Fecal Microbiota Transplants in the 21st Century

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March 23th, 2015

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Objectives
Fecal Microbiota Transplant (FMT)

- Review the burden and patient outcomes related to C. difficile infection and disease.
- Understand the rationale for FMT as an option in treating recurrent C. difficile disease.
- Describe the options for preparing and administering FMT.
- Review the challenges related to donor testing and FD’s enforcement policy on FMT as an investigational new drug.

Definitions and acronyms

- **Clostridium difficile** = C. difficile = C. dif
  - Anaerobic spore-forming bacteria ubiquitous in nature, often found in soil. Some strains make toxins that cause inflammation and diarrhea.
- **Clostridium difficile infection** = C. difficile disease = CDI
  - CDI is of concern as a hospital associated infection. It is one of the most common causes of antibiotic associated diarrhea (10 – 25%)
- **Pseudomembranous colitis** – infectious, inflammatory condition of the gut resulting from CDI.
- **Microbiota** or microbiome = bacteria, viruses, and eukaryotic microbes in and on our bodies, which impact physiology in health and in disease.
  - Note: In stool culture results, “normal flora” refers to healthy gut microbiota
- **Fecal microbiota transplant** = FMT = “stool transplant”

C. difficile disease (CDI) CDC information


Burden of Clostridium difficile in U.S.

Lessa FC et al. Study estimate of 500,000 cases (2011 data)
- 21% after Healthcare Associated (HCA) CDI event
- 14% after Community associated (CA) CDI event
- 83,000 CDI cases – at least one recurrence
- 29,000 died within 30 days


Estimated U.S. Burden of Clostridium difficile Infection (CDI), According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.

- CO-HCA: community-onset healthcare associated
- NH: Nursing Home onset
- HO: Hospital onset

Risk to patients: poor antimicrobial prescribing practices

- 50% hospitalized patients get an antibiotic in hospital
- 30-50% of those antibiotics are unnecessary or incorrect

CDI can be prevented by using infection control recommendations and more careful antibiotic use.

**HOW C. DIFFICILE SPREADS**

**SOURCE: CDC 2012**

- George, a 68-year-old man, goes to the doctor’s office and is diagnosed with pneumonia.
- Antibiotics are prescribed to treat the pneumonia.
- These drugs put him at risk for C. difficile infection for several months.

**ONE MONTH LATER**

- George breaks his leg.
- He is admitted to a hospital.
- A health care worker forgets to wear gloves when caring for a C. difficile infected patient prior to providing care to George.

**TWO DAYS LATER**

- George transfers to a rehab facility and begins to experience diarrhea.
- He is not tested for C. difficile.
- The health care worker doesn’t wear gloves and infects other patients.
THREE DAYS LATER

• George goes back to the hospital for treatment of diarrhea
• He tests positive for *C. difficile*
• Health care workers wear gloves and do not spread *C. difficile*
George recovers upon completing treatment: Metronidazole, oral Vancomycin, or Fidaxomicin for 10 – 14 days

Background: Pathogenesis of CDI

1. Ingestion of *C. difficile* spores
2. Germination into growing (vegetative) form
3. Altered lower intestinal flora (due to antibiotics) allows proliferation of *C. difficile* in colon
4. Toxins A & B production leads to colon damage + pseudomembrane

ONE MONTH LATER

George has symptoms of UTI and is treated with antibiotics at local ED
A few days after starting antibiotics, he is still weak, lethargic, slightly feverish (UTI?)
Symptoms worsen and he starts having diarrhea
He is admitted for dehydration and sepsis. He tests positive for *C. difficile*
Severe pseudomembranous colitis is found.

Pseudomembranous colitis

Endoscopic image of pseudomembranous colitis
Yellow pseudomembranes On wall of the sigmoid colon
Suggestive for CDI

GEORGE HAS RECURRENT *C. DIFFICILE* DISEASE

Recurrent CDI: episode ≤ 8 weeks after a previous resolved event
Historically, recurrent CDI occurs in 20%–25% of patients after the initial event
Recurrent CDI patients experience additional events more than 45% after the first recurrence
Mortality rate if *C. difficile* infection becomes fulminant may be up to 50%
RISK FACTORS FOR RECURRENCE OF C. DIFFICILE INFECTION

CDI due to epidemic strain B/NAP1/027
Failure to mount systemic anti-toxin antibody response. This may be due to age, or genetic factors
Use of antibiotics for non-C. difficile infections
Use of proton-pump inhibitors (gastric acid suppressive agents)
Severe underlying illness

RECURRENT C. DIFFICILE DISEASE

• Study during a 30 day follow-up period after original episode
• Molecular testing of original and recurrent strain per enrolled patient

Treatment Of Recurrent CDI

American College of Gastroenterology

ACG guidelines for the management of recurrent CDI

1. repeat metronidazole or a pulsed vancomycin regimen
2. consider fecal microbiota transplantation after 3 recurrences

An old therapy comes of age

Fecal transplantation consists of putting healthy donor stool into the stomach, small intestine, or colon to restore normal flora.

This is more effective than vancomycin for the treatment of patients with recurrent CDI, but natural antipathy toward fecal therapy hinders its wide implementation.

Treatment Options : FMT

“Re-establish the balance of nature”

1958: Denver doctors used enema of a stool infusion to treat patients with life-threatening pseudomembranous enterocolitis with “immediate and dramatic” responses.

“This simple yet rational therapeutic method should be given more extensive clinical evaluation.”

What has happened since 1958?

Why is this therapy not adopted?

A: Aesthetically unappealing
B: Logistically challenging
C: Lack of efficacy data from randomized, controlled trials

However, today there is sufficient evidence in randomized, controlled trials to prove efficacy and sustainable outcomes.

Fecal microbiota transplant can successfully re-establish appropriate microbe diversity and normalcy.

Evidence........

Treatment Options : FMT

Disruption of fecal microbiome CDI and non-CDI

Evidence......

Disruption of fecal microbiome CDI and non-CDI

Supplementary Figure 7. Interindividual variation in the proportion of major phyla. Each bar is a subject. The y-axis shows the relative proportion of reads that mapped to each phylum. Subjects are ordered from left to right according to increasing proportion of Firmicutes reads.

(A) HC: healthy cohort (n=40)
(B) CDI: C. difficile infection (n=38)
(C) CDN: subjects with nosocomial diarrhea but C. difficile negative (n=38).

Compositional comparison of donor, pre-, and post-FMT samples.

Anna M. Seekatz et al. mBio 2014; doi:10.1128/mBio.00055-14

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

This trial was closed to new enrollment after only 43 of a planned 120 patients had undergone randomization.

Almost all patients in the two control groups had a recurrence.

Of patients having 1 or 2 infusions, nearly 95% had not recurred.


Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection

Study:
Multicenter long-term follow-up study of 77 of 94 eligible patients
Follow-up timeframe > 90 days post FMT
Average suffering prior to FMT was 11 months
Patients had failed an average of 5 conventional antimicrobial regimens

Results:
Diarrhea resolved in 82% and improved in 17% of patients within an average of 5 days after FMT.
- **Primary cure rate was 91%**.
- 7 patients failures had subsequent FMT success
- **Secondary cure rate was 98%**

All late recurrences of CDI occurred after antimicrobial therapy for infections unrelated to C. difficile.
In all, 13% of patients stated they would have FMT as their preferred first treatment option if CDI were to recur.
No definite adverse effects of FMT were noted based on current standards.

"Physician attitudes toward the use of fecal microbiota transplantation for the treatment of recurrent Clostridium difficile infection"

Physicians greatly overestimated intensity of patients' aversion and how much the gross factor would act to deter patients' willingness to consider FMT

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But there are other significant considerations and/or impediments to FMT:

- FDA guidance
- Fees and insurance
- Harvesting and processing donor stool
- Testing protocols
- In-patient vs Out-patient procedure

### FDA guidance on FMT

May 2013 FDA statement

Fecal microbiota defines FMT as a biologic product

Therefore it requires an investigational new drug (IND) before use in humans.

→big outcry! Stakeholder meeting convened

July 2013 UPDATED guidance


### FDA guidance on FMT

March 2014 update “Guidance for Industry” for FMT in treatment of recurrent CDI

Point #1:

Interim FDA decision: will exercise discretion on IND use provided that the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative. This enforcement discretion does NOT extend to other FMT uses.

“ Informed consent should include, at a minimum, a statement that the use of FMT products to treat C. difficile is investigational and a discussion of its potential risks. “


### FDA guidance on FMT

March 2014 update “Guidance for Industry”

Point #2:

the FMT product is obtained from a donor known to either the patient or to the licensed health care provider treating the patient

Point #3

the stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product to treat his or her patient.

Consensus guidelines – donor screening and stool testing

Recipient
Who is a Candidate for FMT?

FMT may be an option for people who have had one of the following:
• At least three episodes of mild to moderate C. difficile infection that have not responded to six to eight weeks of treatment with antibiotics.
• Have had at least two episodes of severe C. difficile infection that required them to be admitted to the hospital.
• Moderate C. difficile infection that did not respond to antibiotics (namely vancomycin) for at least a week.
• Severe C. difficile infection or severe colitis caused by C. difficile that did not respond to antibiotics within two days.

Recipient
Who is NOT a Candidate for FMT?

Not everyone is a good candidate for FMT. The procedure may be risky for people who:
• are taking immunosuppressive drugs
• have had a recent bone marrow transplant
• have cirrhosis of the liver
• have advanced HIV or AIDS

Donors
Preferred donor is
– an intimate, long-time partner of adult patient
– in the case of a pediatric patient, an adult first-degree relative
– close family friend
– well-screened universal donor
– over the age of 18

Donor questionnaire – similar to current screening blood donors
http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/ucm164185.htm

Donor exclusions
Donor exclusion criteria:
• Antibiotic treatment during the preceding 3 months
• History of intrinsic GI illnesses, including inflammatory bowel disease, irritable bowel syndrome, GI malignancies or major GI surgical procedures
• History of autoimmune or atopic illnesses, or ongoing immune modulating therapy
• A history of chronic pain syndromes (fibromyalgia, chronic fatigue) or neurologic, neurodevelopmental disorders
• Metabolic syndrome, obesity (BMI of >30), moderate-to-severe undernutrition (malnutrition)
• A history of malignant illnesses or ongoing oncologic therapy

Donor Testing - Guidelines
Serum Testing (to be performed within 4 weeks of donation):
• HIV-IgM - hepatitis A virus Antibody (IgM)
• HBsAg - hepatitis B surface antigen
• HCV-Ab - hepatitis C virus antibody
• HIV-EIA - HIV screening test
• RPR - syphilis screening test

Stool Testing (to be performed within 4 weeks of donation):
• C. difficile toxin B (preferably by PCR)
• Culture for enteric pathogens
• O+P, if travel history suggests
Insurance, coding, Medicare beneficiaries


CPT code 44705, “Preparation of fecal microbiota for instillation, including assessment of donor specimen”

Preparation and testing of the donor and specimen may be covered by the recipient’s insurance – but even with insurance this may cost the donor several hundred dollars.

Medicare does not cover the costs of screening of the donor specimen, thus beneficiaries should be advised of the cost of screening, which they may be at risk of paying for out-of-pocket.

The Procedures

All appropriate donor testing has been completed and patient has been approved per protocol.

Patient and donor have met pre-FMT questionnaire requirements.

Donor Preparation

• Purgative (night before)
• Formed soft stool
• Deliver to lab fresh day of procedure

Patient Preparation

Thorough laxative prep - no residual stool on day of procedure
Stop antibiotics 2-3 days prior

The Procedures

• A “fistful-sized” amount (50 gms) stool collected in “hat”
• Saline added and stool blended, emulsified
  o Onsite: use blender in biolevel 2 safety hood
  o At home: some sites require initial emulsifying prior to bringing in specimen
• Strained (coffee filter, layers of gauze, etc)
• Refrigerate if not used immediately
• Used within 6 hours of collection
• Reconstitute in 500-600 ml sterile water or nonbacteriostatic sterile saline

Procedure

• Performed by colonoscopy
  – Multiple syringes, approx. 300 ml total prepared suspension
• Colonoscope is advanced through the colon, as withdrawn, the prepared suspension is delivered
• Outpatient Procedure discharge instructions
  – Retain contents 35 – 45 minutes (as long as possible)
  – Regular activities within a few hours
  – Transient diarrhea, abd pain, rectal bleeding, fever
• Alternate procedure: administer via NG tube*

Rectal tubes and retention enemas have been used with some success but this route is not as thoroughly studied and vetted.

Current and future research

• Recent literature unequivocally supports the use of FMT in treating relapsing CDI.
• Trials are underway to determine the therapeutic potential of FMT in other conditions, particularly inflammatory bowel disease.
• Possible potential in autoimmune disease and metabolic diseases
• Therapeutic FMT is a dynamic field with new and emerging indications along with ongoing developments in optimal mode of administration.
• New methodologies for reconstitution of gut microbiota

Therapeutic faecal microbiota transplantation: current status and future developments

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3868025/


ClinicalTrials.gov Identifier: NCT01914731 updated: October 22, 2014
Massachusetts General Hospital
Experimental: Capsule Fecal microbiota transplant (“stool transplant”) from healthy, unrelated donor via frozen capsule

• Healthy volunteers were screened as potential donors
• FMT capsules were generated and stored at −80 °C

Patients received 15 capsules on 2 consecutive days and were followed up for symptom resolution and adverse events for up to 6 months.
Bacteria – our friends (usually!)

Fig 1. Association of the microbiota with humans.

Microbiota presents in all parts of our body, which has direct contact with external environment. The numbers of bacteria in the mouth ($10^{10}$), on the skin ($10^{12}$), and in the distal gut ($10^{14}$) are presented in relation to total number of parenchymal cells ($10^{12}$).

The composition of the microbiota in the digestive tract greatly differs in each of specialized compartments as illustrated.

Physiological functions and chemical environment of each compartment are likely key factors influencing the bacterial inhabitants.

J Obes. 2012; 2012: 879151. Published online 2012 Jan 24