Host-Gut Microbiota Metabolic Interactions

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Objectives

At the conclusion of the activity, the audience should be able to:

1. Define prebiotics, probiotics and synbiotics
2. Outline the influence of delivery type, feeding type and environment on bacterial colonization of a newborn’s intestinal tract
3. Explain how the intestinal microflora influences immune responses
4. Appraise the research that supports tolerance, safety and efficacy of probiotic bacteria in specific medical conditions
Objectives

At the conclusion of the activity, the audience should be able to:

1. “Understand how these trillions of bacteria orchestrate your physiology; including thoughts, food cravings and level of body fat”

2. “Help patients tune up their metabolism, balance blood sugar and reduce inflammation all by increasing the health of gut microbiome”
Intestinal Microflora

• Are a complex ecosystem that depend on multiple host and environment factors
• A balanced intestinal ecosystem is essential for survival
• Intestinal bacteria support gut mucosal structure and function
• Intestinal bacteria are critical in inducing maturation and adequate gut barrier function and immune response (cellular and humoral)
Adult Microbiota: A Complex Ecosystem

**Esophagus**
- No own microbiota
- Microbes from food and oral cavity

**Duodenum**
- $10^3$-$10^4$ CFU/g
- *Bacteroides*
- *Candida albicans*
- *Lactobacillus*
- *Streptococcus*

**Stomach**
- $10^4$ CFU/g
- *Candida albicans*
- *Helicobacter pylori*
- *Lactobacillus*
- *Streptococcus*

**Jejunum**
- $10^5$-$10^7$ CFU/g
- *Bacteroides*
- *Candida albicans*
- *Lactobacillus*
- *Streptococcus*

**Ileum**
- $10^7$-$10^8$ CFU/g
- *Bacteroides*
- *Clostridium*
- *Enterobacteriaceae*
- *Enterococcus*
- *Lactobacillus*
- *Ruminococcus*
- *Streptococcus*

**Colon**
- $10^10$-$10^{11}$ CFU/g
- *Bacteroides*
- *Bacillus*
- *Bifidobacterium*
- *Clostridium*
- *Enterococcus*
- *Eubacterium*
- *Fusobacterium*
- *Peptostreptococcus*
- *Ruminococcus*
- *Streptococcus*

500 - 1000 species
Mucus (Mucin) Keeps pathogens from invading

Tight Junctions (between cells) Decrease gut permeability

Immune cells
Gut-associated lymphoid tissue (GALT)
70% of immune cells are located in the GI tract
Innate: Macrophages, White cells, Mast cells
Adaptive: T and B lymphocytes
Role of Intestinal Microflora

- Occupy adhesion sites of other bacteria
- Fermentation of substrates
- Metabolism of proteins, bile acids, choline
- Vitamin synthesis

**Modulate gut immune function**
- Barrier function (non-immune factors)
- Immune stimulatory function
  - Innate immunity
  - Adaptive immunity
Bacteria support Gut Barrier and Immune Function

• Gut microflora help support gut barrier function, part of the **innate immune response**
  » ↑ Mucin production
  » ↓ Permeability
• Gut microflora help support the **adaptive immune response**
  • Generate IgA activity (humoral)
  • Balance in T helper cell subclasses (cellular)

Determinants of Intestinal Microflora

- Ingested bacteria
- Original bacterial inoculum
- Breast milk (Including skin microbes)
- Newborn
- Environment
Bacterial colonization of the neonatal gut: delivery and feeding

- Vaginal delivery: anaerobic bacteria, primarily Bacteroides, Lactobacillus, Prevotella, and Atopobium
- C-section: delayed colonization by anaerobes; primarily non-E. coli Enterobacteriaceae (flora resembles hospital more than mom!!!)
- Breast-fed
  - lactobacilli and bifidobacteria outnumber Enterobacteriaceae 1000-fold
  - More adult pattern after weaning: fewer E. coli and Clostridium and more Bacteroides and Gram+
- Formula fed
  - flora develops quicker
  - primarily Enterobacteriaceae (E. coli)
  - iron fosters growth of more complex flora
Acquisition of Indigenous Flora by the Newborn

- Gestational age, mode of delivery, type of feeding → all can affect formation of the newborn’s indigenous flora
  - VLBW infants: Intestinal colonization delayed, development of anaerobic flora diminished
  - Infants born by Cesarean section → delayed intestinal colonization with anaerobic bacteria, and gut colonization can be altered for as long as 6 months after birth

Development of Intestinal Microbiota

Weaning

Bifidobacteria
(Anaerobic)

Rapid accumulation of anaerobic growth

Anaerobes

Bacteroides
Clostridia

Coliforms
Staphylococcus
Klebsiella
Salmonella
Shigella
Lactobacillus
Streptococci
Enterococcus

CRITICAL PERIOD

Day 1-3
Microbiota influenced by:
Genetics
Mode of delivery

Day 4 – 10
Microbiota influenced by:
Feeding type
Environmental exposure

Day 11 - 120

Microbial diversity

- Occurs over the first few weeks of life
- Forms a complex anaerobic community
- Coincides with activation of hypothalamic pituitary adrenal axis
- Impacts the enteric nervous system
Intestinal Microbiota: A Balanced Ecosystem

**Potentially Harmful Bacteria**
- Diarrhea/constipation
- Infections
- Production of Toxins
- *Pseudomonas*
- *Proteus*
- *Staphylococci*
- *Clostridia*

**Potentially Helpful Bacteria**
- Inhibition of exogeneous and/or harmful bacteria
- Stimulation of immune functions
- Aid in digestion and/or absorption
- Synthesis of vitamins
- *Enterococci*
- *E. coli*
- *Lactobacilli*
- *Streptococci*
- *Eubacteria*
- *Bifidobacteria*
- *Bacteroides*

**Potential Probiotic Bacteria (When Ingested)**

"The anaerobic ones are just sitting there, but the aerobic bacteria are doing jumping jacks, sit-ups, leg lifts...."
Microbial metabolites

- Affect enteroendocrine cells of the gut
- Secrete a variety of metabolically related peptides connected to food intake, lipid storage, energy homeostasis
- Short Chain Fatty Acids (SCFAs):
  - act through G protein–coupled receptors, such as the GPR41 receptor expressed by enteroendocrine cells
Microbiome and Age

- Gut microbiota appears to become more stable throughout adulthood.
- Adolescents have a higher abundance of bifidobacteria and clostridia than adults.
- After age 60 with immune senescence, increase in facultative anaerobes, shifts in the ratio of Bacteroidetes to Firmicutes and marked decrease in bifidobacteria.
Development of Intestinal Microbiota

- **Bifidobacteria** (Anaerobic)
  - Rapid accumulation of anaerobic growth

- **Anaerobes**
  - Bacteroides
  - Clostridia
  - Coliforms
  - Staphylococcus
  - Klebsiella
  - Salmonella
  - Shigella
  - Lactobacillus
  - Streptococcus
  - Enterococcus

- **Facultative anaerobes**

- **Microbiota influenced by:**
  - Genetics
  - Mode of delivery
  - Feeding type
  - Environmental exposure

Birth

- Vaginal delivery
- Breast feeding

**Promote**

- Establishment of “healthy” intestinal microbiota
- Predominance of bifidobacteria

**Probiotic bifidobacteria**

- Development of adequate gut barrier function
- Development of adequate immune response

- C-section
- Formula feeding
- Antibiotic use
- Environment (hospital & sterility)

**Hinder**
Intestinal Microflora and Feeding Type* (%)

Breast fed
- Bifidobacteria
- Bacteroides
- Coliforms

Formula fed
- *representative subjects

Harmsen JPN 2000
Chronic Disease Prevalence in the last 50 Years

Decrease in infections is associated with increase immune disorders

In the last 100 years, we drastically changed our ingestion of microbes and our microbial environment.
The Hygiene Hypothesis

More sterile foods
Decreased consumption of fermented foods
Less Exposure to LPS from Gram-negative bacteria (animals, pets)
Urban life
Antibiotics

Less exposure to bacteria

Elie Metchnikoff
(1845-1916)

Ingestion of Bacteria Proposed as Beneficial

• Suggested that ingested bacteria could have positive influence on normal microflora in intestinal tract

• Hypothesized that Lactobacilli were important for human health and longevity

• Promoted yogurt and fermented foods as healthy
Probiotics

• “Pro-biotics” mean “for life”
• Live microorganisms, which when consumed in adequate amounts, confer a health effect on the host
• Live microbial food supplement which affects host animal by improving “microbial balance”
• Examples: yeast, Lactobacilli, Bifidobacteria
• Example: feeding probiotics to chickens lessens colonization with Salmonella
A probiotic “should”

- Be nonpathogenic in nature
- Be resistant to destruction by technical processing
- Be resistant to destruction by gastric acid and bile
- Adhere to or transiently colonize intestinal epithelial tissue
- Provide a measurable benefit to the host
Common Probiotics

• **Lactobacillus**
  – can adhere to gut mucosa
  – L. acidophilus, L. rhamnosus GG, L. bulgaricus

• **Bifidobacteria**
  – predominant colonic flora of breast fed infant
  – B. bifidum, B. longum, B. breve, B. infantis, B. animalis

• Both are normal intestinal flora
• Both can be recovered in the stool after ingestion
  - suggests colonization of gut
Prebiotics

• Pre = before
• Dietary substance which PROMOTES the growth of beneficial gut flora
Best Studied Prebiotics: Oligosaccharides – Fiber-like Substrates

- **Milk Oligosaccharides**
  - Galacto-oligosaccharides (GOS)
  - Found in human breastmilk

- **Plant Oligosaccharides**
  - Fructo-oligosaccharides (FOS)
    - Examples: inulin from chicory root, onion, wheat, garlic, artichoke, banana

Carabin I & Flamm W. Reg Toxicol Pharm 1999
Synbiotics

• Syn = together, with, joined
• Synbiotics = prebiotics + probiotics
• Example:
  – combining live active probiotic strains and several plant fibers in one product
Probiotics

i.e. specific Bifidobacteria and Lactobacilli

Direct impact
Support Gut Barrier function throughout the GI tract
Support GI and systemic immune function

Substantial Evidence
Extensive clinical research
Positive clinical outcomes including treatment of acute diarrhea, antibiotic associated diarrhea and NEC

Prebiotics

Stimulate growth of multiple species of bacteria (preferentially some bifidobacteria, which are already present in the colon).

Indirect Impact
Some of these species may support gut barrier function in the colon.
May support and modulate immune function.

Limited Evidence
Limited clinical research
Limited areas of benefit

Antibiotics

• Anti = against or opposing
• Kill or prevent the growth or spread of bacterial organisms
• Alter microbial flora
• Promote overgrowth of resistant bacteria and fungi
• A major cause of diarrhea
So are you pro-biotic or anti-biotic?
Outcomes Associated with Probiotics

- Modification of Intestinal microflora
- Treatment of acute diarrhea
- Prevention of acute diarrhea
- Decrease of antibiotic associated diarrhea
- Emerging evidence in
  - Treatment and prevention of allergy
  - Prevention of NEC, sepsis and death in premature infants
  - FMT for C. difficile colitis
  - Obesity, diabetes and NAFLD (prebiotics)
BIFIDOBACTERIA

- Anaerobic, non motile, Gram + curved rods
- Produce acids: acetate and lactate
- Growth inhibited at pH of 5.5
- Can survive intestinal digestion and appear in stool
- Constitute most of the microflora of breastfed infants

* Bifidobacterium lactis

Nomenclature: *B. lactis* also: *B. animalis* sub-species *lactis*, also *B. bifidum*, strain Bb12
Bifidobacterium lactis fed to infants can modify intestinal microflora

- Increased counts of Bifidobacteria in infants fed B. lactis
- Increase in short chain fatty acids, lower stool pH
- Decrease in Clostridia, Coliforms and Bacteroides

Effects of B. lactis supplementation on immunity

• Decreased gut permeability
• Induction of tolerance by increasing tolerance-related cytokines
• Increased IgA secreting cells and secretory IgA

Fukushima Int J Food Microbiol 1998
Stratiki Early Human Develop 2007
Rautava Pediatr Res 2006
Risk Factors for the Development of Allergies

**Infants**
- C-section
- Not breastfeeding
- Exposure to intact cow milk casein or whey or soy protein
  - 4-fold increase in allergies if given 1st week of life
- Maternal hx allergy

**Children**
- Urban living
  - wheezing, hay fever, RASTs
- Antibiotics first 2 years of life
  - eczema, allergic rhinitis, asthma

Influence of Cesarean Delivery on Relative Risk of Childhood Food Allergy

*P<0.01; adjusted for covariates.
Food Allergy to egg confirmed by testing at age 1 – 2.

Probiotics and Risk of Atopic Dermatitis

LGG compared to placebo by mothers in last trimester of pregnancy and birth through 6 mo by infants


*P<0.05
Treatment of Atopic Disease
With Extensively Hydrolyzed Formula (EHF) and Probiotics LGG or B. lactis

*P=0.01 compared to EHF; SCORAD range in parenthesis

Probiotics Shown to Reduce the Duration of Acute Diarrhea

Meta-analyses of Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduction in Duration (hrs)</th>
<th>CI (hrs)</th>
<th>Number of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szajewska 2001</td>
<td>18</td>
<td>CI (10 – 27)</td>
<td>8 RCTs</td>
</tr>
<tr>
<td>Allen 2004</td>
<td>30</td>
<td>CI (19 – 42)</td>
<td>12 RCTs</td>
</tr>
<tr>
<td>Van Neil 2002</td>
<td>17</td>
<td>CI (7 – 29)</td>
<td>9 RCTs</td>
</tr>
<tr>
<td>Huang 2002</td>
<td>19</td>
<td>CI (14 – 26)</td>
<td>18 RCTs</td>
</tr>
</tbody>
</table>

Adapted from: Szajewska H., et al. JPGN 2006;42:454-475
Probiotics and Risk of Acute Diarrhea

Controlled Clinical Trials

Reduction in incidence (%)

- B. lactis
- LGG
- L. reuteri

* p<0.05 compared to incidence in control of each study
Probiotics and Risk of Antibiotic Associated Diarrhea

Controlled Clinical Trials

% Reduction in incidence

Arvola 1999: RR=0.32 CI (0.10-1.02)
Correa 2005: RR=0.52 CI (0.29-0.95)
Jirapinyo 2002: RR=0.47 CI (0.18-1.20)
Tankanow 1990: NS
Vanderhoof 1999: RR=0.29 CI (0.13-0.61)

*P<0.05
Bifidobacterium lactis in Premature Infants

- 75 prematures, average 31 wks GA
- Improved intestinal maturation
- Significantly reduced intestinal permeability by lactose/ mannitol ratio
- Significantly less courses of antibiotics for suspected sepsis
- Non-significant trend toward reduction in NEC (0.0% for B. lactis vs. 11.0% placebo)
- Non-significant trend toward reduction in sepsis (0.0% for B. lactis vs. 11.0% placebo)
- No adverse effects

Stratiki, Z. et. al., Early Human Develop 2007
### Probiotics in Crohn’s: Clinical Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plein</td>
<td>1993</td>
<td>Active Crohn’s</td>
<td>Conventional +/- S. boulardii</td>
<td>↓ diarrhea</td>
</tr>
<tr>
<td>Malchow</td>
<td>1997</td>
<td>Crohn’s</td>
<td>E. coli Nissle</td>
<td>↓ relapse</td>
</tr>
<tr>
<td>Guslandi</td>
<td>2000</td>
<td>Crohn’s</td>
<td>ASA +/- S. boulardii</td>
<td>↓ relapse</td>
</tr>
<tr>
<td>Campieri</td>
<td>2000</td>
<td>Crohn’s</td>
<td>VSL#3 vs ASA Post op</td>
<td>↓ symptoms</td>
</tr>
<tr>
<td>Prantera</td>
<td>2002</td>
<td>Crohn’s</td>
<td>L. GG vs placebo</td>
<td>No benefit</td>
</tr>
<tr>
<td>10 others</td>
<td></td>
<td>Crohn’s</td>
<td>various</td>
<td>Mixed results</td>
</tr>
</tbody>
</table>
# Probiotics in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Probiotic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuri</td>
<td>1997</td>
<td>E. coli Nissle1917</td>
<td>Equal to Mesalamine</td>
</tr>
<tr>
<td>Venturi</td>
<td>1999</td>
<td>E. coli Nissle 1917</td>
<td>Equal to Mesalamine</td>
</tr>
<tr>
<td>Rembacken</td>
<td>1999</td>
<td>E. coli Nissle 1917</td>
<td>Equal to Mesalamine</td>
</tr>
<tr>
<td>Copaci</td>
<td>2000</td>
<td>S. boulardii</td>
<td>Equal to Mesalamine</td>
</tr>
<tr>
<td>Ishikawa</td>
<td>2003</td>
<td>Bifidobacterium Milk</td>
<td>Superior to placebo</td>
</tr>
<tr>
<td>Fedorak</td>
<td>2003</td>
<td>VSL #3</td>
<td>↑ remission</td>
</tr>
<tr>
<td>Boroday</td>
<td>2003</td>
<td>Stool enema</td>
<td>Improved</td>
</tr>
<tr>
<td>Kruis</td>
<td>2004</td>
<td>E. coli Nissle 1917</td>
<td>Superior to conventional</td>
</tr>
<tr>
<td>Kato</td>
<td>2004</td>
<td>Bifidobacteria milk</td>
<td>Superior to placebo</td>
</tr>
<tr>
<td>Tursi</td>
<td>2004</td>
<td>VSL #3</td>
<td>Superior to conventional</td>
</tr>
<tr>
<td>Furri</td>
<td>2005</td>
<td>Bifidobacteria + Fiber</td>
<td>Improved</td>
</tr>
</tbody>
</table>
I HAVE A SURPRISE FOR YOU...
IT'S POOP.
Fecal Microbiota Transplants (FMT)

• First reported use in 1958 for recurrent C. diff
  
Indications: recurrent disease or refractory disease
  – ≥3 episodes of mild/moderate disease + failure of 6 – 8 week vancomycin taper regimen
  – ≥2 episodes of severe disease resulting in hospitalization
  – moderate disease not responding to standard therapy x ≥1 week
  – severe / fulminant disease not responding to standard therapy x ≥48 hrs

• Method: ≥ 50 g donor stool diluted in saline and administered via nasoduodenal tube, colonoscopy or retention enema
  – Most effective: colonoscopy
FMT for C. difficile 2013

- Van Nood: 1\textsuperscript{st} published prospective, multi-center, RCT
- 43 patients with recurrent C. diff infection
- Vancomycin x 14 days vs. FMT via nasoduodenal tube + vancomycin x 5 days
- Resolution rate: FMT group = 81% vs. vancomycin alone = 31%
- 3 patients in FMT group had recurrence + infection resolved with 2\textsuperscript{nd} FMT
- After FMT: increased diversity of gut microbiota
  - increased Bacteroides and some Clostridium
  - decreased Proteobacteria
- Adverse effects: diarrhea (94%), cramping (31%), belching (19%), later constipation (19%)
Ongoing Areas of Research: Fecal Microbial transplant

- inflammatory bowel disease
- gastroenteric infections
- irritable bowel syndrome /other gastrointestinal functional diseases
- colorectal cancer
- metabolic syndrome and obesity
- liver diseases
- allergic diseases
- neurological diseases such as autism and MS
Fecal Microbiota Transplantation (FMT)
Obesity

- Events early in life, such as delivery mode, maternal pre-pregnancy BMI, and antibiotic treatment during infancy, influence obesity in later childhood.
Can your bacteria make you fat?

- Intestinal microbiota can cause metabolic disease in mice independently of genetic background.
- Gordon et al 2006: colonization of a germ-free mouse with the intestinal microbiota from an obese mouse donor induced a body weight gain that was more substantial than when the microbiota from a lean mouse was transferred.
Can you bacteria make you fat?

- Transplanted microbiota from obese mice promoted absorption of monosaccharides from the gut lumen, selectively suppressed the production of fasting-induced adipocyte factor (a circulating lipoprotein lipase inhibitor)
- Results in induction of de novo hepatic lipogenesis and deposition of triglycerides in adipocytes and liver
Obesity in humans

- Intestinal microbiota of obese individuals differed in microbial diversity compared with that of lean persons.
- Lower prevalence of Bacteroidetes and a higher prevalence of Firmicutes.
- Because of differences in the composition of their gut microbiota, obese persons may be more effective at extracting energy from food and stimulating lipogenesis.
• An increase in lipopolysaccharide (LPS), a component of the outer membranes of Gram-negative bacteria, generates low-grade chronic inflammation (metabolic endotoxemia) in mice, resulting in insulin resistance.

• High-fat diet increases the proportion of Gram- to Gram+ microbes, increasing the liberation of LPS.

• Can be suppressed with prebiotics.
Non-alcoholic fatty liver disease

• Intestinal microbiota may contribute to NAFLD through the complex and cooperative activities of two microbe-sensing protein families:
  – Nucleotide oligomerization domain receptors (NLRs)
  – Toll-like receptors (TLRs)
• Prebiotics can affect expression of TLRs
Non-alcoholic fatty liver disease

- Loss of NLRP3 and NLRP6 inflammasomes in mice associated with intestinal dysbiosis
- Results in abnormal accumulation of bacterial products such as LPS and bacterial DNA in the hepatic portal circulation
- These stimulate TLR4 and TLR9, enhancing liver expression of TNF–α and steatohepatitis
Bariatric Surgery (human and mice)

- Induces metabolic alterations in energy metabolism
- Affects urinary excretion of gut microbial metabolites such as 4-cresyl sulfate, phenylacetate, and choline degradation products
- Shifts the composition of the gut microbiota from predominantly Firmicutes and Bacteroidetes towards gammaproteobacteria
Questions and Concerns Surrounding Changing the Gut Microbiome

- Which probiotic strain or combination is best to use?
- Do currently available probiotic supplements contain the species, strain and number of organisms specified on the label?
- Are the probiotic bacteria viable?
- Do they contain extraneous organisms?
- What is the appropriate dose?
- When should probiotic administration commence and be discontinued?
- There are no licensed products for use in premature infants outside of clinical trials.

# Probiotic Products - Foods

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Probiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dannon</td>
<td>Dan Active</td>
<td>L. casei Immunitas</td>
</tr>
<tr>
<td></td>
<td>Danimals</td>
<td>L. rhamnosus GG</td>
</tr>
<tr>
<td>General Mills / Yoplait</td>
<td>Yo-Plus</td>
<td>B. lactis BB-12</td>
</tr>
<tr>
<td>Horizon Organic</td>
<td>YoGurt Tubes</td>
<td>B. lactis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L. acidophilus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L. casei</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L. bulgaricus</td>
</tr>
<tr>
<td>Kraft Foods</td>
<td>LiveActive Cheese</td>
<td>B. lactis</td>
</tr>
<tr>
<td>Stonyfield Farm</td>
<td>YoBaby YoKids yogurts and drinks</td>
<td>B. bifidus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L. acidophilus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L. casei</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L. Rhamnosus GG</td>
</tr>
<tr>
<td>Yakult</td>
<td>Yakult (probiotic drink)</td>
<td>L. casei Shirota</td>
</tr>
</tbody>
</table>

Dose ranges between $10^8 - 10^{10}$ per serving
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Type of supplement</th>
<th>Probiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby’s Only Essentials</td>
<td>Powdered packet</td>
<td>B. longum BB536, B. breve M-16V, B. infantis M-63</td>
</tr>
<tr>
<td>Probiotic from Nature’s One</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culturelle</td>
<td>Tablet or gelatin capsule</td>
<td>L. rhamnosus GG</td>
</tr>
<tr>
<td>VSL #3</td>
<td>Powder packet</td>
<td>B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. bulgaricus, S. thermophilus</td>
</tr>
<tr>
<td>Soothe Drops Nestle/ Gerber</td>
<td>Drops</td>
<td>L. reuteri</td>
</tr>
</tbody>
</table>

Dose ranges between $10^8 – 10^{10}$ per serving
Mechanisms

- ↑ Ratio of Bifidobacteria & Lactobacilli to pathogens
- Modulate gut immune response
- Humoral immunity (IgA)
- Decreased gut permeability
- Promote mucin production
- Immune tolerance development

Clinical Outcomes

- Balanced intestinal microflora
- ↓ Duration of acute diarrhea
- ↓ Incidence of acute diarrhea
- ↓ Antibiotic associated diarrhea
- ↓ In severity & incidence of atopic disease
- Prevention of NEC
Knowledge Gaps

- Dynamics and impact of maternal microbiota transfer influence of infant nutrition on development of the gut microbiota in early childhood

- Influence of host genome variations and the fetal environment on the future gut microbiota
Knowledge gaps

• Map the impact of early antibiotic use on the developmental ecology, function, and resilience of the microbiota during childhood

• How variation in the gut microbiota influences drug metabolism, drug bioavailability, and drug toxicity with repercussions for patient stratification and personalized health care
Knowledge gaps

• Understanding the changing immunological and metabolic interactions between the host and its gut microbiota to elucidate how these changing interactions affect gut, liver, and brain function.

• Understanding the temporal dynamics of metabolic communication between the host and its gut microbiota, in relation to global changes in diet and environmental stressors.
Whenever I get mad at you, you never seem to get upset. How do you manage to control your temper?

I just go and clean the toilet.

How does that help?

I use your toothbrush.
References


ESPGHAN Committee on Nutrition. Probiotic bacteria in dietetic products for infants: a commentary by the ESPGHAN committee on nutrition. Journal of Pediatric Gastroenterology and Nutrition 38:365-374, 2004

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