Fecal Microbiota Transplantation (FMT): Current Concepts in *Clostridium difficile* and beyond

Amir Patel, MD
Assistant Professor of Medicine
Froedtert Hospital and the Medical College of Wisconsin

I have no financial disclosures
Objectives

- Understand the changing epidemiology of *Clostridium difficile infection* (CDI)
- Be able to apply CDI treatment guidelines
- What is fecal microbiota transplantation (FMT)
- Understand the role of fecal microbiota transplantation (FMT) in the management of CDI

*Clostridium difficile*
Microbiology

- Anaerobic, spore-forming, gram-positive bacterium
- Releases two exotoxins responsible for causing disease (diarrhea/colitis)
  - Toxin A and B cause inflammation leading to intestinal fluid secretion and mucosal injury
- Strains have varying degrees of virulence
  - NAP1/BI/027 = hypervirulent strain


Asymptomatic Colonization

- Most common outcome after exposure (85%)
- Associated with a decreased risk of CDI
- For every 1 patient with CDI, 9 others likely to be colonized (silent transmitters)
- Do not test formed stools!

Dansinger et al. CID 1996.
**C.Difficile Infection**

- 15% of patients exposed develop disease
  - May occur days to weeks to months after antibiotic exposure
- Watery stools ≥ 3 a day that persists for greater than 24 hours
- Additional symptoms:
  - Abdominal cramping, nausea, vomiting, anorexia, fatigue, fever
- Clinical / Radiologic findings
  - Leukocytosis/Leukomoid reaction
  - AKI
  - Hypoalbuminemia
  - Colitis/ileus/toxic megacolon

*Kelly et al. NEJM 2008.*

---

**C.difficile: Changing Epidemiology**

- More frequent infections
- More serious infections
- More refractory infections
Hypervirulent Strain – NAP1/BI/027

McDonald et al. NEJM 2005.

More Refractory Disease

1991 - 2002
2003 - 2004

60 day probability of recurrence among patients with CDI treated with only metronidazole

Out With Metronidazole?

- Randomize controlled trial
- Tlevamer was inferior to vancomycin
- Metronidazole was inferior to vancomycin as well


CDI Treatment
General Principles

- Discontinue inciting antibiotics, if able
- Empiric therapy is appropriate pending the results of a diagnostic assay
- What about asymptomatic patients with a positive toxin assay?
- Do not perform “test of cure” assays
- Stop unnecessary PPI

Defining Severe Disease

- No consensus definition
- WBC > 15k, serum creatinine ≥ 1.5 x pre-morbid baseline
- WBC > 20k
- RCT vancomycin vs metronidazole
  - One point for: age > 60, Temp > 38.3 Celsius, Albumin < 2.5 mg/dl, WBC > 15k within 48 hours
  - Two points for pseudomembranous colitis on endoscopy
  - Patients with 2 or more points considered “severe”
- ≥ 10 BM per day, WBC ≥ 20k, or severe abdominal pain

Non-severe Disease

- Metronidazole 500 mg oral every 8 hours for 10 to 14 days
- Vancomycin 125 mg orally every 6 hours for 10 to 14 days
- IV metronidazole 500 mg every 8 hours can be used if patient is NPO (drug has biliary excretion)
- IV vancomycin is not effective in CDI


Severe Disease

- Oral vancomycin 125 mg every 6 hours for 14 days
- If ileus is suspected, add metronidazole 500 mg IV every 8 hours
- If severe ileus/toxic megacolon and patient is critically ill:
  - Increase vancomycin to 500 mg and add intracolonic vancomycin 500 mg in 100 mL normal saline every 4 to 12 hours via retention enema (foley catheter with 30 cc balloon in rectum, inflate, instill vancomycin, clamp for 1 hour, then deflate and remove)
- Surgery and ID consultation

Relapse is Common

- Relapse is common and occurs in 15 to 35% of patients after their first episode
- 45% of patients who have one relapse will experience a subsequent relapse
- 65% of patients who have another relapse will experience a subsequent relapse

Fidaxomicin

- Bactericidal agent against *C. difficile*
- Narrower antimicrobial spectrum than metronidazole or vancomycin
- Phase 3 RCT: Fidaxomicin (200 mg PO BID) vs. vancomycin (125 mg PO QID)
  - Similar clinical cure rates (88.2% vs 85.8%)
  - Recurrence occurred less often with fidaxomicin among patients with non-NAP1 strains

Surawicz et al. Am J Gastroenterol 2013
“a course of fidaxomicin would need to cost ≤$150 to be cost-effective in the treatment of all CDI cases and between $160 and $400 to be cost-effective for those with a non-NAP1/BI/027 strain”


Emerging Therapies

- Monoclonal Antibodies (bezlotoxumab)
- Tigecycline
- Fecal Microbiota Transplantation (FMT)
- Stool Substitutes
- Non-toxigenic *C. difficile*
- Bile salt analog blocks germination (CamSA)
- IVIG
Fecal Microbiota Transplantation (FMT) in CDI

What is Fecal Microbiota Transplantation?

- Infusion of a liquid stool preparation obtained from a healthy donor into the gastrointestinal tract to restore normal flora
History

- **4th Century, China**
  - Ge Hong described the use of human fecal suspension by mouth for patients with food poisoning or severe diarrhea

- **16th Century, China**
  - Li Shizhen described oral fecal ingestion for the treatment of severe diarrhea, fever, pain, vomiting, and constipation

- **17th Century, Italy**
  - Fabricus Aquapendente described transfaunation (transfer of cecal contents of fresh feces) from healthy horses to treat horses with diarrhea


History

- **1939-1945: WWII** “consumption of fresh warm camel feces has been recommended by Bedouins as remedy for bacterial dysentery; efficacy confirmed by German soldiers in North Africa”
- **1958** FMT for pseudomembranous colitis
  - *Micrococcus pyogenes*
  - Retention enema, 4 patients
- **1983** first FMT for *C. difficile* infection
  - Retention enema in 1 patient
- **1991-2014**: Multiple reports for FMT for *C. difficile* infection

Efficacy – It Works!

- Systematic review in 2011
- 317 patients, 27 case series and case reports
- Resolution of symptoms in 92% of cases
- No significant adverse events reported
FMT for CDI: Systematic Review and Meta-Analysis

- 11 studies, 273 patients
- Pooled resolution rate was 89%
- No significant adverse events
- Trend that lower GI administration had higher resolution rate (91%) compared to UGI route (81%)


FMT Randomized Trial

The NEW ENGLAND JOURNAL of MEDICINE

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkstra, Ph.D., and Josbert J. Keller, M.D., Ph.D.
FMT Randomized Trial

- 43 patients with recurrent *C. difficile* infection
- Initially planned 30 patients in each 3 arms
- Primary endpoint: cure of CDI without relapse within 10 weeks
- *C. difficile* tests at weeks 2,3,5,10
- Interim analysis: study terminated early because efficacy already demonstrated
- No serious adverse events

Van Nood et al. NEJM 2013.

Microbiota Diversity Restored

- After donor-feces infusion there was an increased number of diverse bacteria
- Increased microbiota diversity proved beneficial in CDI treatment

Van Nood et al. NEJM 2013.
Cost-effectiveness of FMT in CDI

- Cost-utility analysis of 4 strategies
  - Metronidazole
  - Oral vancomycin
  - Fidaxomicin
  - FMT via colonoscopy
- Modeled 2 additional recurrences
- Most cost-effective approach was FMT via colonoscopy
  - Incremental cost-effectiveness ratio was $17,016 per QALY relative to oral vancomycin
- In order for fidaxomicin to be cost-effective, cost would need to be less than $1359

Indications for FMT in CDI

- Recurrent or relapsing CDI (success rate 85-89%)
  - At least 3 episodes of mild to moderate CDI and failure of 6- to 8-week taper with vancomycin with or without an alternative antibiotic (rifaximin, nitazoxanide, fidaxomicin)
  - At least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity
- Severe (and perhaps even fulminant *C. difficile* colitis) with no response to standard therapy after 48 hours
  - Single FMT: 50% cure rate
  - Sequential FMTs: 87-100% cure rate


Fischer et al. AP&T 2015.
Fischer Microbiomes 2016.
Details of FMT

- Donor Selection
  - Frozen Stool
  - Modes of instillation
  - Safety
  - Follow up

Donor Selection

**Patient Directed**
- **Pros**
  - Patient comfort
- **Cons**
  - Expensive screening test not paid for insurance
  - Delays care
  - Unreliable donors

**Universal**
- **Pros**
  - Routinely tested
  - Minimize costs of screening
  - Readily available material
  - Timely
- **Cons**
  - Who pays for the material?
  - Exposure of multiple recipients to disease
Donor Selection

- Patient selected vs. anonymous
- Systematic Review
  - No significant difference
  - 196/219 (89.5%) patient selected
  - 49/54 (90.7%) anonymous

Details of FMT

- Donor Selection
  - Frozen Stool
- Modes of instillation
- Safety
- Follow up
**Fresh vs. Frozen?**

- Allows for stool banking and potential cost savings
- Clinical experience in Minnesota – FMT via colonoscopy
  - 21 patients frozen, 22 fresh
  - No significant difference in success rates
- RTC of 72 patients – FMT via colonoscopy
  - Fresh: 100% success rate
  - Frozen: 83% success rate
- RTC of 232 patients – FMT via enema
  - Fresh: 95% success rate
  - Frozen: 96% success rate

*Jiang et al. AP&T 2017.*
*Lee JAMA 2016.*

---

**Details of FMT**

- Donor Selection
- Frozen Stool
- Methods of instillation
- Safety
- Follow up
Methods of Instillation

- **Upper:**
  - NGT: placement, risk (perforation, aspiration)
  - EGD: risk, cost, anesthesia
- **Lower:**
  - Colonoscopy: risk, cost, anesthesia
  - Enema: cost (low), risk (low), retention issues
- **Systematic Review:** lower > upper (p=0.046)
  - 203/222 lower: 91%
  - 42/51 upper: 82%


Oral Capsulized Frozen FMT for CDI

- 20 patients with recurrent CDI received capsulized frozen FMT from healthy volunteer donors
- 70% resolution of diarrhea after single capsule-based FMT
- After retreatment of non-responders overall response rate 90%

Youngster et al. JAMA 2014.
Mode of Delivery Impacts Cure Rate


Details of FMT

- Donor Selection
- Frozen Stool
- Methods of instillation
  - Safety
- Follow up
Safety

- Two cases of Norovirus following FMT
  - One donor tested negative, other not tested and did not have symptoms
- 4 patients in follow up study developed new disorders
  - Peripheral neuropathy
  - Sjogren’s Disease
  - ITP
  - Rheumatoid Arthritis
- One patient with Crohn’s Disease and multiple episodes of *E.coli* bacteremia developed *E.coli* bacteremia 24 hours after FMT


Safety

- 50 studies/1089 patients
- Non-severe self limited adverse events within 1 week of FMT are common (about 30% of patients)
  - Upper > lower (40 vs 20%)
  - Abdominal discomfort, bloating, borborygmi
  - Constipation, low-grade fever, nausea
- Possible related severe adverse events about 0.2 to 2% of FMTs
  - Lower > upper
  - Mostly due to procedural complications
- Long term safety
  - National FMT registry (NIH/AGA): 4000 patients over 10 years

Wang et al. PLOS 2016.
FDA Regulation

- Public workshop: May 2-3, 2013

- “When used to cure, treat, mitigate or prevent a disease, fecal microbiota for transplantation meets the legal definition of a drug and biological product.”

- “If the fecal microbiota are being used to cure, treat, mitigate or prevent a disease or condition, it is considered an unapproved new drug for which an Investigational New Drug (IND) application is required.”

FDA Regulation

- FDA stance: Patient Safety
- Standardize Therapy
  - Appropriate patient selection and consenting
  - Donor selection and consenting
  - Donor screening tests
  - Stool preparation
  - Route of instillation
- Added oversight
- Encourage development of reliable products
- Communicable diseases
- What we do not know about our microbiome and other disease states
FDA Regulation

• Advocates of FMT (physicians, patients)
  – Time and cost of submitting an IND
  – Decreased utilization of a potentially life saving procedure.

• One month later...FDA made an informal statement to “exercise enforcement discretion and allow practitioners to conduct FMT procedures without INDs.”

• IND applications published for all to use
  – IND not needed for CDI indications
  – IND needed for other indications


FDA Regulation

• 2014 and 2016: FDA Draft guidance issued, but not enacted

• Stool donor and stool testing has to be performed under the guidance of a treating physician

• If material is obtained from a stool bank, an IND is needed (sub-investigator on a stool bank’s IND)

• FMT material can be ordered from a stool bank without an IND
Details of FMT

- Donor Selection
- Frozen Stool
- Methods of instillation
- Safety
- Follow up

Follow up

- Do not continue antibiotics for CDI
- Home disinfection
- Do not test for cure
- Short and long-term outcome
  - Majority of failures occur within 1 month
  - 10% chance of CDI recurrence about 1 year post successful FMT
  - 17% chance when non-CDI antibiotics are taken
  - 6% chance without antibiotics

Fischer et al. AJG 2016.
Brandt et al. AJG 2012.
Fischer et al. DDW 2016.
Potential Applications of FMT

Conditions with Potential Links to Imbalances in the Microbiome

- Other non-GI disorders
  - Obesity
  - Asthma
  - GVHD in bone marrow transplant
  - Fibromyalgia
  - Metabolic syndrome
  - Parkinson’s disease
  - Mood disorders
  - Arthritis
  - Food allergy
  - Atopic dermatitis
  - Multi-drug resistant colonization

*Smits et al. Gastro 2013.*
Human Microbiome

- Pubmed: 4000 articles
- 100 trillion microbes in the gut (10 x more than human cells)
- Serves a broad range of function in and out of the GI tract

http://www.unitn.it/en/cibio/28516/laboratory-of-computational-metagenomics

Beyond CDI

- Treatment of Inflammatory Bowel Disease?
- Treatment of CDI in Inflammatory Bowel Disease?
- Irritable Bowel Syndrome?
- Obesity?
- Multi-drug Resistant Organisms?
- Neuropsychiatric Illness?
FMT: Ongoing Clinical Trials

- CDI (38)
- IBD (32)
- IBS (6)
- Constipation (4)
  - NAFLD/NASH (3)
- PSC
- Intestinal Pseudo-obstruction
- Metabolic Syndrome (5)
- Hepatitis B
- MDRO (4)
- Hepatic Encephalopathy (2)
- Post-stem cell transplant (2)
- HIV
- DM Type II

Clinicaltrial.gov 2016.

Conclusions

- There is an increasing incidence of refractory CDI
- Fecal microbiota transplantation is a promising treatment for CDI
- Fecal microbiota transplantation is safe
- There may be more potential applications for FMT outside of CDI, but our expectations need to be tempered
Thank You