Health Benefits of Probiotic Strains LGG & BB-12 in Infants and Children
Effects of the Gut Microbiota on Infant Health and Long-term Disease Risk
Establishment of the Gut Microbiota

At birth, the GI tract and immune system are immature
Colonization with microbes builds after birth

Once the microbiota are established around age 2-3, the community is relatively stable over time within an individual

Initial Colonization of the Gut

- Factors affecting initial colonization of the gut in infants:
  - Gestation length
  - Mode of delivery
  - Feeding practices
  - Antibiotic exposures
  - Birth order

- Negative influences on the establishment of a healthy gut microbiota and factors that decrease microbial diversity in infants and young children can have lifelong detrimental health impacts


Gestation Length

- 11% of all live births are preterm (before 37 weeks)
- Compared to healthy full-term infants, preterm infants have:
  - Lactobacilli and bifidobacteria levels that are absent or low
  - Increased abundance of potential pathogens including *C. difficile* and *Klebsiella pneumoniae*


Mode of Delivery

- 31% of births in the US are by Cesarean delivery
- Infants born by C-section:
  - Have lower gut flora diversity
  - Have altered microbial profiles
  - Are more likely to be colonized by pathogens

Mode of Delivery - Long Term Sequelae

- Children born by C-section are at increased risk of developing:
  - Conditions of the “Atopic Triad”
    - Atopic dermatitis
    - Allergic rhinitis
    - Asthma
  - Type 1 diabetes


Feeding Practices

- Breast-fed infants show higher counts of lactobacilli and bifidobacteria compared to formula-fed infants
  - Breast milk contains complex oligosaccharides that act as prebiotics, encouraging colonization by protective microorganisms
- Formula feeding alters gut-barrier function by increasing intestinal permeability and encourages the growth of pathogens

Feeding Practices - Long Term Sequelae

- Formula fed infants are at higher risk of:
  - Atopic dermatitis
  - Pediatric inflammatory bowel disease (Ulcerative colitis, Crohn’s disease)
  - Type 2 diabetes later in life
  - Obesity later in life

Antibiotic Therapy

- Early exposure to antibiotics:
  - Reduces fecal microbial diversity
  - Delays colonization by lactobacilli and bifidobacteria


Antibiotic Therapy - Long Term Sequelae

- Children exposed to antibiotics in infancy are more likely to develop:
  - Food allergy
  - Conditions of the “Atopic Triad”
    - Atopic dermatitis, Allergic rhinitis, Asthma
  - Inflammatory bowel disease
    - Ulcerative colitis, Crohn’s disease
  - Irritable bowel syndrome (IBS)
  - Celiac disease
  - Early childhood obesity


Most Common Contagious Infections Affecting Infants
Infections in Infants – RTIs & AOMs

- Respiratory tract infections (RTIs) are the most common diseases of infancy
  - Infants contract an average of 3-6 RTIs in their 1st year

- 40% of children who contract a respiratory infection also suffer from acute otitis media (AOM)
  - AOM is the most common reason for antibiotic use in infants

Antibiotic Treatments

- May disrupt the initial colonization of gut flora and increase the risk of long term adverse outcomes (allergies and eczema, bowel disease, early childhood obesity)
- In the short term, antibiotics affect the mucosa and may alter motility causing diarrhea, the *most common* side effect of infant antibiotic use
- Rates of antibiotic-associated diarrhea (AAD) can be as high as 39%

Infections in Infants - Gastrointestinal

- Gastrointestinal (GI) infections are the second most common diseases in childhood
- Gastroenteritis represents 16% of all illness in US children under the age of five
  - Etiology is typically viral (Rotavirus, Adenovirus, etc.) and rarely bacterial (Salmonella, Shigella, etc.)
  - Symptoms include diarrhea, vomiting, fever, chills and abdominal pain

Child Care and Risk of Infection

- Children who attend day care are at up to 3X greater risk of developing GI and respiratory infections than children who stay home.

Financial Burden of Childhood Infections

- Direct medical care costs
  - Office visits
  - Prescription and OTC medications
  - Hospitalization in some cases
- Indirect costs of parents taking time from work to care for ill children
Most Common Skin Conditions Affecting Infants
Dermatitis in Infants

- Dermatitis is a general term to describe skin inflammation
- Most common forms in infants include:
  - Diaper rash (Diaper dermatitis)
    - Form of contact dermatitis
  - Cradle cap (Seborrheic dermatitis)
    - Prevalence peaks at age 3 months, with 70% of infants affected
    - However, is self-limited and typically resolves spontaneously
  - Eczema (Atopic dermatitis)
    - Affects up to 25% of infants and children
    - Clinical course is chronic and relapsing
    - May persist into adulthood

Eczema / Atopic dermatitis

- A chronic, pruritic, inflammatory skin condition, eczema is considered the most common skin disorder in infants and children, affecting up to 25%.
- Onset is most frequently between age 3 and 6 months, with 60% of first-time skin eruptions in the first year of life.

- Pruritus (itching) is the most prominent disease burden with 83% of affected children suffering from sleep disturbance.
Eczema Risk Factors

- A family history of atopy is a major risk factor for the disease

- Formula feeding can increase the risk of eczema through the promotion of colonization with *C. difficile* which is associated with eczema


Eczema Pathogenesis

- The pathogenesis of the disease involves immune and epidermal barrier dysfunction

- Individuals with eczema also exhibit gut barrier dysfunction with increased intestinal permeability

- Probiotics have been shown to reduce intestinal permeability in children with eczema

Probiotics – Major Mechanisms

- Proposed mechanisms through which probiotics confer health benefits include:
  - Enhancement of epithelial barrier function
    - Includes increased tight junction function
  - Competitive exclusion of pathogenic microorganisms
  - Secretion of antimicrobial substances
  - Increased adhesion to intestinal mucosa
    - Important for the interaction between probiotic strain and host
  - Modulation of host immune responses through strain-specific local and systemic effects

Probiotics – Major Mechanisms

Probiotics – Strain-specific Effects

- Many probiotic products are available on the market
- However, not all probiotics are equal
- Genus, species, and strain determine specific effects
Probiotics: LGG & BB-12
LGG & BB-12

- Strains of *Lactobacillus* and *Bifidobacterium* are the most commonly used probiotics
- Two specific strains, *Lactobacillus rhamnosus* GG (LGG) and *Bifidobacterium animalis subsp. lactis* BB-12 (BB-12), have been extensively studied in infants and young children
LGG & BB-12 – Clinical Data

- Multiple randomized controlled clinical trials evaluating the efficacy of LGG and BB-12 (individually or in combination) in infants or children have been conducted.
- The oral administration of LGG and BB-12 in combination represents a primary preventive and management strategy for the most common infectious diseases and skin disorder affecting infants and young children.
BB-12 Reduces the Risk of Respiratory Tract Infection (RTI)

<table>
<thead>
<tr>
<th>Study Population</th>
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</table>
| Newborns (1-2 months old at baseline)| RCT, double-blind, placebo-controlled 1. BB-12 (10 billion CFU) 2. Placebo | 109             | 6-7 months (through age 8 months) | • Infants in the BB-12 group experienced 29% fewer RTIs than those in the control group (P=0.014)  
  • Risk ratio (RR) of 0.69 indicated that the BB-12 treatment decreased the risk of RTI by 31% |

LGG Reduces the Risk of RTI in Children Attending Day Care

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<tbody>
<tr>
<td>Children (mean age 4-5 y/o) attending day care</td>
<td>RCT, double-blind, placebo-controlled 1. LGG (1 billion CFU) 2. Placebo</td>
<td>281</td>
<td>3 months</td>
<td>LGG significantly reduced the risk of: •Upper RTIs (RR=0.66); 34% reduced risk •RTIs lasting &gt; 3 days (RR=0.57); 43% reduced risk LGG group had lower number of days with respiratory symptoms (P&lt;0.001)</td>
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<tr>
<td>Children (1-6 y/o) attending day care</td>
<td>RCT, double-blind, placebo-controlled 1. LGG (100-200 million CFU) 2. Placebo</td>
<td>571</td>
<td>7 months</td>
<td>LGG group had: •16% fewer absences from day care due to illness (P=0.03) •17% relative reduction in # of children with RTI with complication and lower RTI •19% relative reduction in antibiotic treatments for RTI</td>
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LGG & BB-12 Reduce the Risk of AOM and Need for Antibiotic Treatment

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| Infants that required formula before age 2 months | RCT, double-blind, placebo-controlled 1. LGG (10 billion CFU), BB-12 (10 billion CFU) 2. Placebo | 81 | Until age 12 months | LGG/BB-12 group had significantly reduced risk of:  
• Acute otitis media by 56% (RR=0.44) in the first 7 months of life  
• Need for antibiotic treatment by 48% (RR=0.52) in the first 7 months of life  
• Recurrent RTIs by 49% (RR=0.51) in the first 12 months of life |

## LGG & BB-12 Reduce the Risk of and Treat Acute Diarrhea

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<tr>
<td>Children (mean age 1.6 y/o) who were hospitalized for acute watery diarrhea, 57% were + for Rotavirus</td>
<td>RCT, double-blind, placebo-controlled 1. Oral rehydration solution (ORS) + LGG (20 billion CFU) 2. ORS + LGG (2 trillion CFU) 3. ORS only</td>
<td>559</td>
<td>At least 7 days or until diarrhea stopped</td>
<td>In the LGG groups, there was:  • Significantly reduced risk of daily frequency of diarrhea from the 4th day onwards  • Significantly shorter mean duration of diarrhea (by about 2 days)  • Significantly shorter length of hospital stay (by about 3.5 days)  • No significant difference between the 2 dosages of LGG</td>
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<tr>
<td>Healthy infants (age less than 8 months) living in residential nurseries or foster care centers</td>
<td>RCT, double-blind, placebo-controlled, multi-center 1. BB-12 (&gt;100 million CFU) 2. Placebo</td>
<td>90</td>
<td>20-21 weeks (mean)</td>
<td>BB-12 group:  • Mean # of days with diarrhea was significantly lower (P=0.0002)  • Risk of diarrhea (as incidence per child-year) was reduced by 44% (RR=0.54; P&lt;0.001)</td>
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## LGG Reduces Antibiotic-Associated Diarrhea (AAD)

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<tr>
<td>Children (6 months -10 y/o) on an oral antibiotic for acute infectious disorders</td>
<td>RCT, double-blind, placebo-controlled</td>
<td>202</td>
<td>Varied</td>
<td>In the LGG group, there were fewer cases of AAD; 25 children in the placebo group but only 7 in the LGG group. LGG significantly reduced stool frequency and increased stool consistency.</td>
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<tr>
<td></td>
<td>1. LGG (10-20 billion CFU)</td>
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<td>2. Placebo</td>
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<td>There were fewer cases of AAD during the first 2 weeks after the beginning of the antimicrobial treatment; 16% in the placebo but only 5% in the LGG group.</td>
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<tr>
<td>Children (mean age 4.5 y/o) on oral antimicrobials for acute RTIs</td>
<td>RCT</td>
<td>119</td>
<td>Varied</td>
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<tr>
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<td>1. LGG (40 billion CFU)</td>
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<td>2. Placebo</td>
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**LGG & BB-12 Reduce the Severity of Atopic Eczema**

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<tr>
<td>Infants with atopic eczema (mean age 4.6 months)</td>
<td>RCT, double-blind, placebo-controlled 1. LGG (300 million CFU) 2. BB-12 (1 billion CFU) 3. Placebo</td>
<td>27</td>
<td>2 months</td>
<td>In the LGG and BB-12 groups, there was a significant reduction in the extent and severity of atopic eczema as per “SCORAD” scores (P = 0.002)</td>
</tr>
<tr>
<td>Infants with atopic eczema (mean age 5.5 months)</td>
<td>RCT, double-blind, placebo-controlled 1. Viable LGG (30 billion CFU/kg body weight) 2. Heat-inactivated LGG (30 billion CFU/kg body weight) 3. Placebo</td>
<td>35</td>
<td>Mean duration of 7.5 weeks</td>
<td>The extent and severity of atopic eczema, as per “SCORAD” scores, was improved in all 3 study groups. However, the mean decrease in SCORAD scores was greater in the viable LGG group than in the placebo group (post hoc analysis, P = 0.02)</td>
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**SCORAD = SCORing Atopic Dermatitis**

**LGG Reduces the Risk of Developing Atopic Eczema**

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<td>Pregnant women from atopic families</td>
<td>RCT, double-blind, placebo-controlled 1. LGG (20 billion CFU) 2. Placebo</td>
<td>62 mother-infant pairs</td>
<td>Starting 4 weeks before birth and continuing for the first 3 months of breastfeeding</td>
<td>In the LGG group, there was a 68% reduction in risk of developing atopic eczema during the first 2 years of life (RR=0.32; P=0.0098)</td>
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</tbody>
</table>


Summary – Gut Flora and Long-term Health Outcomes

- Negative impacts on establishment of healthy gut flora may have long term consequences
- Many children are born preterm and/or by C-section, are exposed to antibiotics early in life or are formula-fed
- Unfortunately, these exposures may increase the risk of developing:
  - The “Atopic Triad” - Atopic dermatitis, Allergic rhinitis, Asthma
  - Food allergy
  - IBS, Ulcerative colitis, Crohn’s disease, Celiac disease
  - Type 1 and Type 2 diabetes
  - Early childhood obesity and obesity later in life
Summary – LGG & BB-12

- LGG and BB-12 are two of the safest, most extensively studied probiotic strains available.
- The oral administration of LGG and BB-12 represents an evidence-based option for the prevention and management of common infectious, immune and allergic diseases affecting pediatric populations, such as:
  - Respiratory tract infections (RTIs)
  - Acute otitis media
  - Gastrointestinal infections and diarrhea
  - Need for antibiotic treatments
  - Antibiotic-associated diarrhea (AAD)
  - Atopic eczema
Summary –
Recommending LGG & BB-12

- LGG and BB-12 may provide a useful application in clinical practice as a recommendation for parents and soon-to-be parents looking for a safe and effective daily probiotic supplement to support:

  - Establishment of a healthy gut microbiota
  - Immune function
  - Gastrointestinal health
  - Skin health