The Gut Microbiome; the forgotten organ?

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2. Rebiotix: advisory board.

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 mcirobiota

2. Appreciate the role of the gut microbiome in maintaining health

3. Understand the role of the gut microbiome in pediatric disease

3

Definition

"The community of microorganisms that share our body space".

Lederberg, J; McCray, AT (2001). ""Ome Sweet 'Omics—a genealogical treasury of words". Scientist 15: 8.
"The NIH Human Microbiome Project". Genome Res 19 (12): 2317–2323. 2009.

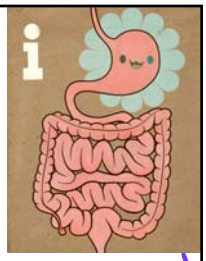
Facts about the gut microbiome

Only 10% of our cells are human cells!

1% of genes are human genes!

NIH; Human microbiome project 2012
Savage; Annu Rev Microbiol 1977:31:107-33
Berg; Trends Microbiol 1996;4:430-5

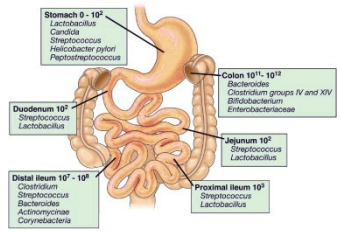
Gut microbial composition



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

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

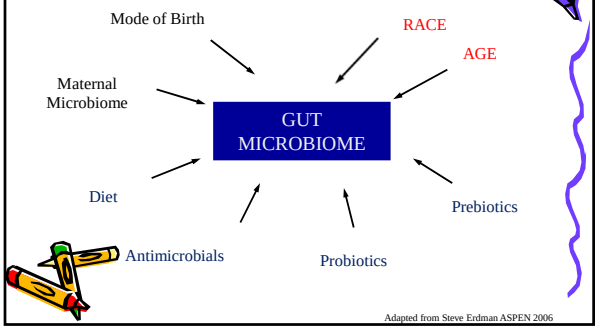
NUTRITION
- Absorption of carbohydrates: conversion to SCFA
- Lipid digestion and micronutrient/vitamin synthesis
- Metabolism of xenobiotics and endogenous toxins

DEVELOPMENT
- Stimulation of angiogenesis
- Post-natal intestinal maturation

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

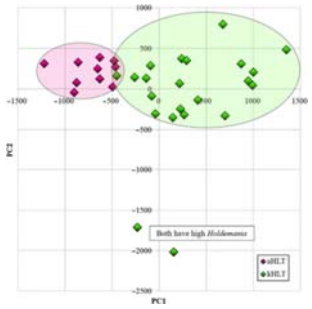
Savage; Annu Rev Microbiol 1977:31:107-33. Berg; Trends Microbiol 1996;4:430-5

FACTORS INFLUENCING COLONIZATION



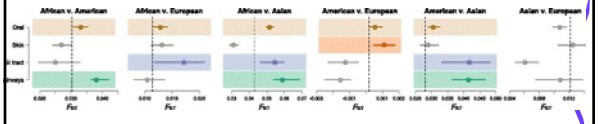
Adapted from Steve Erdman ASPEN 2006

Age and the microbiome

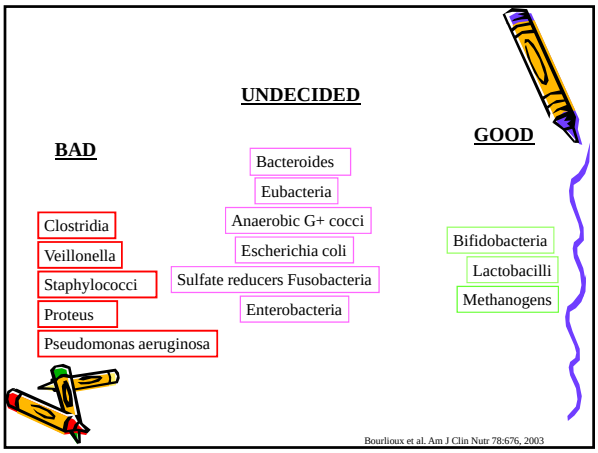


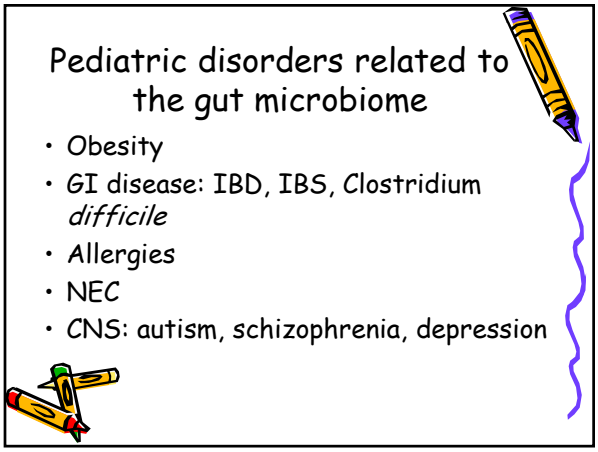
Agans, Rigsbee, Kenche, Michail et al. FEMS Microbiol Ecol. 2011

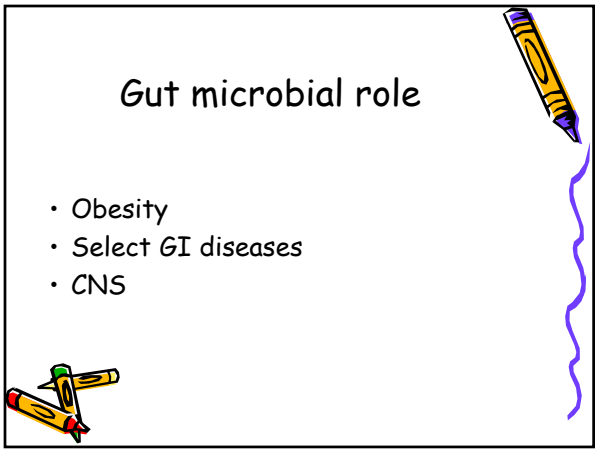
Microbiome and race



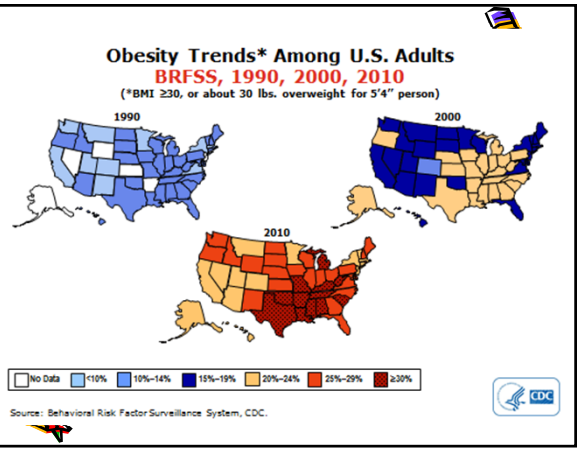
Blekhman R. Genome Biol. 2015; 16(1): 191.


UNDECIDED
BAD
GOOD
Bacteroides
Eubacteria
Anaerobic G+ cocci
Escherichia coli
Sulfate reducers Fusobacteria
Enterobacteria
Clostridia
Veillonella
Staphylococci
Proteus
Pseudomonas aeruginosa
Bifidobacteria
Lactobacilli
Methanogens
Bourlioux et al. Am J Clin Nutr 78:676, 2003

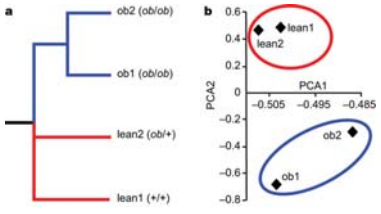

Pediatric disorders related to the gut microbiome
• Obesity
• GI disease: IBD, IBS, Clostridium *difficile*
• Allergies
• NEC
• CNS: autism, schizophrenia, depression


Gut microbial role
• Obesity
• Select GI diseases
• CNS

Obesity and Microbiota

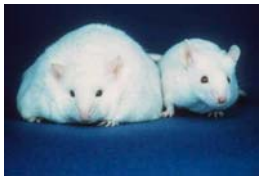


Microbiome clusters by host obesity genotype



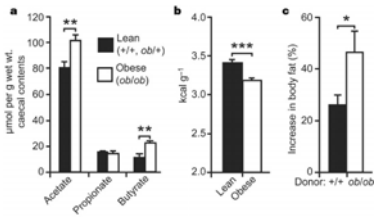
Peter J. Turnbaugh, Ruth E. Ley, Michael A. Mahowald, Vincent Magrini, Elaine R. Mardis & Jeffrey I. Gordon. Nature 444, 1027-131(21 December 2006)

Gut microbial "obesogenicity" is transferrable



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

Obese microbiome and increased capacity for energy harvest



Peter J. Turnbaugh, Ruth E. Ley, Michael A. Mahowald, Vincent Magrini, Elaine R. Mardis & Jeffrey I. Gordon. Nature 444, 1027-131(21 December 2006)

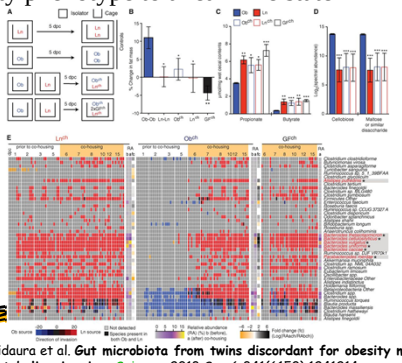
FMT and obesity

- 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

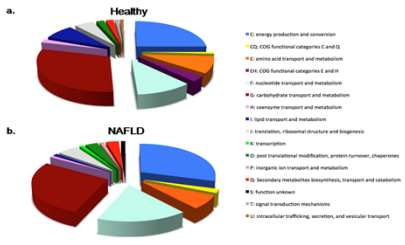
Can we prevent obesity?

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



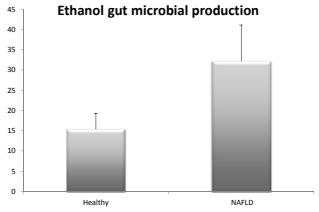
Ridaura et al. **Gut microbiota from twins discordant for obesity modulate metabolism in mice.** Science. 2013 Sep 6;341(6150):1241214.

Obesity and fatty liver



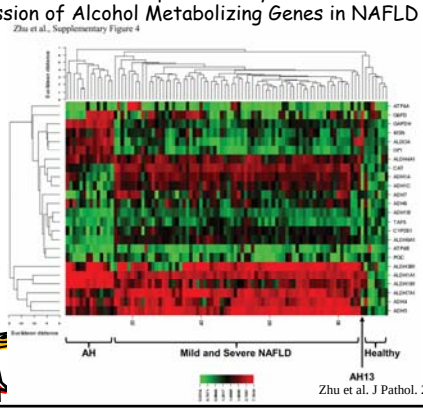
Michail et al. FEMS 2015

Obesity and fatty liver



Michail et al. FEMS 2015

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



Zhu et al. J Pathol. 2015 Sep 28.

Irritable Bowel Syndrome

IBS and microbiota

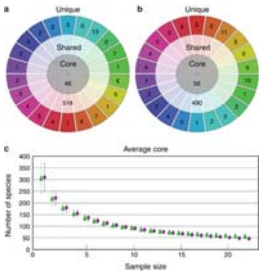
- Many subjects develop microbial related symptoms such as bloating
- Suggested link to small bowel bacterial overgrowth
- Post-infectious IBS

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.

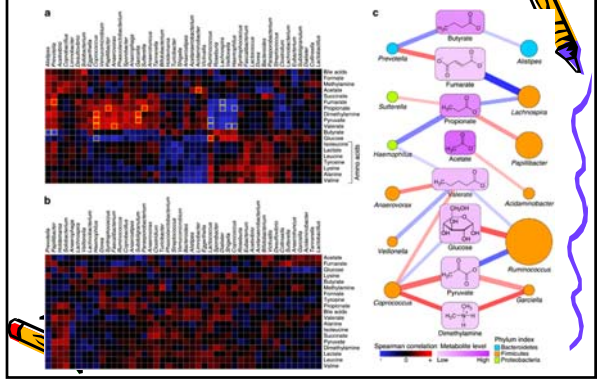
Saulnier et al. Gastroenterology 2011

Pediatric IBS microbiota profile



Rigsbee, Agans, Michail, Paliy. Am J Gastroenterol. 2012

Gut Metabolite profile in pediatric IBS

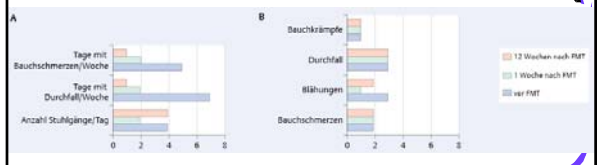


Pediatric IBS

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

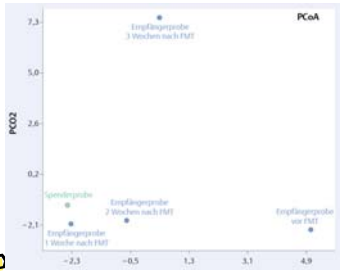
Shankar et al. ISME J. 2015

FMT in IBS



Zoller et al. Fecal microbiota transfer (FMT) in a patient with refractory irritable bowel syndrome. Dtsch Med Wochenschr. 2015 Aug;140(16):1232-6. Abdominal pain, diarrhea, bowel movements, bloating

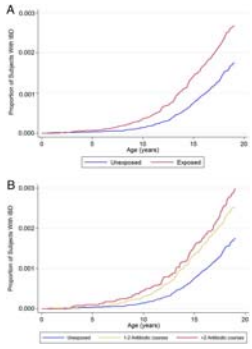
FMT in IBS



Zoller et al. Fecal microbiota transfer (FMT) in a patient with refractory irritable bowel syndrome. Dtsch Med Wochenschr. 2015 Aug;140(16):1232-6.

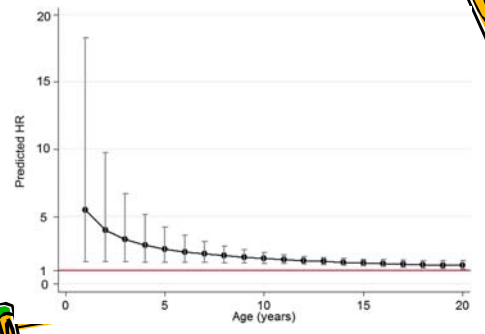
Pediatric Ulcerative Colitis

A, Proportion of subjects developing IBD according to age and antianaerobic antibiotic exposure status.



Kronman M P et al. Pediatrics 2012;130:e794-e803

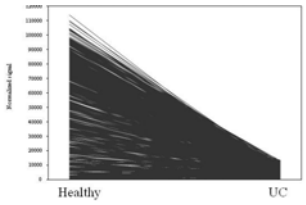
Hazard of developing IBD if ever previously exposed to antianaerobic antibiotics, according to age.



Kronman M P et al. Pediatrics 2012;130:e794-e803

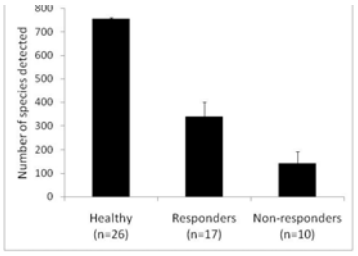
Pediatric IBD data

- Children hospitalized with severe ulcerative colitis (n=27)
- Compared to healthy children (n=26)
- US and Canada
- Responders and non-responders



Pilot plot representation of normalized signal intensities of each of the phylospecies in children with ulcerative colitis (UC) versus healthy controls (Healthy).

Michail DDW 2010



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 both of 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

Bacterial Species	Autism	Controls	*P*
Bacteroides vulgatus	↓	↑	0.05
Escherichia sp	↓	↑	0.01
Ruminococcus gnavus	↓	↑	0.01
Neisseria sp	↓	↑	0.02
Blautia coccoides	↓	↑	0.03
Enterobacter hormaechei	↓	↑	<0.005
Burkholderia cepacia	↑	↓	0.02
Pedobacter sp	↑	↓	0.04

Buie, Clinical therapetutics 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.

Castro-Nallar. PeerJ. 2015 Aug 25;3:e1140. doi: 10.7717/peerj.1140. eCollection 2015.

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?

FMT

Future directions

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

Acknowledgement

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- Ebi Zandi