Modulating the Gut Microbiome: The Role of Probiotics & Prebiotics

Presented by:
Stephen Olmstead, MD

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Modulating the Gut Microbiome: The Role of Probiotics & Prebiotics

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Chief Science Officer ProThera Inc
The Human Intestinal Microbiota

- 100 trillion microorganisms
- 10 x number human cells
- >150 x number human genes
- >1800 genera by rRNA
- 15,000-36,000 species by rRNA
- >500 cultured species
- Dominated by 2 divisions
  - Firmicutes (64%)
  - Bacteroidetes (23%)
- 99% anaerobic

The Intestinal Microbiota Organ

- Unique & vital organ
- Weighs 1.5 Kg
- Metabolic activity rivals liver
- Immune & GI maturation
- Normal CNS development
- Colonization resistance
- Immune system modulation
- Metabolic modulation

Colonic mucosa scanning electron microscopy
Transfer of Maternal Microbiota

Maternal microbiota secreted in breast milk

Maternal microbiota transferred to lymphocytes

Dendritic cells sample maternal microbiota

Breast Milk *Bifidobacterium* Content

Quantitative Real-Time PCR
43 Nursing Mothers

Log cells/mL

Gueimonde et al. 2007
Prenatal Microbial Exposure
Bacteria Isolated from Amniotic Fluid & Meconium

- Enterococcus
- Staphylococcus
- Streptococcus
- Leuconostoc
- Bifidobacterium
- Rothia
- Enterobacter
- Klebsiella
- Parabacteroides
- Bacteroides

Changes in Microbiota with Age

- **Clostridium perfringens**
- **Bifidobacterium**
- **Escherichia coli, Enterococcus**
- **Lactobacillus**
- **Bacteroides, Eubacterium, Peptococcaceae**

GI Microbiota – A Balanced Microecosystem

Potentially Harmful Bacteria
Diarrhea/constipation
Pain
Infections
Production of Toxins
Inflammation

Pseudomonas
Proteus
Staphylococci
Clostridia

Potentially Helpful Bacteria
Inhibition of exogenous and/or harmful bacteria
Modulation of immune functions
Aid in digestion and/or absorption
Stimulate GI motility
Synthesis of vitamins

Potential Probiotic Bacteria

Enterococci
E. coli
Lactobacilli
Streptococci
Eubacteria
Bifidobacteria
Bacteroides

Gibson GR. J Nutrition 1995;125:1401-12
Metagenomic Analysis of the Human Distal Gut Microbiome

28-y/o female

- Methanobacteria 9.1%
- Misc. bacteria 3.2%
- Spirochaetes 2.2%
- Bacteroidetes 2.8%
- Fusobacteria 1.7%
- Proteobacteria 9.1%
- Actinobacteria, other 4.8%
- Bifidobacteriales 21.8%

37-y/o male

- Methanobacteria 7.9%
- Misc. bacteria 3.3%
- Spirochaetes 2.2%
- Bacteroidetes 3.4%
- Fusobacteria 2.0%
- Proteobacteria 9.0%
- Actinobacteria, other 2.6%
- Bifidobacteriales 5.3%
- Clostridia 35.9%

Direct blastX contig analysis of DNA sequencing
~78 million base pairs

Gill et al. Science 2006;312:1355-9
Gut Microbiota Enterotypes

33 Sanger metagenomes
- Danish
- French
- Italian
- Spanish
- Japanese
- American

85 Sanger metagenomes
- Danish

154 pyrosequenced 16S sequences
- American females

Microbiota Maintains Intestinal Integrity

Lumen

Pathogens

Defensins

Microcins

Mucus

SCFA

Commensal bacteria

Epithelium

Lamina propria/
Peyer’s patch

PMN

TNF
IFNγ
IL-1β
ROS
NO

IL-6
IL-8
IP-10

TGFβ
IL-10

T_{reg}

T_{eff}

Genova Diagnostics
Gut Associated Lymphatic Tissue
T Cell Activation & Differentiation

Epithelium

Lumen
Mucosa

Antigen Presentation

Th0
Th1
Th2
Th9
TReg
Th17
Th22

IL-10
IL-4
IL-5
IL-17A
IL-21
IL-22
TGFβ
IFNγ

IL-9 → ASTHMA
IL-10 → ALLERGY
TGFβ → TOLERANCE
IL-17A → AUTOIMMUNE DISEASES

Over Expression

O’Shea & Paul. Science 2010;327:1098-1102
Modulating the Gut Microbiome

• Diet

  • Probiotics
  • Prebiotics
  • Antibiotics

• Fecal transplantation
Definitions

Probiotics

1965   Lilly & Stillwell - microbe produced growth promoting factors

1989   Fuller - live microbial feed supplements, which benefit the host by improving intestinal microbial balance

2001   “viable microbial food supplements which beneficially influence the health of humans.”
       International Life Sciences Institute Europe, consensus document
Definitions

Prebiotics

Gibson & Roberfroid - non-digestible substances that stimulate the growth and/or metabolic activity of selected GI microbes leading to health benefits

Synbiotics

Gibson & Roberfroid - a food or supplement that combines pro- & prebiotics
Probiotics - A Brief History

• Essential probiotics
• Probiotics on fruit & vegetables
• 10,000 BCE fermented beverages
• 3,000 BCE yogurt
• Hippocrates (460-370 BCE)
  Sour milk for GI disorders
• Pliny the Elder (23-79 CE)
  Health benefits of sour milk
• Francis I (1476-1531)
  Cured of dysentery by yogurt
The Godfather of Probiotics

“The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and replace the harmful microbes with useful microbes.”

*The Prolongation of Life* 1907

Eli Metchnikoff
Nobel laureate 1908
1848-1916
Types of Probiotics

- **Lactic acid bacteria**
  - *Lactobacillus* species
  - *Bifidobacterium* species
  - *Streptococcus thermophilus*
  - *Enterococcus faecium*
  - *Lactococcus* species
  - *Leuconostoc* species
  - *Pediococcus* species

- **Non-lactic acid bacteria**
  - *Bacillus* species
  - *Propionibacterium* species
  - *E. coli* Nissle 1917

- **Non-pathogenic yeast**
  - *Saccharomyces boulardii*
**Lactobacillus Characteristics**

- Gram-positive, non-sporulating rods or coccobacilli
- Homofermentative (primarily lactic acid)
- Heterofermentative
  - (lactic acid, CO₂, ethanol & acetic acid)
- Digest & metabolize proteins & carbohydrates
- Synthesize B vitamins & vitamin K
- Catabolize bile salts
- Enhance innate & acquired immunity
- Inhibit pro-inflammatory mediators
- Antimicrobial activities against array of pathogens:
  - *Pseudomonas*, *E. coli*, *Staph. aureus*, *Salmonella*,
  - *Shigella*, *C. difficile*, *Candida* & *Helicobacter pylori*
Lactobacillus Probiotics

- L. acidophilus
- L. brevis
- L. bulgaricus
- L. casei
- L. crispatus
- L. fermentum
- L. gasseri
- L. helveticus
- L. jensenii
- L. johnsonii
- L. paracasei
- L. plantarum
- L. reuteri
- L. rhamnosus
- L. salivarius
Lactobacillus acidophilus

- Prototypic probiotic
- Many strains reclassified
- Transient GI species
- Obligate homofermentative; DL-lactate isomers
- Resistant to acid, bile, pepsin & pancreatin
- >20 known peptidases; breaks down casein & gluten
- Ferments lactose, other sugars & polysaccharides
- Antagonizes array of pathogens
- Reduces GI concentrations of carcinogenic enzymes
Lactobacillus rhamnosus

- Most studied probiotic
- Relatively fragile
- Transient GI species
- Facultative heterofermentative; L(+)-lactate isomer
- Excellent colonic mucosal adherence
- More peptidases than any other Lactobacillus
- Enhances innate & acquired immunity
- Inhibits proinflammatory cytokines
- Antagonizes rotavirus & C. difficile
- Suppresses enterohemorrhagic E. coli internalization
Lactobacillus casei

• Hardy, adaptive probiotic
• Closely related to L. rhamnosus
• Transient species
• Proline-specific peptidases
• Facultative heterofermentative; L(+)-lactate isomer
• Critical for dendritic cell differentiation
• Augments number intestinal IgA-producing cells
• Decreases proinflammatory cytokines secretion
• Inhibits EHEC intestinal cell adherence & invasion
Lactobacillus plantarum

- Ubiquitous on plants
- Lacking in modern diets
- Transient GI species
- Facultative heterofermentative; DL-lactate isomers
- Highly resistant to acid & bile
- Facilitates induction IL-10, central regulatory cytokine
- Decreases production of inflammatory mediators
- Supports intestinal barrier function
- Reduces translocation of gut flora
- Antagonizes C. difficile
**Bifidobacterium Characteristics**

- Gram-positive, non-sporulating rods or Y-shaped
- Strictly anaerobic & fastidious
- Unique metabolic hexose pathway – “Bifidus shunt”
- All metabolize lactose
- Ferment non-digestible oligosaccharides
- Synthesize B vitamins & vitamin K
- Enhance innate & acquired immunity
- Inhibit proinflammatory mediators
- Inhibit pathogens via organic acids & $\text{H}_2\text{O}_2$
Bifidobacterium Probiotics

- *B. adolescentis*
- *B. animalis*
- *B. bifidum*
- *B. breve*
- *B. infantis*
- *B. lactis*
- *B. longum*
- *B. thermophilum*
**Bifidobacterium longum**

- Often dominant GI bifidobacteria
- Ferments array of oligosaccharides
- Resistant to bile salts
- Inhibits enterotoxigenic *E. coli* receptor binding & translocation
- Inhibits *Clostridium* proliferation
- Enhances GI sIgA response to dietary antigens
- Modulates cytokine response to respiratory antigens
**Bifidobacterium bifidum**

- Present in large numbers
- Reduced in allergic infants
- Populations decline with age
- Suppresses total & antigen-specific IgE production
- Enhances IgM & IgG responses to select antigens
- Activates B cell IgA secretion
- Enhances IgA response to *C. difficile* toxin A
- With *L. acidophilus*, supports normal flora during antibiotic Rx; reduces (+) *C. difficile* toxin A testing
Bifidobacterium infantis

- Frequent in infants
- Rare in adults
- Suppresses populations of Bacteroides vulgarus
- Reduces proinflammatory cytokine production
- Improves cytokine ratios in IBS
- With L. acidophilus, reduces risk of necrotizing enterocolitis in very low birth weight infants
- Promotes normal microbiota in children with diarrhea
Bifidobacterium breve

• Reduces *Bacteroides fragilis* & *C. perfringens* populations
• Improves weight gain in very low birth weight infants
• Stimulates Peyer’s patch B cell proliferation
• Resistant to acid, bile, pepsin & pancreatin
• Enhances B cell antibody production
• Eliminates *Camphylobacter jejuni*
• Antagonizes rotavirus & decreases rotavirus shedding
**Bacillus Characteristics**

- Gram-positive, sporulating rods
- Facultative anaerobes
- Fermentation end products include lactate, acetate, ethanol, acetoin, 2,3-butandiol
- Transient commensals
- Used in traditional fermented fish, manioc, soy foods
- Enhance innate & acquired immunity
- Inhibit pathogens via bacteriocins & lipopeptides
- Promote colonocyte health via heat shock proteins
Bacillus Probiotics

- B. cereus
- B. coagulans
- B. clausii
- B. laterosporus
- B. licheniformis
- B. pumilus
- B. subtilis
Streptococcus thermophilus

- Yogurt & cheese starter
- Highly adapted to lactose
- Transient GI species
- Protocooperation with *L. bulgaricus*
- Formate, acetoin, acetylaldehyde, diacetyl & acetate
- Inhibits pathogen proliferation
- Reduces DNA damage & premalignant lesions
- Clinical uses from rotavirus to ulcerative colitis
- Protection from pathogenic *Streptococcus* spp.
**Saccharomyces boulardii**

- Transient, non-pathogenic yeast
- Heat & pH resistant
- Active ingredient in Asian medicinal teas
- Increases brush border enzyme activities
- Secretes leucine aminopeptidase; supports against dietary protein allergies
- Increases gut short-chain fatty acid concentrations
- Increases intestinal sIgA; crypt cell Ig receptors
- Protease that inhibits *C. difficile* toxins A & B
- Antagonizes *Candida albicans* in the gut
- Effective against *Entamoeba hystolytica* & *Giardia*
Probiotics - Documented Uses

• Antibiotic-associated diarrhea
• *C. difficile*-associated diarrhea
• Community acquired diarrhea
• Traveler’s diarrhea
• Inflammatory bowel disease
• Irritable bowel disease

• Vaginal dysbiosis
• Urinary tract infections
• Allergies, atopic dermatitis, eczema
• Lactose intolerance
• Hyperlipidemia
Antibiotic-associated Diarrhea

- Disrupted GI microbiota
- Associated with ↓ short-chain fatty acids (SCFA)
- Occurs in 5-39% of adults; 11-50% of children
- Up to 50% of cases due to *Clostridium difficile*
- High relapse rate with *Clostridium difficile*
- Onset up to 2 mos. post antibiotics
Meta-analysis: Probiotics & Antibiotic-associated Diarrhea

Of 25 RCT:
Overall RR = 0.43 (95% CI 0.31-0.58)
Probiotics, Prebiotics & Antibiotics

- Use *Saccharomyces boulardii* 10 billion CFU/d
- Use *Lactobacillus rhamnosus* 5 billion CFU/d
- Use multistrain formulation with *Bifidobacterium*
- Consider prebiotics to increase SCFA-producing populations - *Eubacterium, Roseburia*
- Use during antibiotic Rx
- Take 1 hr before or 2 hrs post antibiotic dose
- 30 day total duration
Inflammatory Bowel Disease (IBD)

• Crohn’s disease
• Ulcerative colitis
• Pouchitis
• Abnormal response to certain commensal bacteria
• High numbers of *Bacteroides, Enterobacteriaceae, & Peptostreptococcus*
• Low numbers of *Bifidobacterium*
IBD Animal Model

HLA B_{27} Transgenic Rat

Germ-free, no colitis

Cecal bacteria

Bacteroides vulgatus

E. coli

Lactobacillus rhamnosus + cecal bacteria

Aggressive colitis

Colitis

No Colitis

Summary of 25 RCTs of Probiotics for IBD

Treatment of Crohn’s Disease by *S. boulardii*

32 patients with CD in remission

Mesalamine (3 g/d) vs. mesalamine (2 g/d) & *S. boulardii* (2 x 10^{10}/d)

6 mos. Rx

Clinical Relapses

- **Control:** 37.5%
- **S. boulardii:** 3.2%

p < 0.05

Prevention of Post Operative Crohn’s Disease by VSL #3

40 patients with CD in remission

Mesalamine (4 g/d) vs. VSL #3 (3 x 10^{11}/d) after rifaximin

9 mos. Rx

Clinical Relapses

- Control: 40% with % relapse
- VSL #3: 20% with % relapse

p=NS

Compieri et al. Gastroenterol 2000;118:A781
Treatment of Pouchitis by VSL #3

**Gionchetti 2000**
- 40 adults (2 x 10^{12} CFU/d)

**Mimura 2004**
- 36 adults (3 x 10^{12} CFU/d)

**Gionchetti 2003**
- 40 adults (9 x 10^{11} CFU/d)

Followed for relapses (9-12 months)

![Bar chart showing clinical relapses](chart.png)

- **Gionchetti 2000**
  - 100% relapses
- **Mimura 2004**
  - 56% relapses
- **Gionchetti 2003**
  - 40% relapses

* *p<0.05*
# Prebiotic Trials in IBD

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<td>DBRCT</td>
<td>Inulin</td>
<td>24 g/d</td>
<td>Ileal pouch-anal anastomosis. Pts. (20) with pouchitis randomized for 6 wks &amp; assessed clinically, endoscopically &amp; histologically</td>
<td>Inulin lowered pH, increased butyrate, reduced <em>B. fragilis</em>, decreased inflammation, &amp; effectively treated pouchitis</td>
<td>Welkers et al. <em>Dis Colon Rect</em> 2002;45:621-7</td>
</tr>
<tr>
<td>DBRCT</td>
<td>Inulin/FOS + <em>B. longum</em> 2x10^{11}/d</td>
<td>6 g/d</td>
<td>Pts. (18) with active ulcerative colitis randomized for 1 mo. &amp; assessed clinically, sigmoidoscopically &amp; histologically</td>
<td>Significant clinical improvement. Improved sigmoidoscopy scores. Decreased tissue inflammation. Increased healing.</td>
<td>Furrie et al. <em>Gut</em> 2005;54:242-9</td>
</tr>
</tbody>
</table>
Probiotics, Prebiotics & IBD

• Crohn’s Disease
  – Use *Saccharomyces boulardii* 10 B CFU/d
  – 3 mos on/1 mo off indefinitely
  – Inulin-based prebiotics 6-15 g/d
  – Multispecies probiotics (200-400 B CFU/d)

• Ulcerative colitis
  – Use *Saccharomyces boulardii* 10 B CFU/d
  – Multispecies probiotics (400-800 B CFU/d)
  – Inulin-based prebiotics 6-15 g/d

• Pouchitis
  – Multispecies probiotics (200-400 B CFU/d)
  – Inulin-based prebiotics 6-15 g/d
Irritable Bowel Syndrome (IBS)

- Common (10-20% adults) benign disorder(s)
- Abdominal pain, bloating, diarrhea/constipation
- Intestinal transit disturbances
- Heightened visceral sensitivity
- Altered GI microbiota
  - Decreased *Lactobacillus, Collinsella*
  - Increased *Clostridium, Ruminococcus, Veillonella*
Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors

Meta-analysis of Probiotics & IBS

- 19 RCTs; 1650 Pts
- Probiotics significantly better than placebo
  
- RR = 0.71 (95% CI 0.57-0.88)
- NNT = 4 (95% CI 3-12.5)
- Efficacious organisms/formulas
  - *Bifidobacterium infantis*
  - *Lactobacillus plantarum*
  - High-dose, multispecies formula
- Difficult population to study
Probiotics & IBS

• High-dose (200-400 B CFU/d) multispecies probiotic

• Consider inulin-based prebiotic 10-15 g/d

• If there is a response, indefinite therapy

• Assess for food allergies/sensitivities

• Rule out gluten sensitivity

• Consider digestive enzymes
Allergies, Asthma & Dermatitis

- Pandemic effecting >20% of world’s population
- Incidence of asthma ↑ by 50% from 1980 to 2000
- Related to post industrial lifestyle (Old Friends)
- Altered GI microbiota is implicated
Probiotics Inducing Immunotolerance

- *L. casei*
- *L. bulgaricus*
- *L. paracasei*
- *L. rhamnosus*
- *B. bifidum*
- *B. breve*
- *S. thermophilus*

T cell & dendritic cell
Probiotics & Atopic Dermatitis/Eczema

• 10 RCT
• 90% show significant reduction in incidence/severity
• Effective at prevention when given to pregnant women
• Effective given to breast-feeding women
• Effective given to infants in formula
• Protection up to 4 (RR=0.57) & 7 yrs (RR=0.64)
• Probiotics shown to be effective
  – *L. rhamnosus*, *L. acidophilus*, *B. lactis*, *L. reuteri*
  – Combination formulae effective
Probiotics & Allergic Rhinitis

• Probiotics reduce Sx & improve QOL measures

• Probiotics shown to be effective
  – L. bulgaricus, L. paracasei, S. thermophiles
  – Combination formulae effective
Prebiotics & Allergies

• GOS & oligofructans increase regulatory T cells
• Prebiotics upregulate sIgA
• GOS/oligofructans ↓ atopic dermatitis in infants
• GOS/oligofructans ↓ allergies to cow’s milk
• GOS/oligofructans ↓ allergies, eczema & wheezing up to 18 mos post Rx
• beta-Glucans (1→3; 1→6) reduce allergic rhinitis
• beta-Glucans (1→3; 1→6) reduce IgE levels
Prebiotics, Probiotics & Allergies

- Consider pre- & probiotics for pregnant women
  - Multispecies, broad spectrum 50-100 B CFU/d
- Consider low D(-)-lactate probiotics for infants
  - Multispecies Infant Formula 10-20 B CFU/d; doses up to 110 B CFU/Kg safe
- Consider GOS/beta-glucan for bottle-fed infants
  - Use 225-550 mg/d until weaned
- Multispecies, broad spectrum for children & adults
  - 50-100 B CFU/d indefinitely if response
- GOS/beta-glucans for children & adults
  - 5-10 g/d indefinitely if response
Probiotic Formulation Selection

• Monostrain probiotics
• Multistrain probiotics
• Multispecies probiotics
• Protocooperation & synergism
• ? antagonisms among species - no evidence
• Efficacy of multispecies formulation for ADD, IBS, URI, UC & pouchitis
Are Probiotic Benefits Strain-specific?

- Strain-specific benefits a marketing claim
- Uncritically echoed by academics & regulators
- Validity requires head-to-head studies - Rare
- *L. rhamnosus* GG has unique pili
- Pili not linked to clinical benefit
- Multiple strains & species have benefit in studies
- Toxicity definitely strain-specific
Lactobacillus acidophilus Gene Sequencing

No significant differences between patented *L. acidophilus* NCFM & *L. acidophilus* La-14

- Genome 99.98% identical
- Single 416-bp deletion in ABC transporter
- 16 single-base pair indels
- 95 SNPs

*L. acidophilus* NCFM Genome
Probiotic Dosing

• Start low – 10-25 billion CFU/d

• Go slowly – increase dose weekly or as tolerated

• Minimizes gas, abdominal discomfort, diarrhea
Probiotic Dosing

With or without food?

Stomach pH:
- Fasting: 0.8 – 1.5
- With food: 5 – 7

Transit time:
- 30 min – 1 hr

Take with food.
Probiotic Safety

• Daily doses >1 trillion CFU safe in adults;
  110 billion CFU/Kg in infants

• *Lactobacillus* bacteremia rare; usually endogenous

• *Bifidobacteremia* only in bowel perforation or PID

• *S. boulardii* fungemia in Pts w/ CV catheters

• Probiotics safe in immunosuppressed patients

• Probiotics safe in hospitalized & surgical patients
Conclusions: Modulating the Gut Microbiome
The Role of Prebiotics & Probiotics

• Use of multispecies probiotics supported for a variety of GI conditions
• Use of S. boulardii supported for AAD, CDAD, IBD, & traveler’s diarrhea
• Use of multispecies probiotics supported for prevention & treatment of allergic disorders
• Prebiotics show benefit for IBD and allergies
• Clinical trials to document formulation efficacy
• Outcomes studies - aging, cancer prevention
Questions?

Moderator: Michael Chapman, ND

Presenter: Stephen Olmstead, MD

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