Stool Transplant for C. diff Colitis: Beyond the Blender

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SESSION OBJECTIVES

• Discuss the growing epidemic of C. difficile colitis.
• Describe the concept of fecal transplant for C. difficile.
• List the current FDA-approved indications for fecal transplant.
Fecal Transplant for Recurrent/Refractory C. diff Colitis

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I have nothing to disclose.
Outline of Discussion

Recurrent C. diff colitis
The history of fecal transplant (FMT)
The all-powerful gut microbiome
Indications for FMT
Fresh vs. frozen stool
Current data
The Lahey experience
Future directions
Background of C. Diff Infection (CDI)

C. diff bacteria first described in 1935
First episode of antibiotic-associated C.diff colitis in 1978
Carriage rate:
  • Healthy adults 3%
  • Adults in long-term care facilities/hospitals 25-50%
  • New exposures rather than colonization more likely to lead to CDI
Accounts for 15-25% of all antibiotic-associated diarrhea
The Growing Epidemic of CDI

Hospitalizations and mortality from C. diff have doubled over the past 10 years
Increase in utilization cost of 237% since 2000
C.diff now 9th leading cause of in-house GI death
Death from C. diff has increased 203% from 2002 to 2009
Multiple different populations affected
Newer more virulent, antibiotic-resistant strains are emerging

Standard Treatment of CDI: Mild-Moderate Disease

1\textsuperscript{st} episode: Flagyl 500 mg TID for 2 weeks

1\textsuperscript{st} relapse: Flagyl 500 mg TID for 2 weeks

2\textsuperscript{nd} relapse: Vancomycin with taper/pulsing
• 125 mg po 4x/day for 7-14 days
• 125 mg po 2x/day for 7 days
• 125 mg po daily for 7 days
• 125 mg po every other day for 7 days
• 125 mg po every 3 days for 14 days
• Consider fidaxomicin 200 mg po 2x/day for 10-14 days

Additional relapses:
• Vancomycin with maintenance suppressive dosing
• Vanco followed by xifaxan
• Fidaxomicin: less recurrent disease, parameters still undefined
Standard Treatment for CDI: Severe or Fulminant Disease

Oral vancomycin 250 mg 4x/day
- Some advocate for up to 500 mg 4x/day, data shows no added benefit
- Vancomycin enemas can be added
- IV metronidazole 500 mg 3x/day

Consider fidoxamicin if not responding

Surgical consult, especially if signs of toxic colitis
- Rising white count
- Persistent fever
- Tachycardia
- Worsening abdominal pain
Recurrent CDI

Reurrence is common:
- 35-40% have at least one recurrence
- For those with recurrence, 65% will continue to have recurrence
- Prolonged therapy can be expensive and not well standardized

Why Recurrence?
- Spores difficult to eradicate, certain hosts may not mount immune response
- Additional infection with new strains, 33% in one series
- Persistently altered state of flora from antibiotics
- Antibiotic resistance appears less likely

We clearly need a better solution
A Lahey Case Study: The Pioneer

2011:

35 yo female with highly functioning Down’s syndrome
Received antibiotics for UTI after knee surgery
Developed C. diff infection
Relapsed 3 times despite treatment with metronidazole, vancomycin then vanco taper
Usually relapses within 1 week of discontinuing antibiotics
Mom is desperate: “We’ll do ANYTHING”
Fecal Transplant (FMT)

Performed by emperor’s physician in 4th century China for variety of GI disorders
German soldiers in Africa used camel feces for dysentery in WWII
Made official in Europe in 1958
Media blitz in 2012
Now well over 1,000 FMTs performed worldwide
The Concept of FMT for C. diff Colitis

Antibiotics cause derangement of the colonic bacteria

FMT re-establishes healthy colonic microflora

Durability of transplant over time inhibits new infections
The All-Powerful Gut Microbiome

Intestinal bacteria
- Integral to host immune system, metabolism, auto-immunity, possibly malignancy
- Mostly anaerobes
- Thousands of species, 7 main bacterial divisions, dominated by Firmicutes and Bacteroides
- $10^{12}$ bacterial cells/gram of stool
- 90% of immune system housed in the GI tract

Gene sequencing of the microbiome
- Variations in the microbiome have been linked to differences in overall health
- Sequencing will help to refine FMT from the crude to the key players
- Gene clone libraries demonstrate durability of donor microflora several months after transplant
- Commercial labs can now sequence YOUR stool
Fecal Transplant (FMT)

Methods of stool administration:
- Enemas (inpatient, outpatient, at home) 1958
- Nasogastric/nasoduodenal tube 1991
- Colonoscopy 1998

Advantages:
- Lower cost (considering the alternative)
- Low risk
- High success rate
- Response occurs within hours to days
- Few serious adverse events noted, other than those associated with administration (i.e. endoscopic procedures)
FDA Approved Indications for FMT

Recurrent or relapsing CDI

• At least 3 episodes of mild to moderate CDI with failure 6-8 week vancomycin taper with/without alternative antibiotic
• At least 2 episodes of severe CDI requiring hospitalization or significant morbidity

Moderate CDI not responding to standard therapy for one week
Severe CDI with no response after 48 hours

AGA Guidelines 2011
FMT Proposed for Other Diseases

Irritable bowel syndrome

Chronic fatigue syndrome

Inflammatory Bowel Disease
- Reduced diversity of the microbiome, ?cause or effect of IBD
- Interaction with bacteria and host cells, different from C. diff
- Repeated treatments likely needed

Obesity/Cardiovascular disease, insulin resistance
- Increased intestinal permeability → bacterial translocation → chronic inflammation
- Altered short chain fatty acid production

NAFLD

Autoimmune diseases
- Idiopathic Thrombocytopenic Purpura (ITP)

How FMT is Performed at Lahey: via Colonoscopy

Nov 2011 to Nov 2013: Patient-selected Donors (Blenderized Stool)

Nov 2013 to Present: Frozen Stool from Universal Donors (Blender Be Gone!)
Patient-Selected Donors

Family or household member (shared infectious risk factors), friend, healthy anonymous donor

Adults age 18 or older

Donor screening

- History (can use same questionnaire for screening blood donors)
  - Known communicable disease
  - Systemic autoimmunity or atopic disease
  - High risk sexual behavior, illicit drugs, tattoos/piercings, prison
  - Active infection, travel to high risk area
  - IBD, IBS, GI malignancy
  - Antibiotics within past 3 months, immunosuppression

- Blood for HIV, syphilis, hepatitis A/B/C

- Stool for C. diff, bacterial culture, Giardia, Cryptosporidium, Isospora, Cyclospora
Colonoscopy-Assisted FMT Protocol

Donor pre-transplant:
- Avoid recipient-allergic foods for 1 week
- Collect stool within 24 hours of transplant, goal < 6 hours
- Option for donor to take laxative (performance anxiety)
- Disqualified if develop diarrhea within 24 hours of donation

Recipient pre-transplant:
- Standard colonoscopy prep
- Stop antibiotics night before transplant
- Take 1-2 loperamide one hour before transplant

Stool preparation

• Mix 100 gram (or available quantity) donor stool with 500 cc normal saline or sterile water
• Blenderize to thin liquid consistency then strain
• Draw up into syringe flushes for target volume 240-420cc
• Alternative:
  - Take 1 L bottle of saline/sterile water and pour out 500cc
  - Add stool to remaining saline/sterile water
  - Shake vigorously for 30-60 seconds then strain
Performing the Procedure Itself

Fecal transplant via colonoscopy

- Recipient consented specifically for fecal transplant
- Intubate to the cecum
- Suction as much remaining stool as possible, minimize air insufflation
- Flush entire amount of donor stool into cecum
- Withdraw scope blindly without suctioning

Limitations

- Added risk of prep and procedure
- Biopsies allowed but no polypectomies performed
- Only limited views of colon obtained, not for colon cancer screening
- Any abnormalities may require future repeat colonoscopy
Post-Transplant

Immediately after FMT
- No diet restrictions
- No further antibiotics
- Adverse events
  - Constipation, abdominal cramps
  - Fever
- Repeat transplant in 2 weeks if no response

Subsequent recurrence after transplant
- 2 week course of vancomycin

If need future antibiotics for other infections
- Confirm with prescribing physician absolute need for antibiotics
- Use concomitant vancomycin, extend one week beyond antibiotic course
The Latest: Frozen Stool from Universal Donors

The players:
- Several institutions have in-house stool banks
- OpenBiome open-access nonprofit frozen stool bank

The donors:
- Healthy anonymous donors
- Applicants screened with blood/stool testing

The process:
- Stool obtained and processed into liquid form
- Frozen in sealed plastic bottles

The advantages:
- No pressure on patients to find donors
- No waiting for transplants
- Faster, easier transplants
- Better access to providers
Frozen Stool from Universal Donors
Published Data for FMT

Meta-analysis

- 27 reports (mostly case reports) from 1958-2011
- 317 patients from 8 countries
- Average age 53
- Follow up 36 hours to 5 years
- Recurrent or relapsing CDI (91%) PMC (9%)
- Majority transplant by enema (35%) or NGtube (23%)

Results

- 92% success rate
  - 89% after single treatment
  - 5% after retreatment due to initial failure
- 13 deaths, 3 due to CDI (1%)
- No serious adverse events attributed to transplant

*Gough, et al. CID. 2011:53 (15 Nov).*
Published Data for FMT

NEJM Jan 2013:

• 43 patients randomized to 3 groups
  - Vancomycin alone
  - Vancomycin + bowel lavage
  - Vancomycin + bowel lavage + FMT via nasoduodenal tube

• Results
  - 23% vs 31% vs 81% resolution of C. diff
  - Study discontinued early due to high relapse rates in control groups, as well as significant difference in treatment response

<table>
<thead>
<tr>
<th>Trial Date</th>
<th># of patients</th>
<th>Primary Cure Rate 12 weeks</th>
<th>Duration of Followup</th>
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</thead>
<tbody>
<tr>
<td>Gough et al Clin Infect Dis 2011</td>
<td>317 patients/27 case series (1957-2011)</td>
<td>92%</td>
<td>36 hours-60 months</td>
</tr>
<tr>
<td>Matilla et al Gastro 2012</td>
<td>70 patients (36 with strain 027)</td>
<td>100% and 89%</td>
<td>12 months</td>
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<tr>
<td>Brandt et al Am J Gastro 2012</td>
<td>77 patients</td>
<td>91%</td>
<td>3-68 months</td>
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<tr>
<td>Khorutz et al Am J Gastro 2012</td>
<td>43 patients</td>
<td>70% fresh PS donors</td>
<td>12 months</td>
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<td></td>
<td></td>
<td>92% fresh universal donors</td>
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<td></td>
<td></td>
<td>90% frozen universal donors</td>
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<tr>
<td>Kelly, et al 2014</td>
<td>99 patients/16 centers immunocompromised</td>
<td>78%</td>
<td>3-46 months</td>
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<tr>
<td>Didyk et al, 2014</td>
<td>50 patients</td>
<td>96% frozen universal donors</td>
<td>2 weeks</td>
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Back to Our First Transplant Patient…

Finished 2 weeks of xifaxan
Underwent colonoscopy with fecal transplant
Within 24 hours, patient felt well

3 years later…….

The patient is still doing well!
The Lahey Experience

Over 200 colonoscopy-assisted FMTs for C. diff Nov 2011-Present
  • 100 with patient-selected donor stool
  • Over 100 with frozen universal donor stool

Patient characteristics
  • Average age 72, no significant gender difference
  • Average # of recurrences prior to FMT: 3
  • 20% underlying colonic disease (diverticulitis, IBD)

95% primary success rate fresh patient-selected donor stool
  • 3 patients had subsequent spontaneous C. diff recurrence
  • 6 patients required subsequent antibiotics that caused recurrent C. diff

90% primary success rate frozen universal donor stool
  • 4 primary failures in 1 month, traced back to specific donor with lower effective concentration of stool, microbiome sequencing pending

Safety outcomes
  • 1 patient had microperforation with peritonitis in setting of peritoneal dialysis catheter and underlying chronic diverticulitis
FDA Update

No prior regulation before now—media explosion leads to scrutinization

May 2013:
• FDA officially announces stool is a drug, specifically a biologic
• Workshop convened with FDA and fecalists
• FDA decides an IND (investigational new drug) approval required for all FMT indications, specifically C. diff

June 2013:
• FDA modifies statement, now not currently requiring IND for C. diff patients
• Need specific consent form for all recipients
• Still need IND for other indications such as IBD
The Best Way to Perform FMT?

Current protocols:
• Is bowel lavage key?
• What is smallest effective volume of stool?
• Distilling stool to its essence-what are the key components?
• Which route is truly best, is enema therapy sufficient?

New directions:
• Encapsulated stool preparations
  - Entering phase III trials
  - Similar success rates
  - Lahey to enroll
• Expanding the indications for FMT
• Using FMT sooner, preventatively
Crappuccino

Crapsicle

Crapsule
Further Concerns Regarding FMT

Transfer of infectious pathogens not as of yet known or screened
Transfer of current ??and future?? noninfectious diseases from donor to recipient
Long-term data needed
Standardization needed to reduce risk, catalog and prevent poor outcomes
Summary

C. diff infection has reached epidemic proportions
Recurrence is common despite treatment
Fecal transplant is safe and cost-effective
Efficacy of FMT is high
Pre-processed frozen stool allows provides multiple advantages
FMT is fast approaching standard of care for patients with recurrent or refractory C. diff
Thank You!