ADVANCING GI PATIENT CARE 2022

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Fecal Transplant for C diff: Past, Present, and Future

Tim Miller, MD

Lubbock Digestive Disease Associates

Disclosures

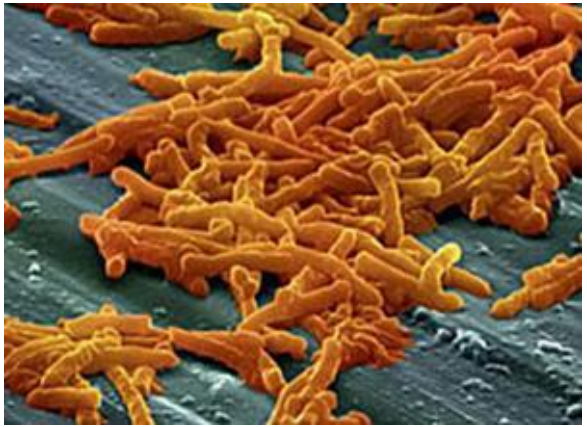
- No relevant financial relationships to disclose.

Objectives

- Review indications for fecal transplant in the setting of C diff infection
- Discuss effectiveness of FMT in recurrent and refractory cases of C diff
- Outline past and future methods of FMT, including risks and benefits of both

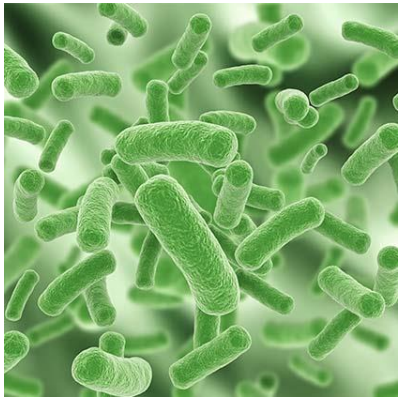
C Diff Infection

- Clostridium difficile
  - Anaerobic, spore-forming, gram positive bacillus
  - Ubiquitous in nature
  - Prevalent in soil
  - 3-10% of healthy adults are colonized with c diff
  - Up to 50% of patients hospitalized for 4 weeks become colonized



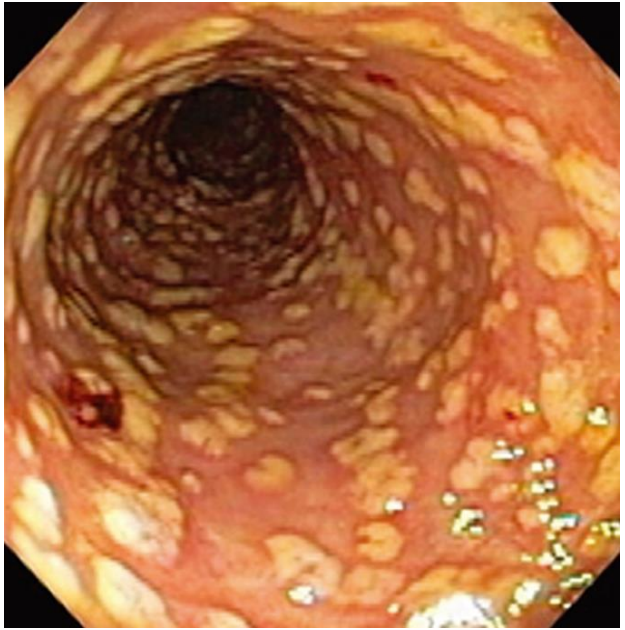
C Diff Infection

- First identified in 1935
  - Osler described a c diff like illness in 1892
- Leading cause of antibiotic and nosocomial diarrhea and colitis
- Transmitted fecal-orally
- Resistant to commonly used decontaminates
- Spores can remain viable outside the body for 5 months!

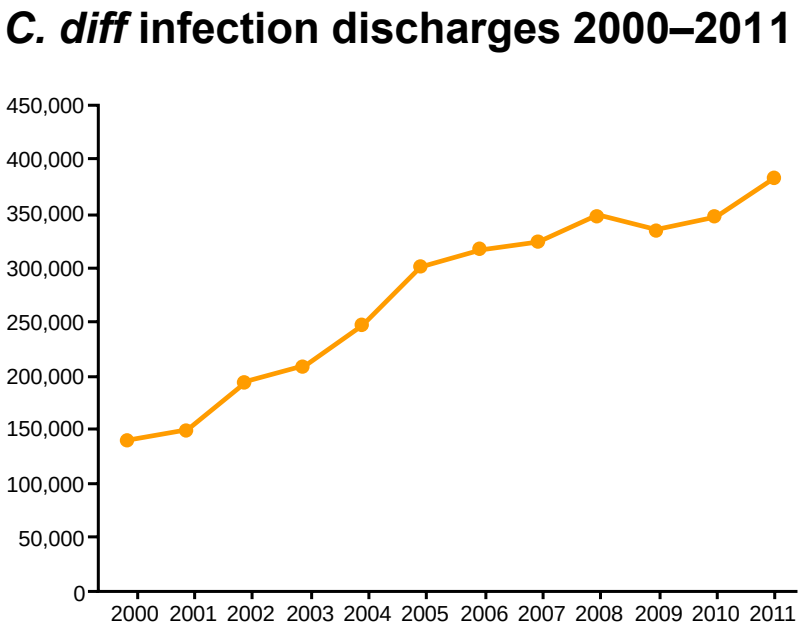


C Diff Infection

- Clinical manifestations
  - Asymptomatic carrier
  - Diarrhea, including severe
  - Abdominal pain
  - Colitis and bleeding
  - Pseudomembranes
  - End organ damage
  - Death



C Diff Infection



- 500,000 cases annually
- 170,000 recurrent cases annually
- 20,000 deaths per year

Microbiome

- Biodiversity of human gut is vast
  - 10^{14} bacterial cells representing thousands of species
    - 100,000,000,000,000 (one hundred trillion!)
  - Examples of major bacterial phyla
    - Firmicutes, Bacteroidetes, Actinobacteria, Verrucomicrobia, Proteobacteria, Fusobacteria
  - Fungi, Protozoa, Bacteriophages
  - All play a role in preventing pathogens from gaining a foothold in the gut
    - Competitive exclusion of pathogens

Medical Treatment

- Mild to moderate disease
- Metronidazole no longer considered first line therapy in new IDSA guidelines
- Vancomycin 125 - 250 mg po q 6 hrs for 14 days

  or

- Fidaxomycin 200 mg po bid x 10 days
- Add Metronidazole 500 mg IV q 8 hrs for severe disease

Recurrent C Diff

- Recurrence is defined as complete abatement of symptoms while on treatment, followed by reappearance after treatment has been stopped
  - 25% recur within 30 days
  - C diff can recur as late as 3 months
  - Multiple recurrences are likely after the first recurrence
    - Older
    - Female
    - Recent antibiotics
    - PPI use
    - Steroid use
    - CKD
    - Nursing home

Fecal Microbiota Transplant (FMT)

- History of FMT
  - First used in 4th century China
  - First used in the US in 1958 – retention enemas
  - Has gained popularity and become mainstream in the last 10-15 years
  - FMT temporarily put on hold by the FDA in Spring 2013 and classified it as a Investigational New Drug and a Biologic
    - Only allowed physicians participating in IND trial to perform it
    - FDA reversed their position in June 2013
      - Mandated informed consent from the patient
      - Encouraged clinical trials

FMT

- Efficacy
  - At least 17 meta analyses have been done showing efficacy of FMT after recurrence
  - Cure rates range from 81-94%
  - Time to resolution of symptoms is 1-12 days on average
  - Infused donor fecal microbiota remains stable in composition for ~24 weeks

FMT

- Multicenter, long term follow up of 77 patients who had received FMT
- Primary cure rate after 90 days
- Secondary cure rate after another course of Vancomycin following FMT +/- 2nd FMT
- Average duration of symptoms was 5 months
- Average courses of antibiotics was 5
- 74% had resolution of diarrhea in 3 days
- Primary cure rate 91%
- Secondary cure rate 98%
- All recurrences had re-exposure to antibiotics for other infections

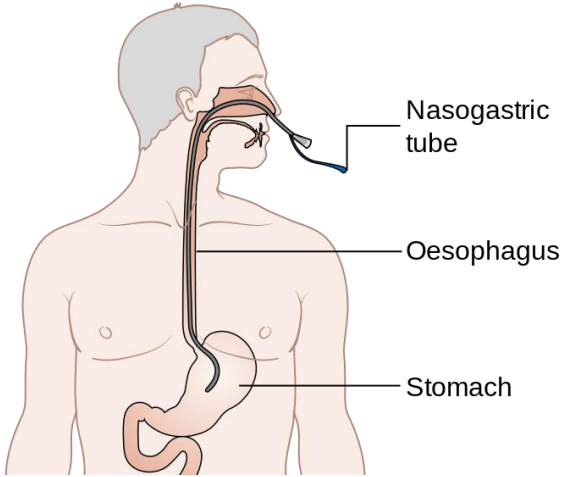
Brandt et al. *Am J Gastroenterol*. 2012.

FMT

- Routes of administration
  - Colonoscopy (preferred)
  - Upper endoscopy with push enteroscopy
  - Retention enema
  - Nasoenteric feeding tube (discouraged, especially if ileus present)

Routes of Administration

- Routes of administration
  - Postigo, Infection 2012
    - Pooled analysis comparing colonoscopy to NG tube
    - 182 patients from 12 studies
      - 148 colonoscopy
      - 34 NG tube
    - Higher stool volume in the colonoscopy group
    - 93.2% cure in colonoscopy group (138/148)
    - 85.3% cure in NG tube group (29/34)
    - P 0.162 (not significant)
  - Conclusion: colonoscopy and NG tube are equivalent routes of administration for FMT



Routes of Administration

- Colonoscopy
  - Theoretical advantages
    - Allows for administration throughout the colon and even small bowel
    - Permits inspection for colitis or pseudomembranes
    - Delivers flora to the site where most C diff is located
  - Disadvantages
    - Cost
    - Risk of complication such as perforation

Routes of Administration

- Oral capsules
  - Open label feasibility study
  - 20 patients with at least 3 episodes of mild-moderate c diff
  - Treated with up to 30 FMT capsules over 2 days
    - 14/20 (70%) cured after one treatment
    - 4/6 nonresponders cured after second treatment (90%) total

Ilan et al. *JAMA*. 2014.

FMT for Severe Disease

- 111 patients with c diff
  - 66 early FMT group
  - 45 non-FMT group
- 3 month mortality of those with severe disease
  - 12.1% in FMT group
  - 42.2 % in non-FMT group
- FMT improves survival in severe cases (OR 0.08), but not in non-severe cases

Hocquart et al. *Clinical Infectious Disease*. Feb 2018.

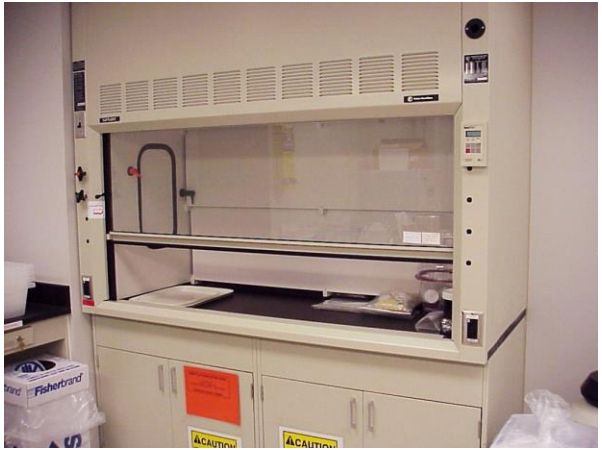
FMT – Past

Early Protocols

- Stool Preparation
  - 50 gm of stool
    - Preferably given on the same day as the procedure
  - 250 ml of saline or sterile water
  - Liquefy in blender
  - Store in refrigerator until procedure is done

Early Protocols

- Donor preparation
  - Proper screening
  - Dulcolax at bedtime prior to procedure
  - Collect stool in Tupperware
  - Deliver to microbiology lab for dilution under hood



Protocol

- Recipient preparation
  - Stop all antibiotics 48 hours prior to FMT
  - Preferably undergo bowel preparation
    - Theoretically reduces the density of c diff organisms in the colon, including spores

Donor Screening

- Health history exclusions
  - Antibiotic use within 3 months
  - Tattoos, body piercings, or incarcerations within 3 months
  - Recent acute or chronic GI illnesses
  - Immunocompromised
  - Metabolic syndrome
- Originally thought that household contact was ideal

FMT – Present (Soon to be Past)

Open Biome

- Non-profit organization founded in 2012
  - Expanding access to FMT providing research into the microbiome
- Stool bank for FMT donations
- Donor paid $40 per each stool donation!
- Distributed over 57,000 specimens through 2020 to 1250 hospitals

OPENBIOME

Open Biome

- Stool Donor Criteria
  - Age 18-50
  - BMI < 30
  - Live in the Boston area
  - Two rounds of rigorous stool and blood testing over a 60 day period
  - Only 2.5% of screened patients end of being eligible to donate

Donor Screening

- Stool testing
  - C diff PCR
  - Culture
  - O&P and Giardia
  - H pylori (?)
  - Cryptosporidium
  - Isospora
  - Rotavirus
- Serologic testing
  - Hepatitis A IgM
  - Hepatitis B Surface Ag
  - Hepatitis C Ab
  - HIV 1&2 Ab
  - Syphilis

Fresh vs Frozen Stool Donation

- Randomized, double-blinded, noninferiority study comparing frozen and thawed stool (investigational) to fresh stool (standard)
- 232 adults with recurrent or refractory c diff
  - 114 patients received frozen and thawed stool
  - 118 patients received fresh stool
- Primary outcome is clinical resolution of diarrhea at 13 weeks
- 83.5% cure in frozen group vs 85.1% in the fresh group

Lee et al. *JAMA*. 2016.

National FMT Registry

- NIH Funded National FMT Registry started in 2017
- Goal is to follow 4,000 patients for 10 years
- Identify short and long term outcome data
- Providers that perform FMT are encouraged to participate

Adverse Events

- In 2020, two patients acquired multi-drug resistant E coli infection from FMT
  - Both from same donor
  - One patient died
- FDA issues warning for all FMT patients
- These infections, along with the challenges that Covid presented with screening, caused Open Biome to stop collecting new donations
- Open Biome now used in emergency and fulminant cases only

FMT – Future

FMT in Capsule Form

- Four companies are developing new products
  - Seres Therapeutics
  - Finch Therapeutics
  - Rebiotix
  - Vendanta Biosciences

Seres Therapeutics

- Ecospor III Trial
  - Phase 3 trial
  - Randomized, double blinded, placebo controlled
  - Ser-109 capsules
    - Donor derived live, purified Firmicutes bacterial spores (after a standard antibiotic course)
    - Patients took 4 capsules daily x 3 days (vs Placebo)
    - Unique manufacturing process that inactivates multiple potential pathogens

Seres Therapeutics

- Ecospor III Trial
  - Patient data
    - Age 18 and over
    - 3 or more c diff episodes within 3 months
    - 182 patients enrolled

Ecospor III Results

Treatment Arm

- At 8 weeks
- 11.1% recurrence (88.9% cure rate)
- Patients who took Fidaxomycin were less likely to recur as compared to those that took Vancomycin prior to the oral FMT
- Younger than 65 also did better

Placebo Arm

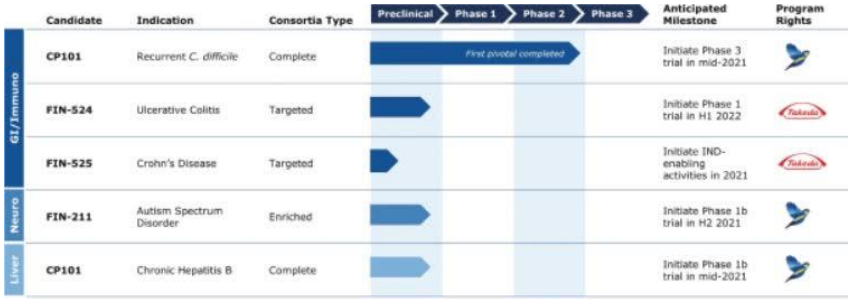
- At 8 weeks
- 41.3% recurrence
- NNT 3
- No difference in adverse events

Finch Therapeutics

- PRISM-EXT Trial
  - Phase 2 trial
  - Randomized, placebo controlled
  - CP 101 capsules
    - Complete microbiome community in one time oral administration

PRISM-EXT Trial

- Results
  - 132 patients
  - Extension of PRISM3 in which 74.5% of recipients achieved remission at week 8 and 73.5% achieved remission at 24 weeks
  - 82 patients received a fist dose, and 20 of the failures from PRISM3 received a second dose
  - 30 placebo failures from PRISM3 received a first dose
  - Overall 88.2% of patients were cured at 8 weeks, either with one or two doses
  - PRISM4 phase 3 trial is currently enrolling

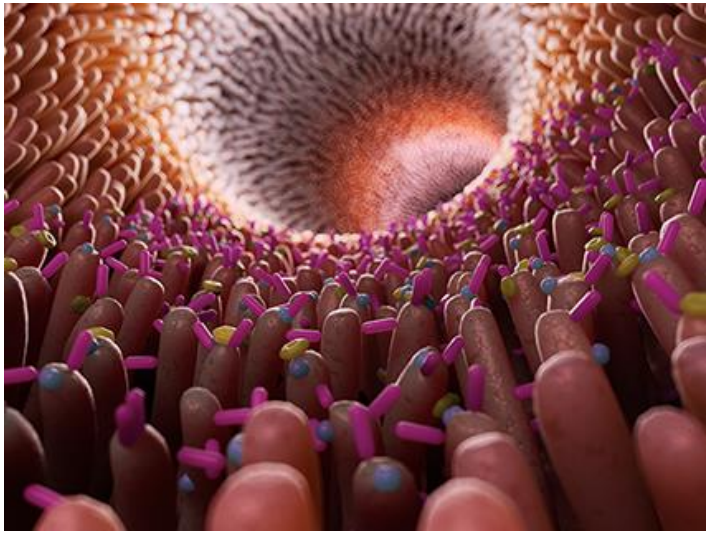


Rebiotix

- RBX2660
  - Five prospective trials have been done
    - 3 phase 2 trials
    - 2 phase 3 trials
  - 723 study participants
  - 78.9% cured after 8 weeks across all the trials
  - Increased gut bacteria associated with good health (Bacteroidia- and Clostridia-class) and reduced bacteria that are potentially harmful
  - No significant adverse events reported

Rebiotix

- RBX7455
  - Room temperature stability
  - Broad spectrum gut microbiota from live donor specimens
  - Phase 1 trial
  - 3 groups
    - 4 capsules bid x 4 days (90% cured)
    - 4 capsules bid x 2 days (80% cured)
    - 2 capsules bid x 2 days (100% cured)
  - No significant adverse events



Vendanta

- CONSORTIUM Trial for VE303
  - Randomized, double blinded phase 2 study
  - Treated c diff patients at high risk for recurrence
  - Oral capsules daily x 14 days
  - VE303 met primary endpoint at preventing recurrence at 8 weeks
- VE303
  - 8 types of human commensal bacteria strains
  - Produced under cGMP conditions from pure, clonal bacterial cell banks
  - Does not rely on live fecal donors

Personal Experience

- Success rates similar to study outcomes
- Since 2012 ~80 fecal transplants
- Ages 25-95
- Typically done for recurrent disease, rarely for acute severe or refractory disease
- Was exclusively using Open Biome, now awaiting oral options
- After FMT failure, treat with Vancomycin and repeat FMT only if that fails

Conclusions

- Clostridium difficile continues to increase in incidence and severity
- C diff recurs up to 35% of cases
- Antibiotics followed by probiotics remain first line therapy in most cases
- FMT, although not FDA approved, is clearly superior to antibiotics in recurrent or refractory cases
- FMT is 85-90% effective, independent of preparation or delivery modality
- Oral options are on FDA fast track for approval