FECAL MICROBIOTA TRANSPLANTATION

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You want to put WHAT WHERE?

***Fecal Microbiota Transplantation (FMT)* aka**

Fecal Bacteriotherapy or Fecal Transplant

The infusion of a fecal suspension from a healthy, prescreened donor into the GI tract of a patient with the goal of curing a specific disease

The most common reason is to attempt to cure recurrent clostridium difficile infection (RCDI)

How did this start?

- First reported in the 4th century in China for the treatment of food poisoning and diarrhea
- In the 16th century it was given orally (“yellow soup”) to treat a variety of GI symptoms and disorders
- First documented use in humans was 1958 for the treatment of pseudomembranous colitis
- First enema treatment for clostridium difficile infection (CDI) was in 1983
- Alternative routes of administration began in 1991 (NG/NE Tube), 1998 (EGD), 2000 (Colonoscopy) and 2010 (Self administered enemas)

So why is this so popular now?

FOUR WORDS:

Recurrent Clostridium Difficile Infection (RCDI)

From the CDC website:

"People getting medical care can catch serious infections called healthcare-associated infections (HAIs). One type of HAI – caused by the germ *C. difficile* – was estimated to cause almost **half a million infections** in the United States in **2011**, and **29,000 died within 30 days** of the initial diagnosis. Those most at risk are people, especially older adults, who take antibiotics and also get medical care."

And why is this scary?

- While the elderly are still most affected, more disease has been reported in traditionally ‘low risk’ persons such as healthy persons in the community, and peri-partum women.

- Possibly due to the new emergence of the current epidemic strain of *C. difficile*, BI, North American Pulsed Field type 1 (NAP1), or PCR ribotype 027, or BI/NAP1/027

And if that isn't scary enough…..

"Recent trends reveal susceptibility in healthy people without antibiotic use or with minimal antibiotic use"

<u>At-risk populations include</u>:

- Inflammatory Bowel Disease (IBD)
- Peri-partum
- >65 years of age
- Immune compromised
- Severe comorbidities

Does it really work?
Oh, and by the way, show me the evidence

- Current literature is predominantly comprised of single-center case series/reports, 1 meta-analysis, 2 systematic reviews and 1 recently published randomized controlled trial (RCT)
- Success rate of **92%** for RCDI
- The only multicenter long-term follow up study showed a cure rate of **98%**
- A systematic review comprising 317 patients from 8 countries shows a cure rate of **92%**
- Presentation at the 78th Annual Scientific Meeting of the American College of Gastroenterology in 2013 stated that FMT is successful

And is it safe?

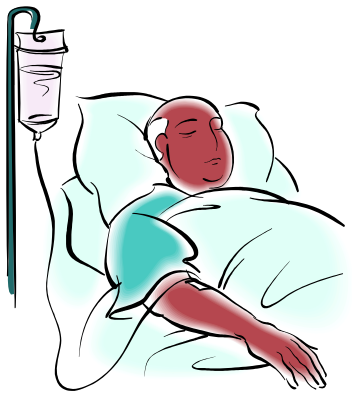
- Only 1 long-term follow-up study to date
  - 5 center
  - 77 patients
  - 3 month follow-up
- 91% primary cure rate (cured with single transplant)
- 98% secondary cure rate (cured with second transplant or follow-up antibiotics)
  - As of 2014, no published RCT's
- Poor reporting of AE due to lack of national registry
- One recent case report of patient becoming obese after transplant

Criteria for PATIENT selection

- Must have documented either **recurrent** (goes away and comes back) or **refractory** (resistant and unresponsive) CDI

- Severe colitis to include pseudomembranous colitis

- Must have failed traditional therapy of vancomycin, metronidazole and/or fidaxomicin



Criteria for DONOR selection
Absolute exclusion:

- Known HIV or Hepatitis infection
- Known exposure to above for last 12 months
- History of high-risk sexual behaviors or illicit drug use
- Tattoos for 3-6 months
- History of incarceration
- High-risk travel within last 6 months
- Risk factor for Creutzfeldt-Jakob disease
- Known current communicable disease

Criteria for DONOR selection

Other considerations:

- No use of any antibiotics for 3 months
- No history of IBD, IBS, GI malignancies, or major GI surgeries
- No history of autoimmune or atopic illnesses or ongoing immune modulating therapy
- No history of chronic pain syndromes or neurologic disorders
- No history of metabolic syndrome, obesity (BMI < 30), or moderate-to-severe malnutrition
- No history of malignant illnesses or ongoing oncology therapy
- History of recent ingestion of potential allergen that recipient might react to

Who should you ask for this ultimate gift??

Is one donor better than another?

- Early literature indicated that the donor should not be anyone living in the same household as the patient

- Recent literature and the multi-society letter to the FDA recommends that the donor be a long-time intimate partner or family member living in the same household

Show me some evidence please. Systematic Review, 2011

Related Stool

Resolution rate of

93%

Unrelated Stool

Resolution rate of

84%

Screening

Recipient

- HIV 1 & 2
- Hepatitis A, B & C
- Syphilis

This is done to eliminate the question of transmission

Donor

SERUM:

- HIV 1 & 2
- Hepatitis A, B & C
- Syphilis

STOOL:

- C diff toxins A & B
- Ova & Parasites
- Culture & Sensitivity

Multi-society letter for donor screening

- http://www.gastro.org/research/Joint_Society_FMT_Guidance.pdf
- Excellent resource for developing P&P
- Mimics screening form for blood donations

Universal Donor

- OpenBiome-first lab for universal stool donations opened last year in Massachusettes
- $250 per sample + $250 shipping/handling
- Shipped frozen on dry ice
- Must have special freezer
- Directly competes with recent FDA guidance
- Eliminates a lot of work/steps
- No personal experience yet

openbiome.org

You've got a patient and a donor, now what?

An evidence-based standardized protocol is lacking

Resources:

fmt.gastro.org (AGA)

fda.gov (Vaccines, Blood and Biologics)

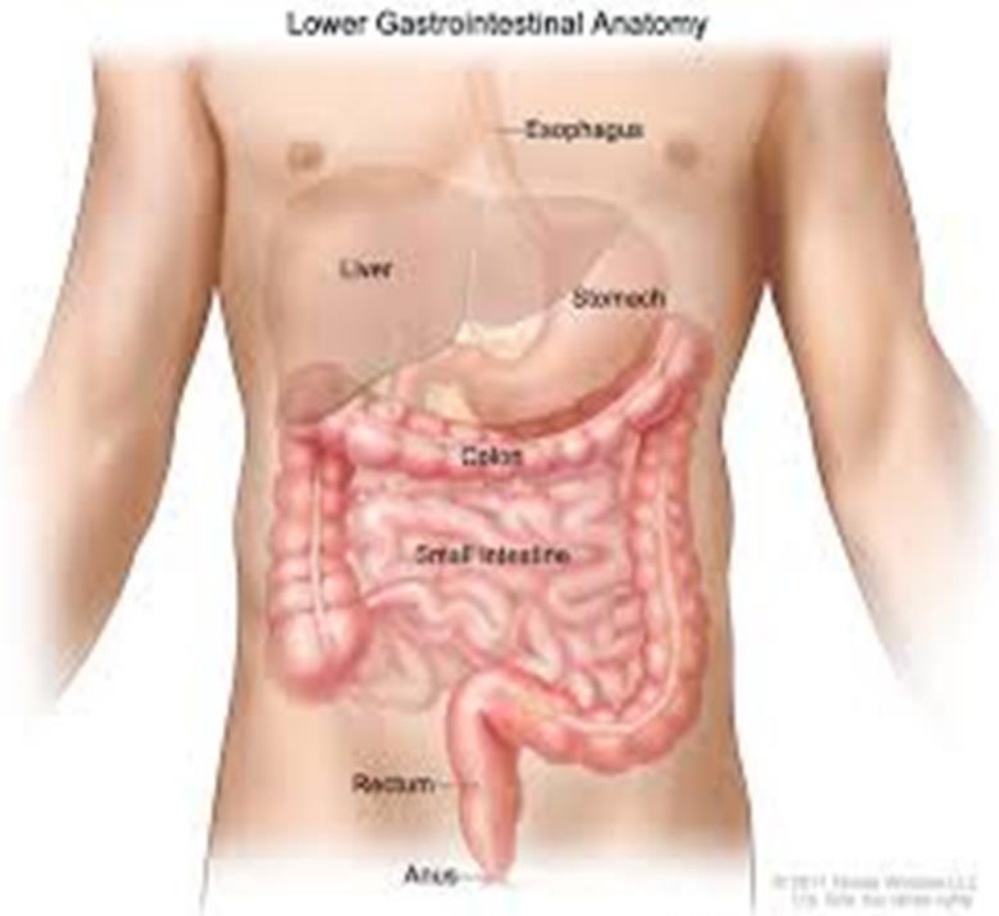
uptodate.com

"An overview of fecal microbiota transplantation: techniques, indications, and outcomes"

Lawrence J. Brandt, MD, Olga C. Aroniadis, MD

Gastrointestinal Endoscopy, Volume 78, No. 2

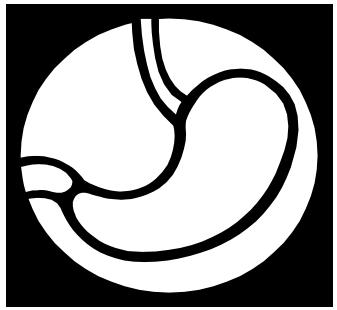
Which route to take?



Routes of administration

Upper

- Naso gastric tube
- Naso enteric tube
- Gastric tube (feeding tube)
- Jejunal tube (feeding tube)
- EGD



Lower

- Enema (retention)
- Flexible Sigmoidoscopy
- Colonoscopy

Routes of administration

- Limited research and data exists comparing different routes for administering FMT and to date no consensus exists on which is best
- Advantages and disadvantages have been described
- Each may be appropriate in a particular set of circumstances based on patient acuity and cost

Upper GI administration

EGD

- Precise and controlled delivery of sample
- Entire GI tract exposed to infusate
- Less risk of aspiration
- More costly
- Sedation risk

NGT/NJT

- Inexpensive
- Does not require MD
- Quick and convenient
- Less risk
- Smaller volumes delivered slower
- Tube placement should be verified by x-ray before transplant

Lower GI administration

Colonoscopy/Flex Sig

- Most traditional method
- Entire colon can be coated
- Patient acceptance
- More costly
- Sedation risk
- Precise and controlled delivery of sample (cecum)
- Allows for examination of colon mucosa

Enemas

- Inexpensive
- Does not require MD
- Quick and convenient
- Retention can be difficult in some patients
- Only reaches splenic flexure
- 300ml slow/50ml squeeze bottle
- Retained for 4 hours

Patient preparation

- Routine colon prep/CL diet is standard for FMT by colonoscopy
- Loperamide is optional
- PPI if administering by NGT (reduce stomach acid)

- Antibiotics are routinely stopped 1-3 days prior to procedure but this has not been compared to continuing antibiotics until procedure date

- **CONSENT**: FDA mandates that informed consent states that FMT is considered “investigational”; also need consent for procedure itself

Patient & Family Education

- Lots of opportunity for education with FMT
- Donor selection
- Assistance with specimen handling
- Overcoming the “ick” factor
- Pre and post questions
- Lots of resources available!

Stool Preparation

- Use a non-bacteriostatic saline solution/sterile normal saline solution/preservative-free normal saline
- Studies have also used tap/bottled water, milk
- Use 50-60 g donor stool
- Use freshest stool (6-8 hours is preferable; 24 hours max); may be refrigerated but never frozen
- 200-300ml saline for lower administration
- 50-75ml of saline for upper administration
- Blend to slurry consistency
- Recommendation to prepare under a hood but impractical and possibly unnecessary
- Strain through a kitchen strainer, gauze/coffee filters
- Draw up into 60cc slip tip syringes

If a little is good, is a lot better?

The amount of transplant has not been standardized but favorable outcomes are seen with larger amounts

Lower GI tract administration: total volume = 300-500ml

Upper GI tract administration: total volume = 60-75ml

Economics

- Study at Massachusetts General in Boston compared four treatments
- Metronidazole, vancomycin, fidaxamicin and FMT
- FMT by colonoscopy was most cost-effective
- Results presented at ACG 2013 Annual Scientific Meeting

Equipment

- In the past we did reprocess our blender/strainer using the same standards as our scopes
- Cleaning with enzyme detergent and high level disinfection soak
- Have since converted to disposable blenders/kits
- Option to prepare the slurry is to shake vigorously in tightly sealed (yikes!) container
- Personnel must follow strict environmental cleaning guidelines after procedures

FMT kit by Medivators

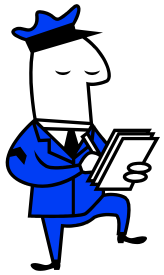
Reprinted with permission- Medivators

Let's talk about the feds

- In May of 2013 the FDA issued a regulation requiring all physicians performing FMT to acquire an IND (Investigational New Drug) permit

- This was met with an outcry from many societies including the AGA, who petitioned the FDA to relax this requirement

- In July of 2013 the FDA issued statement that they will use "discretion" in the requirement but put forth strong language



Food and Drug Administration, 2013

We, FDA, are informing members of the medical and scientific community, and other interested persons that ***we intend to exercise enforcement discretion*** regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat Clostridium difficile (C. difficile) infection not responding to standard therapies.

FDA intends to exercise this discretion provided that the treating physician obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. 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 intends to exercise this discretion on an interim basis while the agency develops appropriate policies for the study and use of FMT products under IND.

Food and Drug Administration, 2014

We, FDA or agency, are informing members of the medical and scientific community, and other interested persons that we intend to exercise enforcement discretion regarding the investigational new drug (IND) requirements for the use of fecal microbiota for transplantation (FMT) to treat *Clostridium difficile* (*C*. *difficile*) infection not responding to standard therapies. FDA intends to exercise this discretion provided that: (1) the licensed health care provider treating the patient obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products; (2) ***the FMT product is obtained from a donor known to either the patient or to the licensed health care provider treating the patient; and (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***. Note that the 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. ***We do not intend to exercise enforcement discretion when the FMT product is manufactured from the stool of a donor who is not known by either the patient or the licensed health care provider treating the patient; or the donor and donor stool are not qualified under the direction of the licensed health care provider treating the patient.***

FDA, cont.

- This guidance, when finalized, will supersede the guidance document entitled “Guidance for Industry: Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies,” dated July 2013 (July 2013 Guidance).

So what does the future hold for FMT?

- Current investigations into treatment for other diseases: Crohns, Ulcerative Colitis, IBD, IBS and even non GI diseases and conditions
- Gut microbiome is a very hot field of science right now; intestinal microbiota plays an important role in immune function and metabolic disorders
- Increasing research into pediatric population
- The FDA is still promising guidance and oversight into the process
- Developing/testing “stool capsules”-Canada

My experience with FMT

- Out unit has done over 30 transplants
- Very successful
- Usually do single transplant via colonoscopy
- Have done via EGD, naso-jejunal tube (used a decompression tube), J tube (replaced patients G tube with J tube for multiple transplants
- Families are asking for this due to desperation
- Changes peoples lives
- Provides huge satisfaction to nurses and doctors
- Is really a simple procedure

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