Probiotics in Intestinal Health
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Objectives
1. Review the physiological significance of the commensal microbiota;
2. Define probiotics and identify sources;
3. Evaluate evidence support clinical use of probiotics in various clinical populations;
4. Underscore importance of probiotic specificity when making clinical recommendations;
5. Outline potential concerns for using probiotics in certain patient populations.

Bacteria in the Gut: Good or Bad?

"Good" bacteria such as Bifidobacterium (top left) and Lactobacillus (blue, bottom right) may help to ward off pathogens such as Salmonella (bottom left) and Clostridium botulinum.
What Is the Intestinal Commensal Microbiota?

- Dynamic mixture of essential microbes
- Population differs along the GI tract, from lumen to mucosa, and from person to person
- Develops due to genetics, environment, diet and disease
- Microbiota population outnumbers the cells in a human body
- Bacteria account for ~35-50% of the volume of contents in the colon

Numerically Dominant Microbial Genera

Physiological Functions of the Commensal Microbiota

1. Production of essential mucosal nutrients, such as short-chain fatty acids

2. Control of epithelial cell proliferation and differentiation

Physiological Functions of the Commensal Microbiota

3. Prevent overgrowth of pathogenic organisms
   - receptor competition
   - nutrient competition
   - antimicrobial substances

4. Stimulate intestinal immunity (GALT)

5. Powerful anti-inflammatory activity
   - Bifidobacterium
   - Lactobacillus

What is a Probiotic?

Oral probiotics are living microorganisms that upon ingestion in specific numbers, exert health benefits beyond those of inherent basic nutrition
   - Nonpathogenic
   - Resistant to technological processing, storage and delivery
   - Resistant to gastric acidity and lysis by bile
   - Viable in the gastrointestinal environment
   - May adhere to the epithelium
   - Produces antimicrobial substances
A story long in the making…

- First reported intakes being the injection of soured milks by Nomads >2000 years ago
- >100 years ago, Elli Metchnikoff, known as the pioneer of probiotics, observed complex microbial population of the colon
  - ‘Autointoxication’
  - Longevity in Bulgarians linked to consumption of fermented milk containing lactobacillus
- Abandoned colectomy with probiotic use

Strong Evidence Supporting Probiotic Use

**Clinical Condition** | **Organism**
--- | ---
**Diarrhea**
Infectious adult – treatment | Saccharomyces boulardii, LGG
Infectious childhood – treatment | LGG, *Lactobacillus reuteri*
Prevention of antibiotic-associated diarrhea | *S. boulardii*, LGG, *L. casei, B. bulgaricus, S. thermophilus*

**Inflammatory Bowel Disease**
Pouchitis - Preventing and maintaining remission | VSL#3

**Immune response**
LGG, *L. acidophilus, L. plantarum, B. lactis, L. johnsonii*

**Atopic eczema associated with cow’s milk allergy**
Treatment | LGG, *B. lactis*
Prevention | LGG, *B. lactis*

VSL#3 induced remission in patients with mild-to-moderately active ulcerative colitis

- PRCT adult patients (n=147)
- Placebo vs 3.6x10^{12} CFU VSL#3
- 1° endpoint – At w6, 50% improvement in UCDAI obtained in 32% of VSL#3 vs 10% of placebo (*P* = .001).

**Recommendation for Use of Probiotics in Diarrhea in Children**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sample Size</th>
<th>Probiotics Studied</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of day-care diarrhea</td>
<td>1700</td>
<td><em>B. lactis/S. thermophilus</em> LGG</td>
<td>+</td>
</tr>
<tr>
<td>Prevention of nosocomial diarrhea</td>
<td>356</td>
<td>LGG <em>B. lactis/S. thermophilus</em></td>
<td>+/-</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhea</td>
<td>2000</td>
<td>LGG Saccharomyces boulardii</td>
<td>+++</td>
</tr>
<tr>
<td>Infectious diarrhea</td>
<td>3000</td>
<td>LGG <em>Saccharomyces boulardii</em> <em>L. acidophilus LB</em></td>
<td>+++</td>
</tr>
<tr>
<td>Persistent diarrhea</td>
<td>235</td>
<td>LGG</td>
<td>++</td>
</tr>
</tbody>
</table>

Sood et al., Clin Gastro Hepatol 2009;7:1202-1209.

**Lactobacillus reuteri** is effective therapy for acute rotavirus diarrhea in children

- PRCT with children (n=40) 6-36 months of age hospitalized with acute diarrhea (75% rotavirus)
- placebo or 10^{10}-10^{11} CFU *L. reuteri* for hospital stay of >5d
- duration of watery diarrhea after treatment was 1.7(sd1.6) days in the *L. reuteri* group and 2.9(sd2.3) days in the placebo group (p =0.07)
- by d2, only 26% of *L. reuteri* group had watery diarrhea, compared with 81% of placebo (p =0.0005)
- stool cultures revealed good colonization of *L. reuteri* in those treated (>75% of *Lactobacilli* detected)

Shornikova et al., JPGN 1997;24:399-404.

**Lactobacillus improves clinical outcomes in children with acute infectious diarrhea**

- Meta-analysis with 9 RCTs
- *Lactobacillus* improves clinical outcomes in children with acute infectious diarrhea


**Moderate Evidence Supporting Probiotic Use**

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td>Prevention of infection</td>
<td>Saccharomyces boulardii, LGG</td>
</tr>
<tr>
<td>Treatment of recurrent C.</td>
<td><em>S. boulardii</em>, LGG</td>
</tr>
<tr>
<td>difficile-associated diarrhea</td>
<td></td>
</tr>
<tr>
<td>Prevention of recurrent C.</td>
<td><em>S. boulardii</em>, LGG</td>
</tr>
<tr>
<td>difficile-associated diarrhea</td>
<td></td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td><em>B. infantis</em>, <em>S. thermophilus</em>, <em>B. bifidus</em></td>
</tr>
<tr>
<td>Irritable Bowel Syndrome</td>
<td><em>B. infantis</em></td>
</tr>
</tbody>
</table>

**Probiotic drink (*L. casei*, *L. bulgaricus*, and *S. thermophilus*) ↓ incidence of AAD and CDD**

- Antibiotic-associated diarrhea (AAD)
  - 7/57 (12%) of probiotic group developed AAD, compared with 19/56 (34%) of placebo group (P=0.007)
  - Logistic regression controlling for other factors RR=0.25 (95% CI, 0.07-0.85) for use of probiotic
  - Absolute risk reduction was 21.6% (6.6% to 36.6%)

- *Clostridium difficile* disease (CDD)
  - None in probiotic group and 9/53 (17%) in the placebo group had diarrhea caused by *C difficile* (P=0.001)
  - The absolute risk reduction was 17% (7% to 27%)

Hickson et al., BMJ 2007;335:80-85
**Clostridium difficile disease (CDD) and antibiotic associated diarrhea (AAD)**

**OBJECTIVES:** To determine the efficacy and safety of probiotics for the prevention of AAD and CDD.

**METHODS:** meta-analysis
- **AAD** was defined as diarrhea within 2 months of exposure to antibiotics
  - 25 trials, 2810 patients
- **CDD** was defined as diarrhea associated with a positive Clostridium difficile culture or toxin within a month of exposure to antibiotics
  - 6 trials, 354 patients

**RESULTS:**
- *S. boulardii*, *L. rhamnosus GG*, and probiotic mixtures significantly reduced the development of AAD
- *S. boulardii* significantly reduced the development of CDD

McFarland. Am J Gastroenterol 2006;101:812-822

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**Clinical Studies of Beneficial Effects of Probiotics in Neonatal NEC**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=73)</th>
<th>Probiotic (n=72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># cases NEC</td>
<td>12 (16.4%)</td>
<td>3 (4%)</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>BW of NEC infants</td>
<td>956 ± 223</td>
<td>949 ± 223</td>
<td>P = 0.85</td>
</tr>
<tr>
<td>GA of NEC infants</td>
<td>27.6 ± 1.9</td>
<td>26.8 ± 26.8</td>
<td>P = 0.52</td>
</tr>
<tr>
<td>Age of diagnosis (d)</td>
<td>21 ± 14</td>
<td>21 ± 9</td>
<td>P = 1.00</td>
</tr>
<tr>
<td>Bell staging</td>
<td>2.33 ± 0.46</td>
<td>1.33 ± 0.46</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>NEC-associated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mortality</td>
<td>3/12</td>
<td>1/3</td>
<td>P = 0.87</td>
</tr>
<tr>
<td>NEC and/or death</td>
<td>17/72</td>
<td>6/73</td>
<td>P = 0.025</td>
</tr>
</tbody>
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**Probiotics reduce risk of NEC in preterm neonates**

- Updated meta-analysis published in May 2010
- 4 new RCTs (n = 783) included
- risk for NEC and death was significantly lower.
- no significant adverse effects were reported.
- Authors conclude 'additional placebo-controlled trials unnecessary' and “non-administration of routine probiotics unethical!”

Deshpande et al., Pediatrics 2010;125:921-930

Deshpande et al., Lancet 2007;369:1614–1620

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**Beneficial Effects of Probiotics on Immature Intestine May Decrease Risk of NEC**

- **Lumen**
  - Bacterial Interference
  - Production of Bacteriocins
  - I Bacterial Adherence
- **Submucosa**
  - Maturation of Cell Surface Glycoconjugate Patterns
  - Induction of Mac1 Genes
  - Improved Barrier Function
  - Modulations of Pre-inflammatory Response
  - Modulation of Immune System

Bifidobacterium bifidum reduces apoptosis in the intestinal epithelium in necrotizing enterocolitis

Khailova et al., AJP-GI epub 8/12/2010

Irritable bowel syndrome symptoms alleviated by B infantis 35624

O’Mahony et al., Gastroenterology 2005;128:541-551

PRObiotics in PAncreatitis TRIAl - PROPATRIA

• multicenter, double-blind, placebo-controlled RCT (n=298) with predicted severe acute pancreatitis aiming to assess the effects of probiotic prophylaxis
• primary outcome → infectious complications
• <72h of symptom onset, randomized to receive enteral probiotic or placebo twice daily for 28 days
• 10^{10}/day Ecologic 641 – Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium bifidum, and Bifidobacterium lactis
• probiotic prophylaxis with this combination of probiotic strains did not reduce the risk of infectious complications

Besselink et al., Lancet 2008; 371: 651-659

Probiotic prophylaxis associated with increased risk of mortality in PROPATRIA
Physiological Functions of the Commensal Microbiota

2. Control of epithelial cell proliferation and differentiation

- Butyrate
- SCFA
- Control


Experimental Design

- Jugular Catheterization
- 80% Jejunoileal Resection
- n = 120 48 hours old

<table>
<thead>
<tr>
<th>TPN</th>
<th>SCFA</th>
<th>9 mM Bu</th>
<th>60 mM Bu</th>
</tr>
</thead>
<tbody>
<tr>
<td>4h</td>
<td>12h</td>
<td>24h</td>
<td>3d</td>
</tr>
</tbody>
</table>

Acute Chronic

Regardless of time, ileal villus length increased by supplemented treatments

- A clinically feasible approach to butyrate delivery

- Butyrate supplemented PN not currently available
- SCFA are produced *in vivo* by bacterial fermentation of carbohydrates and dietary fiber
- Short-chain fructooligosaccharides (scFOS), a rapidly fermented prebiotic, may be a clinically efficacious means for delivering butyrate
- Synbiotic approach
What is a Prebiotic?

‘A prebiotic is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one of a limited number of bacteria in the colon, and thus improves host health’.

Gibson and Roberfroid, 1995
Gibson et al., 2004

Fructans – polymers of different lengths

scFOS – 2-5 fructose units
Oligofructose - ≤10 fructose units
Inulin - >10 fructose units

Hypothesis

Provision of pre- and/or probiotics in partial enteral nutrition is a clinically feasible means of providing butyrate to stimulate intestinal adaptation following massive small bowel resection.

Experimental Design

Jugular catheterization
80% jejunoileal resection

n = 72

Control
20% EN/
80% PN

Prebiotic
10 g/kg BW
FOS

Probiotic
1x10⁹ CFU
LGG

Synbiotic
FOS + LGG

24h, 3d or 7d
Piglet body weight similar among groups

- Energy intake did not differ between treatment groups

Ileal weight is increased over control by synbiotic treatment, regardless of time

- Jejunum shows a similar effect

Ileum mucosal weight is increased by the prebiotic treatment, regardless of time

DNA increased in ileum mucosa by prebiotic treatment on day 7

- TXT, p=0.096; day, p=<0.0001; TXT x day, p=0.050
Prebiotic treatment decreases resistance and increases glucose transport in the jejunum

Glutamine absorption increased in the jejunum by prebiotic treatment on day 7

All treatments increase glutamine transport over control in the colon

Summary

Prebiotic/Synbiotic treatment increased:
- Intestinal mass
- Mucosal weight
- DNA quantity
- Glucose and glutamine transport
Conclusion

The commensal microbiota of the intestine serves a critical role in health and disease. Efforts to support this important microbiome by the consumption of prebiotics and probiotics appear beneficial in many clinical populations.