The Gastrointestinal Microbiome

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Chief of Gastroenterology
VA Maryland Health Care System
Conflict of Interest Disclosure

• I am a pharmaceutical factory
  – The FDA has determined poop is a drug

• I do not have any conflicts
Overview

• Definitions
• Human Microbiome
• GI Microbiome
• GI Microbiome & Disease
  – Inflammatory Bowel Disease
  – Liver Disease
  – Colorectal Cancer
  – *C. difficile* Infection
Definitions

• **Microbiome**: An entire habitat, including the microorganisms, their genomes, and the surrounding environmental conditions

• **Microbiota**: The assemblage of microorganisms in a defined environment

• **Microflora**: Microscopic plants (often misused)

• **Metagenome**: The collection of genomes and genes from the members of a microbiota

• **Dysbiosis**: A disturbance in a biological system, such as changes in type/number of bacteria

Marchesi & Ravel *Microbiome* 2015
Genomics Definitions

• **Next-generation sequencing**: DNA sequencing that harnesses advances in miniaturization technology to simultaneously sequence multiple areas of the genome rapidly and at low cost

• **16S rRNA gene sequencing**
  – Method for determining which bacteria are present

• **Metagenomics**: The process used to characterize the metagenome
  – Sequence all DNA extracted from a sample to determine which genes are present
  – Provides information on the function of the microbiota

Feero, et al. *NEJM* 2010; Marchesi & Ravel *Microbiome* 2015
Figure 1

Transcription

DNA “microbiome”

RNA “transcriptome”

Translation

Protein “proteome”

Enzymatic activity

Metabolites “metabolome”

Clinical phenotype

Technique

Biomarker-based sequencing (e.g., 16S rRNA gene)

Shotgun metagenomics

Metatranscriptomics

Metaproteomics

Metabolomics

Data

Microbial community composition

Total gene product (i.e., functional capacity)

Expressed genes

Protein products

Metabolites

Clinical Gastroenterology and Hepatology 2019 17, 296-306 DOI: (10.1016/j.cgh.2018.08.065)
16S rRNA gene sequencing

CONSERVED REGIONS: unspecific applications
VARIABLE REGIONS: group or species-specific applications

1) http://www.alimetrics.net/en/index.php/dna-sequence-analysis
2) Kong HH, Trends in Molecular Medicine, 2011
The Human Microbiome

- The sum of the microbiomes in all parts of the human body
- The Human Microbiome Project – launched 2008
- “Bacteria cells outnumber human cells by ~10-fold”
  - Or do they?
- Co-evolution/Mutualism
  - Human benefits:
    - Nutrition
    - Immune system education
    - Colonization resistance
  - Microbe benefits:
    - A happy place - warm/moist/nutrients
Microbial Members of the Human Microbiome

- Bacteria
- Archea – single-celled organisms without nuclei
- Fungi – primarily yeasts
- Microbial eukaryotes (e.g. Blastocystis)
- Viruses
- Phages
Variable human microbiome

Core human microbiome

Host lifestyle
Host genotype
Host pathobiology
Host physiology
Host environment
Host immune system
Transient community members

The Human GI Microbiome

- Approximately 100 trillion microorganisms
- Most reside in the colon
- Large increase in microbial density across ICV
- >90% belong to two phyla (Firmicutes and Bacteroidetes)
- ~90% have never been cultured
- Metabolic, immune system, and pathogen resistance functions

Wu & Lewis, CGH 2013
Gastric Fluid Microbiota

von Rosenvinge, et al. ISME J 2013
Inflammatory Bowel Disease

- An inappropriate and persistent inflammatory response to commensal gut microbiota in genetically susceptible people
- In Crohn’s disease:
  - The phylum Firmicutes is commonly reduced
  - The family Enterobacteriaceae are commonly increased

Chehoud, et al. *IBD* 2015
Bacteria typical to the oral cavity:
- Veillonella parvula
- Veillonella dispar
- Aggregatibacter segnis
- Haemophilus parainfluenzae

Gut microbes:
- Faecalibacterium prausnitzii
- Blautia faecis
- Roseburia inulinivorans
- Bifidobacterium longum
Fungal Signatures in IBD

Chehoud, et al. IBD 2015
# Fecal Microbiota Transplantation for Ulcerative Colitis: Not Just Yet

## Table 1. Comparison of the 2 Studies

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Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis

133 Patients assessed for eligibility

- 60 Excluded
  - 19 Not ulcerative colitis
  - 11 Endoscopic Mayo score <2
  - 9 Not meeting other criteria
  - 9 Declined to participate
  - 2 Stool infection
  - 10 Other reasons

73 Randomized

38 Randomized to receive donor fecal microbiota transplantation
  38 Received intervention as randomized
  3 Withdrew
    1 Clostridium difficile colitis (colectomy)
    1 Worsening colitis (rescue therapy)
    1 Declined colonoscopy at 8 wk
  35 Assessed at wk 8
  38 Included in the primary analysis at wk 8

35 Randomized to receive autologous fecal microbiota transplantation
  35 Received intervention as randomized
  1 Withdrew (worsening colitis [rescue therapy])
  34 Assessed at wk 8
  35 Included in the primary analysis at wk 8

Costello, et al. JAMA January 2019
Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis

Table 2. Outcome Measures Comparing Donor Fecal Microbiota Transplantation (FMT) With Autologous FMT at Week 8

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<th>No./Total No. (%)</th>
<th>Absolute Percentage Gain Over Autologous FMT, % (95% CI)</th>
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<td>Steroid-free remission of ulcerative colitis at wk 8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>12/38 (32)</td>
<td>3/35 (9)</td>
<td>23 (4 to 42)</td>
<td>5.0 (1.2 to 20.1)</td>
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<td><strong>Secondary Outcomes</strong></td>
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<td>Clinical response&lt;sup&gt;e&lt;/sup&gt;</td>
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<td><strong>Other Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in total Mayo score from wk 0 to wk 8 (SD)</td>
<td>-1.2 (2.1)</td>
<td>-3.5 (2.5)</td>
<td>-33 (-48 to -17)</td>
<td>-2.4 (-3.5 to -1.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> CI = confidence interval; SD = standard deviation.
Liver Disease and the GI Microbiome

• 70% of the liver’s blood supply comes from the intestine via the portal vein
  – Continuously exposed to bacterial components
    • Endotoxins, peptidoglycans
    • Multiple liver cell types express innate immune receptors that respond to microbial-derived products

• Dysbiosis, integrity of the gut barrier, and hepatic immune responses govern effects

NAFLD

• GF mice colonized with stool from obese mice with NAFLD and fed a HFD develop obesity and NAFLD
• GF mice colonized with stool from obese mice without NAFLD and fed a HFD develop comparable obesity but not NAFLD

All Children and Adolescents

Normal

Obese

NASH

All Children and Adolescents

FMT for Hepatic Encephalopathy

Group 1 (FMT)
- Day 0: Eligibility, cognition, samples
- Day 5: Safety, eligibility, cognition, samples
- Day 6: Safety and tolerability (FMT+1)
- Day 12: Safety and tolerability (FMT+7)
- Day 20 (FMT+15): Safety, tolerability, cognition, samples
- Day 35 (FMT+30): Safety and tolerability

Outpatient cirrhosis and recurrent HE

1:1 randomization

Group 2 (no treatment)
- Day 0: Eligibility, cognition, samples
- Day 5: Safety, continued eligibility
- Day 6: Safety
- Day 12: Safety
- Day 20: Safety, cognition, samples
- Day 35: Safety

Bajaj, et al. Hepatology 2017

PHES Day 0 minus Day 20 (Negative indicates improvement)

P = 0.01
Systemic inflammation and endotoxemia
Luminal secondary bile acids
Gut microbial diversity

Bacterial infections and other complications, PPI, antibiotic use

Healthy → Compensated → Decompensated → ACLF → Post-transplant
Red and processed meat

Heme iron

↑ Mucin-degrading bacteria (e.g., *Akkermansia muciniphila*)

↓ Gut barrier function

Bile acid

↑ Secondary bile acid

↑ Oxidative stress
Altered host metabolism

↑ Colorectal cancer

Sulfur

↑ Hydrogen sulfide

↑ Cell proliferation

Anaerobic bacteria

Sulfur-reducing bacteria
Gram-positive, anaerobic, spore-forming bacillus

**C. difficile** infection (CDI):
- Toxin mediated
- Associated with alterations in the GI microbiota
- Responsible for ~half a million infections and associated with ~29,000 deaths per year in the US\(^1\)
- Rates have surpassed MRSA making CDI the most common HAI\(^2\)

Traditional risk factors are antibiotic use, hospitalization, advanced age, and co-morbidities

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Clinical Presentation

• Asymptomatic carriage
• Non-severe -diarrhea
• Severe
  • Elevated WBC count
  • Renal dysfunction
  • Abdominal pain/distention
  • Fever
  • Pseudomembranous colitis
Clinical Presentation

• Fulminant
  • Hypotension
  • Shock
  • Ileus
  • Toxic megacolon
  • Death
• Recurrent disease
  • 20 ➔ 40 ➔ 60% rule
# Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Supportive Clinical Data</th>
<th>Recommended Treatment*</th>
<th>Strength of Recommendation/Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>L Koucycytosis with a white blood cell count of ≤15,000 cells/mL and a serum creatinine level &lt; 1.5 mg/dL</td>
<td>• VAN 125 mg given 4 times daily for 10 days, OR&lt;br&gt;• FDX 200 mg given twice daily for 10 days&lt;br&gt;• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days</td>
<td>Strong/High&lt;br&gt;Strong/High&lt;br&gt;Weak/High</td>
</tr>
<tr>
<td>Initial episode, severe&lt;sup&gt;a&lt;/sup&gt;</td>
<td>L Koucycytosis with a white blood cell count of ≥15,000 cells/mL or a serum creatinine level &gt; 1.5 mg/dL</td>
<td>• VAN, 125 mg 4 times per day by mouth for 10 days, OR&lt;br&gt;• FDX 200 mg given twice daily for 10 days</td>
<td>Strong/High&lt;br&gt;Strong/High</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.</td>
<td>Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)</td>
</tr>
<tr>
<td>First recurrence</td>
<td>...</td>
<td>• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR&lt;br&gt;• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR&lt;br&gt;• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode</td>
<td>Weak/Low&lt;br&gt;Weak/Low&lt;br&gt;Weak/Moderate</td>
</tr>
<tr>
<td>Second or subsequent recurrence</td>
<td>...</td>
<td>• VAN in a tapered and pulsed regimen, OR&lt;br&gt;• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR&lt;br&gt;• FDX 200 mg given twice daily for 10 days, OR&lt;br&gt;• Fecal microbiota transplantation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Weak/Low&lt;br&gt;Weak/Low&lt;br&gt;Strong/Moderate</td>
</tr>
</tbody>
</table>
Fecal Microbiota Transplantation

• The process of taking stool from a healthy donor and placing it into the GI tract of a patient
• Goal is to restore the healthy gut microbiota by replenishing the intestinal ecosystem of the patient with the microbiota of the healthy donor
• Increasingly popular in the clinical arena and the public media
• Introduction of detrimental microbes during fecal transplantation is a concern
First Fecal Transplant at UMMC – February 2013
Fecal Transplant - Technique

- Healthy donor screened for infectious pathogens and diseases that may be linked to the GI microbiota
- Donor stool processed into a liquid slurry
  - Added to saline, water, or milk
  - Blended or mixed
  - Strained through sieve, gauze, or coffee filter
- Stool solution administered to patient
  - NG or NE tube
  - Upper endoscopy
  - Colonoscopy
  - Enema
• 317 patients from 27 case series and reports
• Resolution in 92% (89% after single treatment)
• Factors that appeared to predict success:
  – Related donor
  – Instillation via colonoscopy or enema
  – Use of > 50g donor stool
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*
Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

How do fecal transplants really work?

• Which bacteria are beneficial?
• Which bacteria are detrimental?
• Can you create a “synthetic stool” using a subset of fecal bacteria?
• What changes in the microbiota occur during a fecal transplant?
Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies

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.
Future of FMT?

• Multiple companies studying FMT products
• The end of enforcement discretion?
• The end of stool banks?
• Still the future is bright!
• >150 trials of FMT registered on clinicaltrials.gov
Questions?
Fecal Microbiota Transplantation Working Group (Indications)

• Recurrent or relapsing CDI
  • At least 3 episodes of mild to moderate CDI and failure of a 6- to 8-week taper with vancomycin
  • At least 2 episodes of severe CDI resulting in hospitalization and associated with significant morbidity

• Moderate CDI not responding to standard therapy for at least a week

• Severe (and perhaps fulminant CDI) with no response to standard therapy after 48 hours