more "mainstream" acceptance

Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection. Ilan Youngster, MD, et al. JAMA. 2014;312(17):1772-1778. doi:10.1001/jama.2014.13875.

## What about using C. diff to cure C. diff

- Administration of non-toxigenic C diff spores prevented recurrent CDI
  - 173 patients, all treated with Flagyl, Vanco or both for clinical recovery
- Rate of recurrence 30% (placebo) vs 11%, NNT= 5.3

Gerding, DN, et al. Administration of spores of non-toxigenic C. diff strain M3 for prevention of recurrent C. diff infection. JAMA 2015; 313 (17):1719-1727

## Subtotal Colectomy Patients

- Important population with current survival rates in post-resection for colon cancer
- Several authors have suggested that FMT may lose its efficacy
  - Case report of a successful eradication of C. diff after a total proctocolectomy
- Further studies are needed

Difficile small bowel enteritis after total proctocolectomy successfully treated with fecal transplant. Miao CL, Mowery AD, Khara HS, et al. Am J Gastroenterol. 2014;109:S442.

## Inflammatory Bowel Disease

- Microbiota one of the "hot" topics in IBD research right now (genomics, etc)
  - Bacterial flora considered to be one of the main causes of IBD
- FMT has been successful in treatment of IBD with refractory C. diff in observational studies
- Major concern is bacterial translocation across an already "leaky colon" due to ongoing inflammation from the underlying IBD + the acute C. diff infection

## Inflammatory Bowel Disease

- Multiple smaller studies demonstrating benefit for treatment with FMT for IBD with C. diff
- However, failure rates tend to be higher with average of 78-82% success rates, with the majority of patients having ulcerative colitis
- In the trials to this point, no colectomies/deaths were observed

Chetan, Mittal, et al. Fecal transplant for recurrent and/or refractory CDI in patients with IBD, 2014 Advances in IBD, abstract

## Inflammatory Bowel Disease

- Interesting case report out of Chicago
- 41 year old female treated with FMT after 4 failed attempts at antibiotic therapy for CDI
- 6 weeks later, new onset BRBPR, abdominal pain
- Colonoscopy and biopsies demonstrated acute ulcerative colitis, all stool cultures negative as well as CMV and AFB

Colleen, Kelly, et al. New diagnosis of crohn's colitis 6 weeks after FMT. 2014 Advances in IBD, abstract.

## IBD-treatment option???

- 50 active UC (mild to moderate) patients in a double blind, randomized trial
- Given healthy donor FMT or autologous microbiota, end point was clinical remission + MAYO score decrease by $\geq 1$
- 30.4% (donor FMT) vs 20% (autologous) achieved primary end point
- However, no statistically difference between the 2 groups, but analysis of the stool demonstrated distinct features in the responders that warrants further evaluation

Rossen, NG et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. Gastroenterology. 2015, July; 149(1)

## IBD-treatment option???

- The 1st randomized controlled trial of FMT for active UC
- 70 patients, enema therapy of 50 cc of FMT or placebo weekly for 6 weeks
- Primary outcome of remission (MAYO score $\leq 2$ and endoscopic MAYO=0 at week 7
- Remission rate was 24% (FMT) vs 5% (placebo), at 12 months 8/9 patients in initial remission were still in remission
  - Important note: 7/9 patients in remission had the same individual donor (?super donor concept)
  - Shorter course of disease (<1 yr) also seemed to predict better outcome

Moayyedi, P et al. Successful fecal microbiota transplantation for active ulcerative colitis. Gastroenterology. 2015 Jul; 149:102

## Conclusions

- Fecal microbiota transplantation appears to be a safe and effective therapy for patients who have failed prior antibiotic therapy
- New forms of administration may make the process more "main stream" and more palatable *(pun intended)*
- Use of FMT in "special populations" requires more research and further studies are needed