On Good Things in With Small Footprints...

"Be faithful in small things because it is in them that your strength lies."

"Not all of us can do great things. But we can do small things with great love."

Mother Teresa
“A SMALL BODY OF DETERMINED SPIRITS FIRED
BY AN UNQUENCHABLE FAITH IN THEIR MISSION
CAN ALTER THE COURSE OF HISTORY.”

MAHATMA GANDHI
Sometimes smaller is not better (if you get caught... )
Bad News for the ‘Kardashians’s Kleanses’
Our Gut Bacteria Are Not ‘Toxins’

“If you don't like bacteria, you're on the wrong planet.” Stewart Brand
Outline

Background on IBD and pathogenesis

What is the microbiome and where can I get one? Overview and Review of Nature and Spectrum

What role in health and disease might it have?

What about IBD: UC/CD and The Gut Microbiome?

• Changes Changes: Chickens vs Eggs?
• Importance ‘Makes Sense’ but does it translate to Tx?
• Can we modify it? Importance of Early vs Late?
• Tx Opportunities: Diet and Pre/Probiotics and Synbiotics
• FMT (Stool Transplant)
  – C. Diff, C. Diff w IBD and what about IBD w/o C. Diff?
• The Future: Targeted Modifications of Microbiome
Know your bugs!

- Viruses
- Bacteria
- Fungus
IBD Etiology and Pathogenesis

IBD affecting about 1.5 million in US
• On the rise in US and around the globe
• At times doubling every decade after 1950’s
• Multifaceted origins: Genes, Immune System and intestinal microbial community and ecosystem

Over past 10 years IBD has been one of the most studied aspects of the human microbiota

Over 165 genes and pathways are enriched for modulation of intestinal hemostasis and microbe interactions with human genetics
• NOD2: Works by ‘sensing’ bacterial presence and talking to the gut’s immune system
• ATG1A1: Mutations allow impaired pac-man functions
Etiologic Theories in IBD

- Genetic Predisposition
- Mucosal Immune System (immunoregulatory defect)
- Environmental Triggers (luminal bacteria, infection)

IBD
Genetics of IBD
163 Confirmed Loci

- CD genes
  - NOD2
  - PTPN22
  - 30 CD-specific loci

- UC genes
  - 23 UC-specific loci
  - MHC

- 110 IBD loci
  - Common pathways:
    - Leprosy
    - Mycobacterial susceptibility
    - Other immune-mediated disease

Genes in common

Recognition of Disease Heterogeneity in the Pathogenesis of IBD

Crohn’s disease-like

- Crohn’s specific genes (Nod2)

- Colonization (bacteria, viruses, fungi, worms)

Ulcerative colitis-like

- Loss of protective flora

- UC specific genes (MHC)

- Core genes Regulating Inflammation, Epithelial barrier, autophagy, etc
Definitions

- **Microbiota**: microbial community.
- **Microbiome**: can refer to microbiota but can also refer to collective genomes and gene products of microbes living within and on humans.
- **Metagenome**: collection of genomes within complex microbial communities and human DNA, some also include RNA and proteins and other metabolites.
- **Biodiversity** is a measure of the complexity of a community. Includes number of taxa (richness) and their range of abundance (evenness).

Johnson, Pediatrics, 2012
THE HUMAN MICROBIOME

Bacteria, fungi, and viruses outnumber human cells in the body by a factor of 10 to one. The microbes synthesize key nutrients, fend off pathogens and impact everything from weight gain to perhaps even brain development. The Human Microbiome Project is doing a census of the microbes and sequencing the genomes of many. The total body count is not in but it's believed over 1,000 different species live in and on the body.

600+ species in the mouth, pharynx and respiratory system include:
- Streptococcus viridans
- Neisseria sicca
- Candida albicans
- Streptococcus salivarius

25 species in the stomach include:
- Helicobacter pylori
- Streptococcus thermophilus

500-1,000 species in the intestines include:
- Lactobacillus casei
- Lactobacillus reuteri
- Lactobacillus gasseri
- Escherichia coli
- Bacteroides fragilis
- Bacteroides thetaiotaomicron
- Lactobacillus rhamnosus
- Clostridium difficile

1,000 species in the skin include:
- Pityrosporum ovale
- Staphylococcus epidermidis
- Corynebacterium jeikeium
- Trichosporon
- Staphylococcus haemolyticus

60 species in the urogenital tract include:
- Ureaplasma parvum
- Corynebacterium aurimucosum

Sources: National Institutes of Health, Scientific American; Human Microbiome Project

Dean Tweed • Postmedia News / Image: Fotolia
The Human Microbiome Overview
Gut Microbiome: The Forgotten Organ?

- Definition: Microbiota vs. Microbiome (bacterial DNA...)
- We are composite of species: a ‘supra-organism’
- We are 10% human based on cellular number
- We are only 1% human based on total DNA content
- Human genes outnumbered by unique microbial genes x 150
  - Human: 30,000 vs. 3 to > 6 million+ microbial unique genes
- Our largest collection of microbes resides in the intestine (~10100 trillion organisms)
  - 100 billion per gram of stool
  - Gut microbiota 1-3% weight-3-5 lbs!
- 1,000+ species, most not cultured
- Anaerobes > Aerobes 1000 X
100,000,000,000,000 bacteria, viruses, and fungal cells/gram of intestinal contents

Community – Ecosystem – A true ‘organ’

Wide range of useful functions

• Educating the immune system (gut and systemic..)
• Digestion and energy extraction (second meal effect)
• Repressing growth of harmful organisms (colonization resistance)

Influenced by Genes, Birth Route, Geography, Age, Cleanliness (playing in the dirt, number of bathrooms), Parasites, Drugs esp. Antibiotics, PPIs, Psychological Stress, Diet and Nutrition, Smoking, Other Exposures to Other Hormones, Toxins, and other Chemicals

Recent data linking sleep and jet lag to make up (and creating a weight gain bacterial make up)

Bowel Prep affects the microbiome! Split dose >> All at night
Beyond the Core Microbiome
Is My Gut Microbiome the Same as Yours?
Variances are Unique ‘Fingerprint’ and May Be Reflective of Health and or Risk of Disease

Central Core Microbiome
we all share
However, the particular species mix, number, and diversity of the many different microbes can vary greatly from person to person.
Figure 1: Bacterial genera and their influence on the host
Intestinal Microbiota: Alterations During Human Life Cycle

- **Unborn**
  - Formula-fed
  - Breast-fed

- **Baby**
  - Antibiotic treatment
  - Solid food

- **Toddler**
  - Malnutrition

- **Adult**
  - Healthy

- **Elderly**
  - Obese
  - 65 to 80 years
  - >100 years

Legend:
- Pink: Firmicutes
- Blue: Bacteroidetes
- Green: Actinobacteria
- Red: Proteobacteria
- Yellow: Others

EFFECTS OF GUT MICROBIOTA ON HOST HEALTH

- Barrier effect
- Immunocompetence/Tolerance
- Synthesis
- Metabolic/Trophic function
- Drug metabolism
- Behavior conditioning

But...specific effects in each GI tract!
<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Extra-Intestinal</th>
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<td>Chronic Fatigue Syndrome</td>
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<td>Chronic Constipation</td>
<td>Insulin Resistance-Diabetes</td>
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<td>IBD: Crohn’s and UC</td>
<td>Metabolic Syndrome</td>
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<td>Coronary Artery Disease</td>
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<td>Gastric Cancer</td>
<td>Multiple Sclerosis</td>
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<td>Gastric Lymphoma</td>
<td>Mood Disorders: Depression Stress</td>
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<td>Anxiety</td>
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Figure 2

Gastroenterology 2014 146, 1489-1499
DOI: (10.1053/j.gastro.2014.02.009)

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Terms and Conditions

Subjects | Samples | Sample handling | Assays
--- | --- | --- | ---
Host | Bacteria | Stool samples (self collected) | Microbe: 16S rRNA gene profiling
Virus | Eukaryotes | Biopsies | Microbe: Metagenome sequencing
| | | | Microbe: Metatranscriptome seq
| | | | Microbe: Metabolite profiling
| | | | Microbe: Single-cell assays
| | | | Microbe: DNA & RNA virome
| | | | Microbe: Proteomic profiling
| | | | Host: Fecal calprotectin test
| | | | Microbe: 16S rRNA gene profiling
| | | Separate microbes and Meta'omic seq
| | | Host: Transcriptome sequencing
| | | Host: Epithelial cell profiling
| | | Host: Bisulfite sequencing (RRBS)
| | | Host: SNP profiling
| | | Host: Serological profiling

Covariates to control for:
- Host genome
- Disease activity
- Treatment details
- Diet info
- Age, gender, race
- Sample type, collection, extraction

Blood samples

Host | Microbial
THE INTESTINAL MICROBIOME

- Home to 10–100 trillion organisms; the most densely packed ecosystem on the planet; separated by a single cell layer!
- Microbial genes outnumber human genes by a factor of 100.
- Bacterial cells outnumber human cells 10:1
- 98% of sequenced bacteria belong to only four bacterial phyla:  
  Firmicutes (64%), Bacteroidetes (23%), Proteobacteria (8%), Actinobacteria (3%).
- Instructs the immune system and influences host physiology, metabolism and brain function
- Subject to environmental influences e.g. diet, antimicrobials
Microbes maketh man

- The Catholic church's unholy mess
- Paul Ryan: the man with the plan
- Generation Xhausted
- China, victim of the Olympics?
- The origin of specie

How 90% of the cells in your body are bacteria. The benefits of faecal transplants and other things you would rather not know before breakfast.
Google Search at 12 AM 1-24-15

‘Microbiome’

1. 2.35 million web page results
2. Over 1,000,000 images
3. 1,460 News stories
4. 41,600 Videos
5. 6,800 Books
6. Appts? > 50 per Google but...
7. Apple App Store search: 0 hits
Explosion in Microbiome Interest, Research and Publications over the past few years....

Using a keyword search of “human microbiome,” the figure shows a compound annual growth rate (CAGR) of 28% for journal category expansion, and 69% for number of publications between 2008–2012.

Source: SciVal custom analysis
GERMS ARE US

Bacteria make us sick. Do they also keep us alive?

BY MICHAEL SPECTER

What's in your beard?
Clinicaltrials.gov Studies on Microbiome in US and Crohn’s Disease

- Metagenomic Analysis of Gut Microbiome in Korean Patients With UC
- Manipulating the Microbiome in IBD by Antibiotics and FMT
- Fecal Microbiota Transplantation in Pediatric Patients (FMT)
- The Effect of Therapeutic Fecal Transplant on the Gut Microbiome in Children With UC
- A Pilot and Feasibility Study of Fecal Microbiota Transplantation for Ulcerative Colitis
- Fecal Microbiota Transplantation (FMT) for Treatment of Ulcerative Colitis in Children
- Personalized "Alberta" Diet for Prevention of Relapse in Ulcerative Colitis
- Canadian Children Inflammatory Bowel Disease Network (CIDscANN) (CIDsCaNN)
- Fecal Microbiota Transplant (FMT) in Pediatric Active Ulcerative Colitis
- Impact of Fecal Biotherapy (FBT) on Microbial Diversity in Patients With Moderate to Severe
- Fecal Microbial Transplant in Pediatric Crohn's Disease (FMTCD)
Are fecal transplants better done at home or by a doctor?

There are many good reasons for doing fecal transplants at home, rather than in a medical setting. First of all, doctors use the same instrument they use in colonoscopies to administer the transplants. The colonoscope, with its camera, is intrusive and harmful because it scrapes off any scabs on deep ulcers that are beginning to heal. If a colonoscope is used repeatedly, the poor person’s intestine never properly heals. There is a theory that healthy bacteria cannot colonize on unhealed intestinal tissue and this seems to be the situation in these unsuccessful cases.
Fecal Transplants in the Media

HUFFPOST HEALTHY LIVING

Repoopulating the Gut
Posted: 03/07/2013 2:43 pm

Los Angeles Times

The New York Times

When Pills Fail, This, er, Option Provides a Cure by Denise Grady Jan. 16, 2013

Fecal Transplant, Leg Breast Implant – Two Procedures You Might Not Have Heard Of
Published November 21, 2008 by: Sylvia Cochran

Fecal transplants may stall as FDA cracks down on docs
By JoNel Aleccia, Senior Writer, NBC News
NBCNews.com, June 3, 2013

Fecal transplants successful in treating intestinal ailment
January 17, 2013
By Monte Morin, Los Angeles Times

The University of Chicago Medicine

Fecal “Transplant” Helps One-year-old Beat Relentless Infection
Posted by John Easton on January 2, 2013 in gastroenterology

Oklahomans’ fecal transplant aims to kill colon superbug
SUSAN SIMPSON 99 0 Comments
Published: July 23, 2009
Some Oklahoma patients are opting for an admittedly gross procedure to kill superbugs living in their colons.
"So tell me, Daniel... when will we get to meet your microbes?"
METABOLIC FUNCTIONS OF THE BACTERIAL FLORA IN THE COLON

- Mucus
- Primary biliary acids
- Undigestible dietary substrates
- Starch, oligo-saccharides
- Lactic acid
- Ramate fatty acids
- Short-chained fatty acids
- Ethanol
- Amine
- Gas, H₂, CO₂
- Ammonium
- Phenols
Multiple sclerosis
Chronic fatigue syndrome
Non-alcoholic fatty liver disease
Obesity

Atherosclerosis
Idiopathic thrombocytic purpura

Insulin resistance/
type 2 diabetes mellitus

C difficile infection
Irritable bowel syndrome
Inflammatory bowel disease

Green: beneficial effect FMT in RCT
Blue: beneficial effect FMT in case series
Black: association between gut microbiota and disease from experimental/observational studies
The gut microbiota are like a garden—you’re less likely to have weeds growing if you have lush vegetation, but without this vegetation the weeds can potentially take over’

Sarkis Mazmanian
California Institute of Technology
Role of Intestinal Bacteria in Mouse Models of IBD
Role of Bacteria in the Pathogenesis of Chronic Intestinal Inflammation

IBD - Pathogenesis

No bacteria
- No immune activation
- No colitis

Resident bacteria
- Macrophage and TH1 immune activation
- Colitis
FACTORS CONTRIBUTING TO ALTERED MICROBIOTA IN IBD

GENETICALLY DETERMINED FACTORS:

- Reduced secretion of antimicrobial peptides.
- Enhanced replication of mucosal adherent bacteria in ileum (E.coli).
- Defective clearance of invading bacteria due to impaired intracellular killing (autophagy); immune activation

ENVIRONMENTAL FACTORS

- Hygiene
  - Reduced acquisition of microbes: "hygiene hypothesis"
  - Loss of ancestral microorganisms: "old friends hypothesis"
- Diet
- Antimicrobials
- Stress

"DYSBIOSIS"

INFLAMMATION & DYSFUNCTION IN HOST TISSUES
COMMENSALS & PATHOGENS

SYMBIONTS
- Lactobacilli
- Bifidobacteria
- F. prausnitzii
- Bacteroides fragilis
  - SCFA, Polysaccharide A

CONDITIONAL PATHOGENS
- Segmented Filamentous Bacteria (SFB)
  - $T_H^{17}$

PATHOGENS
- Clostridium difficile
- Certain E.Coli strains
Bacteria Viruses and Fungi-OH MY!

- Types of certain bacteria (friendly vs not so friendly?)
- Their collective metabolism, released byproducts, production of hormones, chemicals, even vitamins;
- Location (colon, small bowel, anal region, ileal anal pouch..)
- Where in the gut: Location Location Location
  - Lumen (in the middle of the colon) vs
  - Living in one of the mucus layers of the gut vs.
  - Adherent on the surface of the mucosa vs
  - What do they do once the bacteria, their antigens, and DNA are ‘ingested’ by phagocytic cells located in the tissue (macrophages)
Role of the microbiota in inflammatory bowel diseases

Healthy GI microbiota
- Deconjugation of bile acids
- Insulin resistance
- Lipid metabolism
- Epithelial integrity
- Mucus homeostasis
- Development of the immune system
- Inhibition of NF-κB activation
- Production of RegIIIγ
- Production of anti-inflammatory metabolites
- Colonization resistance

Dysbiotic GI microbiota
- Development of Atopy
- Development of Diabetes
- Obesity
- Leaky tight-junctions
- Shallow intestinal crypts
- Increased number of goblet cells
- Abnormal Peyers patches
- Thinner lamina propria
- Altered cytokine profile
- Fewer plasma cells in germinal center
- Altered innate immune response
F. prausnitzii HAS ANTI-INFLAMMATORY PROPERTIES.

- **F. prausnitzii** reduces pro-inflammatory cytokine release from human monocytes.

- **F. prausnitzii** increases the ratio of anti-inflammatory (IL-10) to pro-inflammatory cytokine (IL-12) secretion ratio in human monocytes.

Sokol H et al. PNAS 2008;105:16731-16736
HOMEOSTASIS

- **CONTROLLED RELEASE OF ANTIMICROBIAL PEPTIDES.**
- **SHORT CHAIN FATTY ACIDS SUPPORT EPITHELIAL INTEGRITY.**
- **MINIMAL PENTRATION OF GUT WALL BY BACTERIA.**
- **EFFICIENT KILLING OF INVADING BACTERIA. NO SEQUELAE.**
- **CONTROLLED INFLAMMATORY RESPONSE**

Adapted from Sartor RB
Gastroenterology 2010; 139:1816-33
EPIDEMIOLOGICAL STUDIES FAVOR ENVIRONMENTAL FACTORS

- The impact of urbanization on prevalence of IBD.
- The changing epidemiology of IBD in Japan.
- Increasing prevalence of IBD among young immigrants to westernized societies.
- Exposure to antibiotics in early life.
Implicating the Microbiota in IBD

- Many IBD susceptibility genes suggest microbial involvement
- Circulating antibodies to bacterial antigens in IBD sufferers
- Response to antibiotics in some patients
- Altered microbial composition of the gut in IBD patients
Clinical Evidence Implicating Intestinal Bacteria in the Pathogenesis of IBD

- **Diversion of fecal stream** prevents recurrence of Crohn’s Disease; Reinfusion of fecal contents rapidly induces disease.

- **Antibiotic therapy** attenuates intestinal inflammation in distal bowel disease.

- **Increased numbers of bacteria** are observed in intestinal tissue of patients with IBD.

- IBD-susceptibility genes are involved in **bacterial killing**.

- Composition of intestinal microbiota is altered in IBD (**dysbiosis**).
  - Common Anti-bacterial antibodies in IBD
GENETIC FACTORS

44-55% Crohn's Disease

- Bacterial recognition
- Reduced epithelial barrier
- Impaired bacterial killing

8-10% Ulcerative colitis

Identical (Monozygotic)

Sperm
Egg

"THE ENVIRONMENT"

Halfvarson J Gastroenterology 2003
Pathogenesis: Definition of IBD Subtypes

<table>
<thead>
<tr>
<th>Genetic variants/mutations</th>
<th>Immunologic/Bacterial Phenotype</th>
<th>Clinical Phenotypes</th>
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<tbody>
<tr>
<td>NOD2 OCTN?</td>
<td>ASCA, OmpC, I2+</td>
<td>IBD I-aggressive SB dz</td>
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<tr>
<td>Gene(s) II</td>
<td>pANCA+/E. Coli</td>
<td>IBD II-UC-like</td>
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<tr>
<td>Gene (s) III</td>
<td>All neg</td>
<td>IBD III Mild SB dz</td>
</tr>
<tr>
<td>Gene (s) IV</td>
<td>Flagellin+</td>
<td>IBD IV ?</td>
</tr>
<tr>
<td>Antibody</td>
<td>Antigen</td>
<td>Non-IBD (%)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>DNase Sensitive pANCA</td>
<td>Histone H$_1$, bacterial antigen?</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>ASCA</td>
<td>Anti- <em>Saccharomyces cerevisiae</em> antibody</td>
<td>5%</td>
</tr>
<tr>
<td>OmpC</td>
<td><em>E. coli</em></td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-I2</td>
<td><em>Pseudomonas fluorescens</em></td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Anti-Flagellin</td>
<td>CBir 1 Antigen</td>
<td>8-14%</td>
</tr>
</tbody>
</table>
THE MICROBIOTA IN IBD

- REDUCED DIVERSITY AND ALTERED COMPOSITION

Firmicutes
Bacteroides
Bifidobacteria
Lactobacilli
Clostridium gps IV
XIVa
(F. prausnitzii)

Actinobacteria
Proteobacteria
Enterobacteria
Ruminococci

Mucosal Adherent Invvasive E Coli (AIEC) in ileum of CD
(A) Healthy Microbiome

(B) Dysbiosis (increased Pro-inflammatory bacteria)

(C) Dysbiosis (decreased anti-inflammatory bacteria)

Human Microbiome + Human Genome = Th17/Treg Profile

Healthy

Disease

Bacteroides fragilis (B. fragilis) SFB

B cell
Treg cell
Th17 cell
IL-10+ Treg cell
Strategies for Modifying the Gut Microbiota

More Invasive and/or Less Safe

Less Invasive and/or Safer

- Fiber Complex CH20’s
- Loperamide
- Prebiotics
- Systematic Exclusion Diets
- Stopping PPIs
- FODMAP Diet
- Probiotics
- Gut-directed Antibiotics
- FMT

Simrén M et al. Gut doi:10.1136/gutjnl-2012-302167
Treatment Strategies for IBD are Based on our Understanding of Pathogenesis

**Immune modification**
- Steroids
- Thiopurines/methotrexate
- Anti-TNFα biologicals
- Inhibition of other cytokines
- Leukocyte trafficking inhibitors

**Immune stimulation**
- Trichuris suis
- GCSF

**Microbiota manipulation**
- Antibiotics
- Prebiotics
- Probiotics
- Fecal transplantation
- Bacterial derived proteins
- Diet?¹

Data as of Jan 2015

• Antibiotic therapy for Crohn’s Colitis, Pouchitis, and Peri-Anal Disease (including fistula but not ‘enough’ in most cases)

• Rifaxamin for SIBO seen in post op Crohn’s disease; Flagyl Tx

• Diet: Lots of theory and data being looked at
  • Fat, Protein, Fatty Acid Subtypes
  • Micronutrients on Gut microbiome remodeling

• Prebiotics: Data not strong

• Probiotics: Some success in UC but ESP Pouchitis

• FMT for CDI in Setting of Mild to Mod IBD

• FMT for Severe Cdiff in patients on immunosuppression or with severe disease

• FMT for Primary Treatment of IBD: Await more studies
TIMING MAY BE VERY IMPORTANT
Rationale for Earlier Intervention of any sort
Window of Inflammation

Penetrating

Inflammatory

Stricturing

The Microbiome Diet: Evolving Past Paleo
1% Caffeine
9% Human
90% Microbiome
A dinner plate
From our point of view…

Dutton MK, Turnbugh PJ, Curr Opin Clin Nutr Metab Care 2012
A dinner plate from a METAGENOMIC point of view

Ellagic acid
Coffee fiber
Polyphenols

Starch Polysaccharides
Oligosaccharides
SCFAs (acetate, butyrate, propionate, succinate)

Inulin
Fructans
Soy
Isoflavones
Glucosinolates
Xanthohumol
Porphyrans
Lignans
SCFA

Phosphatidylcholine
Heterocyclic amines
Nitrosamines
Amino acids

Bacteria from foods
Probiotics

PRODUCTS
Are We Really Ready for THIS??

Preferred by 59% of consumers over strawberry
# What are Probiotics?

Probiotics are defined as live microbes which when administered in adequate amounts confer a beneficial health effect on the host---WHO 2002

<table>
<thead>
<tr>
<th>Lactobacillus species</th>
<th>Bifidobacterium species</th>
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<tr>
<td>L. acidophilus</td>
<td>B. bifidum</td>
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<tr>
<td>L. casei (rhamnosus)</td>
<td>B. longum</td>
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<td>L. reuteri</td>
<td>B. breve</td>
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<td>L. bulgaricus</td>
<td>B. infantis</td>
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<td>L. plantarum</td>
<td>B. lactis</td>
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<td>L. johnsonii</td>
<td>B. adolescentis</td>
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<td>L. lactis</td>
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<table>
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<th>Others</th>
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<tr>
<td>Bacillus cereus</td>
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<tr>
<td>Non pathogenic Escherichia coli</td>
</tr>
<tr>
<td>Saccharomyces cerevisiae</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Streptococcus thermophilus</td>
</tr>
</tbody>
</table>
Probiotics

NICU: Given to premature babies: Prevent NEC

Asthma

Allergies

IBS: Diarrhea predominant

IBD: UC or Crohn’s;

Pouchitis

SIBO

Post Abx Diarrhea C. Diff

Recurrent UTIs

Lactose intolerance
VSL#3™ IN MAINTENANCE TREATMENT OF ULCERATIVE COLITIS

VSL#3™
1800 billion bacteria/day

20 PATIENTS INTOLERANT OR ALLERGIC TO 5-ASA

15 PATIENTS IN REMISSION AFTER 12 MONTHS
## Common Probiotics

<table>
<thead>
<tr>
<th>Lactobacillus</th>
<th>Bifidobacteria</th>
<th>Streptococcus</th>
<th>E.coli</th>
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<tbody>
<tr>
<td><em>L. acidophilus</em></td>
<td><em>B. bifidum</em></td>
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<td><em>S. salivarius</em></td>
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<td><em>B. adolescents</em></td>
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<td><em>L. reuteri</em></td>
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<td><em>L. brevis</em></td>
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<td><em>L. plantarium</em></td>
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Safety of Probiotics

Generally safe and well tolerated

Bacteremia with LGG
- Can adhere
- Severe infections in patients with significant underlying co-morbidities

Fungemia with *S. boulardii*

Endocarditis with *L. paracasei*
Cases of infection extremely rare

Account for 0.05% to 0.4% of infective endocarditis and bacteremia

Less than 1 case per million people

Review of 143 human clinical trials from 1961-1988

• Over 7500 subjects
• No reported adverse events

FMT: Fecal Microbial Transplant
AKA Fecal or Stool Transplant
The ‘Ultimate’ Probiotic?

WHAT CAN BROWN DO FOR YOU?
Dear Mrs. Clark

I heard you didn't feel good. Well win that happens hear a trick to learn............

JUST GO POOP!

I am not kidding it works with me every morning I fell bad. SO Just remember win you fell bad the first thing you do is POOP!

I Don't fell good.

I've got +1!
AGA Center for Gut Microbiome Research and Education

The mission of the center is “To advance research and education on the gut microbiome in human health and disease.”

FMT Illustrates the Power of the Microbiome

AGA’s new fecal microbiota transplant (FMT) site offers information for physicians and patients.

News
- AGA’s New FMT Site Has Info for Physicians and Patients
- Joint-Society Letter to FDA with FMT Guidance July 2013
- Analysis of the Human Gut Microbiome and Association With Disease July 2013
- AGA Provides FMT Coding Guidance June 2013
- FDA Announcement About IND Requirements June 16, 2013
- AGA Public Statement: Fecal Microbiota Transplant Is a Promising Treatment June 12, 2013
- AGA Provides Fecal Microbiota Transplant Coding Guidance June 5, 2013
- AGA Confirms IND Is Required for Fecal Microbiota Transplantation May 6, 2013
- AGA Joins FDA in Discussions on Fecal Microbiota Transplant May 2, 2013
AGA Website on FMT

The gut microbiome is one of the most promising areas of science today.

Fecal Microbiota Transplant (FMT) illustrates the potential power of the microbiome. This site will keep you up to date on the latest information on this emerging procedure.

Visit the AGA Microbiome Center  Read FMT News Articles

What is FMT?
Physicians have discovered that giving C. difficile patients microbes from the human gut can cure the infection.
Learn More About FMT

View the Patient Brochure on C. difficile Infection
Not sure exactly what’s involved with the procedure? Read up on it.
View the Brochure

Locate a Practitioner
Find a gastroenterologist who performs FMT.
Browse Our Map
FMT Biotech Options

Stool Banks

Fecal Pills

Selective biotype

Autologous-FMT

FDA Approved Synthetic Microbiomes

Eventually????

Figure 1c: Preemptive banking

1. Sample harvested from patient while healthy
2. Sample tested, frozen, long-term storage
3. Release tests, sample sent to physician on demand
4. "Repopulation" with patients' own sample (e.g. after antibiotics courses, chemotherapy)

Figure 2: "Off-the-shelf" model

1. Samples harvested from healthy "qualified" donors
2. Samples tested in pools, frozen, long-term storage
3. Release tests, sample sent to physician on demand
4. Instillation into recipient by physician
Bacterial fingerprints of the donor and recipient stool before and after FMT

Khoruts A. J Clin Gastroenterol Donor Day 0; Patient Day 14; Patient Day 33 2010;44:354-360
History of Fecal Transplant

4th century Chinese Medicine
• Human fecal suspension by mouth for diarrhea related to food poisoning

17th century Veterinary Medicine
• Transfauntation (transfer of cecal contents or fresh feces) from healthy horses to treat horses with diarrhea

WWII: “consumption of fresh warm camel feces has been recommended by Bedouins as remedy for bacterial dysentery; efficacy confirmed by German soldiers in North Africa”

1958: Fecal enema for pseudomembranous colitis
• Micrococcus pyogenes

1983: Fecal enema for C. difficile infection

1991 – 2014: Multiple reports of fecal transplant for C. difficile

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijsen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

ABSTRACT

BACKGROUND
Recurrent Clostridium difficile infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent C. difficile infection.

METHODS
We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the rate of eradication of C. difficile infection at 1 week (primary intention to treat analysis).

From the Departments of Internal Medicine (E.N., A.V., M.N., P.S.), Microbiology (C.E.V.), Gastroenterology (J.F.W.M.B., J.J.K.), and Cardiology (J.G.P.T.) and the Clinical Research Unit (M.G.W.D.), Academic Medical Center, University of Amsterdam, Amsterdam; the Laboratory of Microbiology, Wageningen University, Wageningen (S.F., E.G.Z., W.M.V.); the Department of Experimental and Medical Microbiology, Leiden University Medical Center, Leiden (E.J.K.); and the Department of Gastroenterology, HagaZiekenhuis, The Hague (J.G.P.T.).
Randomized Trial of FMT vs Vancomycin vs Vancomycin Plus Bowel Lavage for Recurrent *Clostridium difficile* Infection

43 patients with recurrent *C. difficile* infection

Initially planned 40 patients in each of 3 arms

Primary endpoint: cure of CDI without relapse within 10 wks

C diff tests at weeks 2, 3, 5, 10

Interim analysis: study terminated early because efficacy already demonstrated

No serious adverse events

FMT for Recurrent Clostridium difficile Infection: Systematic Review and Meta-Analysis

11 studies, 273 patients

Pooled resolution rate, 89%

Trend that lower GI administration had higher resolution rate (91%) than UGI route (81%)

Microbiota fecal transplantation: Stool transfer from obese mice to wild mice

Con conventionally raised donors

Donor

Germ-free Wild type recipients

Turnbaugh et al., Nature 444: 1027-1031
FMT for Recurrent *Clostridium difficile* Infection in Immunocompromised Patients

Multicenter retrospective analysis of 80 pts with recurrent CDI who were immunosuppressed

- Included 36 pts with IBD on immunosuppressants or biologics

Efficacy in IBD population:

- 86% had resolution of CDI with first FMT
- Overall cure rate (including 2\textsuperscript{nd} FMT), 94%

Safety: SAE in 15% within 12 wks post-FMT

- 2 deaths, including one witnessed aspiration while sedated for scope to administer FMT
- SAE rate for IBD patients similar (11%)

5 IBD pts (14%) had disease flare post-FMT, and 3 UC pts underwent colectomy

FMT in IBD Patients with Recurrent Clostridium difficile Infection: Mayo (cont)

After FMT, 92% noted clinical improvement in symptoms and overall well-being

• 1 patient saw no improvement, was C diff positive
• 6 patients had complete resolution
• 6 patients had partial resolution
• Median time to resolution was 2 days (1-14)

No patients stopped IBD therapies

• In fact, 46% required escalation of IBD therapy at some point after FMT despite being C diff negative

Conclusion: Safe and effective for recurrent C. diff, but doesn’t appear to improve the course of IBD


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FMT As Primary Tx in IBD: An Historical Perspective

The year 1989: Kansas City
- A physician (J.D.B.)
- 7 years: Steroid refractory, active & severe UC
- Controlled with α-tocopherylquinone
- Large volume retention enemas with donor flora
- Symptom free for 6 months, off medications, normal endoscopy and no acute inflammation

The year 1989: Australia
- 45/M with UC for 18 mo (pancolitis) and elevated LFTs
- Refractory to sulfasalazine
- Received FMT and asymptomatic in days
- No recurrence at 3 months

FMT for UC: Variable Clinical, Serological, and Microbiological Response

5 pts with moderate to severe UC refractory to standard therapy, 3 days of FMT via NJT and enema

1 pt had clinical response by wk 12, 2 pts had no change, and 2 worsened

All developed fever and elevated CRP immediately after FMT

FMT in IBD and *C. difficile* infection

15 patients received FMT for CDI

In 12 patients

- 12/12: resolution of CDI
- 11/12: marked reduction / complete resolution of diarrhea

FMT resulted in improved response to IBD medications in 6 patients

Anderson JL, Aliment Pharmacol Ther 2012; 36: 503-516
FMT for UC: The Backlash Continues

6 patients with UC refractory to standard therapy received FMT via colonoscopy

All 6 had short-term improvement in 1\textsuperscript{st} 2 weeks

4 of 6 had increased stool frequency by day 30

No change in fecal calprotectin or CRP

No patients achieved remission

Total Mayo Score Over the Course of the Study

FMT for IBD: Systematic Review & Meta-Analysis 2014

18 studies (9 cohort, 8 case reports, 1 RCT), 122 patients (79 UC, 39 Crohn’s, 4 IBDU)

Overall response rate, 45%

- 22% UC
- 61% Crohn’s

Conclusion: safe, but effectiveness highly variable

Overall response in cohort studies, 36.2%

Colman RJ & Rubin DT, J Crohns Colitis 2014 online early.
**UC Patients Failed to Show Significant Improvement After FMT: Placebo-Controlled RCT**

Prospective, double blind RCT

- 53 active UC patients (Mayo score ≥ 4 with endoscopic Mayo subscore ≥ 1)
- Negative for *C. difficile*
- 42% on steroids, 19% on immunomodulators, and 9% on biologics
- 6 weeks of once-weekly fecal microbiota therapy delivered by retention enemas (n = 27) vs placebo delivered by water enemas (n=26)

**Results**
- No difference in remission between groups at week 6 (assessed by Mayo score, IBDQ)
- No adverse events related to FMT

**Limitations**
- Short duration (6 weeks)

Safety of FMT in Inflammatory Bowel Disease

- Some safety concerns remain
  - Common to have transient fever and some non-specific GI symptoms after FMT
  - Reports of worsening IBD after FMT\(^1\,^2\)
  - Lack of efficacy is a safety concern
  - Other safety outcomes have been described in non-IBD: new immune conditions (ITP, RA, peripheral neuropathy, Sjogrens)\(^3\)

- Unknown consequences of patients doing this at home

IND through FDA Center for Biologic Evaluation & Research required in order to perform FMT in IBD

Current sponsors:
- David Rubin, University of Chicago (UC)
- Alan Moss, Beth Israel-Deaconess in Boston (CD)

Caution is Warranted

• Why FMT may have failed in some studies:
  1. Wrong mechanism
  2. Wrong patients (severe and medically refractory)\(^2,3\)
  3. Additional confounders (such as smoking, diet, medications)
  4. Wrong stool donor (?)
  5. Other factors affecting the microbiome

• Future FMT trials should identify a patient population that is likely to respond such as: newly diagnosed or patients with milder disease.

Conclusions

Fecal microbial transplantation appears to be highly effective in eradicating recurrent *Clostridium difficile* infection

- In the subset of IBD patients with recurrent CDI, FMT also appears to be highly effective and reasonably safe including in patients on immunomodulators and biologics

It is far from certain that FMT will be effective for the treatment of IBD itself in the absence of recurrent CDI

- Placebo-controlled RCT of fecal enemas in UC was negative
FMT New Questions-New Directions

Ongoing US FMT Verification Study:

- RCT - FMT vs. Abx plus Auto-Re-Infusion (sham) of CDI? FMT in children (initial studies safe)

FMT in Immunosuppressed AIDS; ChemoTx

FMT vs. Newer Abx and Novel ImmunoTx for CDI

FMT: Encapsulted vs. Frozen vs. Fresh Stool;

Universal Donor; Unrelated Donors; Stool Banks

Stool Pill-prophylaxis during Abx (Hx of CDI)?

FMT NonCDI GI: IBD; IBS; Constipation; NASH

FMT for Non-GI: Obesity; Metabolic Syndrome; DM; Neurodegenerative; Autoimmune/Autoinflammatory Dx Atopy/Allergy; RA; ITP; Autism; Depression
Conclusions

1. Intestinal inflammation induces dysbiosis via the generation of metabolites that provide a selective growth advantage for disease-producing pathobionts (e.g. facultative anaerobes).

2. Failure to properly regulate this acute (and reversible) immune response allows for outgrowth and invasion of colitogenic microbes; This triggers the initiation and perpetuation of chronic gut inflammation.

3. Disease-producing pathobionts are not classic pathogens as they do not elicit acute or chronic inflammation in healthy wild type or lymphopenic recipients.
Summary: The Emerging Role of the Microbiome in Treatment of IBD

- The concept of modulating fecal microbiota as cause or treatment for IBD is not new.
- Appreciation for the heterogeneity and distinct differences between patients with IBD requires a selective approach to the study of this potential therapy.
- Safety and protection of vulnerable patients must be paramount in the development of future studies of microbiota manipulation.
- FMT is not ready for routine use in IBD at this time, but there is sufficient support to continue a clinical trial program.
- Future approaches should include dietary modifications and microbiome assessments.
PUBLIC SPEAKING IS THE ART OF DILUTING A TWO-MINUTE IDEA WITH A TWO-HOUR VOCABULARY.

John F. Kennedy

THANKS FOR LISTENING
Questions ?