The Gut Microbiome; the forgotten organ?

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I do not intend to discuss unapproved/investigative use of commercial product(s)/device(s) in my presentation.

Presentation Objectives
1. Understand the make up of the gut microbiota
2. Appreciate the role of the gut microbiome in maintaining health
3. Understand the role of the gut microbiome in pediatric disease
Definition

“The community of microorganisms that share our body space”.


Facts about the gut microbiome

Only 10% of our cells are human cells!

1% of genes are human genes!

Gut microbial composition

• Bacteria: most common, 60% stool dry weight
• Fungi: fungome
• Viruses: virome

NIH Human microbiome project 2012
BACTERIAL DISTRIBUTION IN THE HUMAN DIGESTIVE TRACT

The number of bacteria increases along the length of the gut.

Gut bacterial dominance

- Firmicutes
- Bacteroides

Abundance versus diversity
16S RNA, proteomics, metagenomics, metabolomics

Traditional Beneficial Role of the Intestinal Microbiota

NUTRITION
- Absorption of carbohydrates: conversion to SCFA
- Lipid digestion and micronutrient/vitamin synthesis
- Metabolism of xenobiotics and endogenous toxins

DEVELOPMENT
- Stimulation of angiogenesis
- Post-natal intestinal maturation

IMMUNE SYSTEM
- Mucosal barrier fortification
- Protection against infections and other intestinal diseases
FACTORS INFLUENCING COLONIZATION

Mode of Birth  
Maternal Microbiome  
Diet  
Antimicrobials  
Prebiotics  
GUT MICROBIOME  
Prebiotics  
Probiotics

Adapted from Steve Erdman ASPEN 2006

Age and the microbiome

Ageans, Rigsbee, Kenche, Michail et al. FEMS Microbiol Ecol. 2011

Microbiome and race

Pediatric disorders related to the gut microbiome

- Obesity
- GI disease: IBD, IBS, Clostridium difficile
- Allergies
- NEC
- CNS: autism, schizophrenia, depression

Gut microbial role

- Obesity
- Select GI diseases
- CNS
Obesity and Microbiota


Obesity Trends® Among U.S. Adults
BRFSS, 1990, 2000, 2010
(‡BMI 25.0 or about 30 lbs, overweight for 5’4” person)

Source: Behavioral Risk Factor Surveillance System, CDC

Microbiome clusters by host obesity genotype

Gut microbial “obesogenicity” is transferrable

Ley; Proc Natl Acad Sci 2005;102:11070-5

Obese microbiome and increased capacity for energy harvest


FMT and obesity

- Report by Alang and Kelly
- 32 yr woman successfully treated with FMT for c diff developed new-onset obesity after receiving stool from 16 year old daughter with BMI 26.3
- Recipient BMI increased from 26 to 33 then 34.5
- Donor BMI increased as well

Kelly Brief report November 2014
Can we prevent obesity?

Cohousing Obch and Lnch mice transforms the adiposity phenotype to a lean-like state

Obesity and fatty liver

Michail et al. FEMS 2015
Obesity and fatty liver

Michail et al. FEMS 2015

Systematic Transcriptome Analysis Reveals Elevated Expression of Alcohol Metabolizing Genes in NAFLD Livers.


Irritable Bowel Syndrome
**IBS and microbiota**

- Many subjects develop microbial related symptoms such as bloating
- Suggested link to small bowel bacterial overgrowth
- Post-infectious IBS

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**Pediatric IBS microbiota profile**

- Increase in γ-proteobacteria; especially *Haemophilus parainfluenzae*.
- Able to classify different subtypes of IBS
- Ruminococcus-like microbe was associated with IBS.
- A greater frequency of pain correlated with an increased abundance of *Alistipes*.

Saulnier et al. Gastroenterology 2011

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**Pediatric IBS microbiota profile**

Pediatric IBS

- Characterized by increased proteolysis, incomplete anaerobic fermentation and methane production.

Shankar et al. ISME J. 2015

FMT in IBS


Abdominal pain, diarrhea, bowel movements, bloating

Pediatric IBD data
- Children hospitalized with severe ulcerative colitis (n=27)
- Compared to healthy children (n=26)
- US and Canada
- Responders and non-responders
Number of species detected in healthy children and children with severe ulcerative colitis that (1) responded to steroids (Responders) and (2) those that failed to respond (Non-responders). Values depicted as mean ±SEM. Statistically significant differences are noted between responders and Non-responders (p=0.039). In addition, significant differences were also noted between healthy children and the two groups of ulcerative colitis (p<0.0001).

The gut microbiome in CNS disease

- core to the pathophysiology or merely epiphenomenal.
- gut and brain communication mediated by the vagus nerve, immune system, short chain fatty acids and tryptophan

Microbial influence on behavior

- Single microbe: T. gondii, Brucella suis, Leptospira spp, Mycobacterium tuberculosis, Streptococci (PANDAS)
- Improved behavior with Bacteroides fragilis in a mouse model of autism.

Hsiao, Cell 2013
### Prevalence of gut species in children with ASD

<table>
<thead>
<tr>
<th>Bacterial Species</th>
<th>Autism</th>
<th>Controls</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides vulgatus</td>
<td>↓  ↓</td>
<td>↑  ↑</td>
<td>0.05</td>
</tr>
<tr>
<td>Escherichia sp</td>
<td>↓  ↓</td>
<td>↑  ↑</td>
<td>0.01</td>
</tr>
<tr>
<td>Ruminococcus gravis</td>
<td>↓  ↓</td>
<td>↑  ↑</td>
<td>0.01</td>
</tr>
<tr>
<td>Neisseria sp</td>
<td>↓  ↓</td>
<td>↑  ↑</td>
<td>0.02</td>
</tr>
<tr>
<td>Blautia cacoides</td>
<td>↓  ↓</td>
<td>↑  ↑</td>
<td>0.03</td>
</tr>
<tr>
<td>Enterobacter hormaechei</td>
<td>↓  ↓</td>
<td>↑  ↑</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Burkholderia cepacia</td>
<td>↑  ↑</td>
<td>↓  ↓</td>
<td>0.02</td>
</tr>
<tr>
<td>Pedobacter sp</td>
<td>↑  ↑</td>
<td>↓  ↓</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Buie, Clinical therapeutics 2015

### Human studies

- Metabolic disturbances in autism could be produced from gut organism
- Onset of symptoms can be preceded by antibiotic use
- Oral treatment with vancomycin has been associated with transient improvement in behavior in ASD
- Usefulness of FMT in a small case series reported by Borody

Sandler, J child neurol 2000

### Microbiome and schizophrenia

- Shotgun metagenomic analysis of the oropharyngeal microbiome (16 subjects with schizophrenia, 16 healthy).
- Less diverse, more abundant Lactic acid bacteria abundant in schizophrenia and an increased number of metabolic pathways related to siderophores, glutamate, and vitamin B12. In contrast, carbohydrate and lipid pathways and energy metabolism were abundant in controls.

To the bedside

Can we modify the gut microbiome

Antimicrobial drugs
  • Metronidazole
  • Ciprofloxacin
  • Rifaximin
  • Neomycin
Antimicrobial drugs

• Metronidazole
• Ciprofloxacin
• Rifaximin
• Neomycin

**HOW GOOD ARE THEY??**

Probiotics

• AGE
• IBD-UC
• IBS
• Atopic dermatitis
• Allergic colitis
• NEC
• URI
• C-difficile

Probiotics

• How long do they colonize the gut?
• How good are they?
Future directions

- Fecal transplant in pill format...already happening
- Specific micro-organisms for specific disorders...
- More applications? FMT for obesity, NAFLD, IBS, etc.....

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