Health Benefits of Probiotic Strains *Lactobacillus rhamnosus* GG (LGG®) & *Bifidobacterium animalis* subsp. *lactis* BB-12 (BB-12®) in Infants and Children

Research Review

COMMON ILLNESSES AFFECTING INFANTS

Infections. Respiratory tract infections (RTIs) are the most common diseases of infancy, with infants contracting an average of 3 to 6 infections during the first year of life.[1,2] Forty percent of children who contract an RTI also suffer from acute otitis media, the most common reason for antibiotic use during infancy.[3] Unfortunately, oral antibiotic treatments may disrupt the intestinal microbiome and could lead to negative long-term health impacts. In the short term, antibiotics also 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%.[4]

Gastrointestinal (GI) infections are the second most common diseases in childhood, and gastroenteritis represents 16% of all illnesses in US children under the age of 5.[5] Children who attend day care are at up to 3 times greater risk of developing GI and respiratory infections than children who stay home.[6] Children in a hospital setting are especially vulnerable to infection. The incidence of nosocomial infections (also known as healthcare-associated infections) in children is as high as 44%, with respiratory and GI infections still most predominant.[7]

Eczema. A chronic, pruritic, inflammatory skin condition, atopic dermatitis or "eczema" is 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 is the most prominent disease burden with 83% of affected children suffering from sleep disturbance.[8] A family history of atopy (eczema, allergic rhinitis, and/or asthma) is a major risk factor for the disease.[8] Formula feeding can also increase the risk of eczema through the promotion of colonization with *C. difficile,* which is associated with eczema.[9] The pathogenesis of the disease involves immune and epidermal barrier dysfunction. Individuals with eczema also exhibit gut barrier dysfunction with increased intestinal permeability.[10]

GUT MICROBIOTA & INFANT HEALTH

Gut microbiota are trillions of microorganisms living in the GI tract that have many essential roles, including digestion and absorption of nutrients, protection against pathogens, and metabolic and immunologic programing.[11] In infants and children, early establishment of a healthy gut microbiota affects the development and maturation of the immune system, and thus may impact short- and long-term health outcomes.[11,12]

Factors that affect initial colonization include gestation length, mode of delivery, formula and breastfeeding, antibiotic exposure, and birth order (**Table 1**).[13,14] 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. Children born by C-section are at increased risk of developing allergies, atopic dermatitis, asthma, and type 1 diabetes.[9,15,16] Children exposed to oral antibiotics in infancy are more likely to develop atopic disease (eczema, asthma, allergic rhinitis), food allergy, irritable bowel syndrome (IBS), Crohn's disease, ulcerative colitis, celiac disease, and early childhood obesity.[17-20]

[13,14]

Table 1. **Factors Affecting Infants' Gut Microbiota Colonization**

Gestation Length
• Preterm infants have lactobacilli and bifidobacteria levels that are absent or low compared to healthy full-term infants
Mode of Delivery
• Infants born by C-section have lower diversity, altered profiles, and are more likely to be colonized by pathogens
Feeding
• Formula feeding increases intestinal permeability and encourages growth of pathogens; breast milk, in contrast, contains complex oligosaccharides that act as prebiotics that encourage colonization by protective microorganisms
Antibiotics
• Exposure to oral antibiotics delays colonization by lactobacilli and bifidobacteria
Birth Order
• Having older siblings is associated with increased lactobacilli colonization

PROBIOTICS

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host through proposed mechanisms that include:[21]

- Competitive exclusion of pathogenic microorganisms
- Production of antimicrobial substances
- Enhancement of epithelial barrier function including increased tight junction function
- Increased adhesion to intestinal mucosa and epithelium
- Modulation of host immune responses through strain-specific local and systemic effects

Although numerous probiotic products are available, more recent research has found that not all probiotics are created equal; the genus, species, and strain determine their specific effect.

LGG & BB-12

Strains of lactobacilli and bifidobacteria are some of 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. Oral administration of these 2 strains represents a primary preventive and management strategy for the most common infectious diseases and skin disorders affecting children.

CLINICAL TRIALS IN INFANTS & CHILDREN

There have been multiple randomized controlled clinical trials evaluating the efficacy of LGG and BB-12 (individually or in combination) in infants or children. The studies are described below and summarized in **Table 2**.

Reducing the occurrence of RTIs and/or GI infections. In one study, 109 newborns were randomized to BB-12 [10 billion colony-forming units (CFU) daily] or control from age 1-2 months until age 8 months.[22] At the end of the trial, 94% of the children in the control group experienced RTIs whereas only 65% in the BB-12 group had RTIs (P=0.014). The BB-12 treatment decreased the risk of experiencing RTIs by 31% based on the risk ratio (RR) of 0.69.

Two studies investigated the efficacy of LGG in day care settings. In the first study, 281 children (mean age 4-5 y/o) were randomized to LGG (1 billion CFU daily) in fermented milk product or placebo milk product for 3 months.[23] Compared with placebo, LGG treatment:

- Significantly reduced risk of upper RTIs by 34% (RR=0.66)
- Significantly reduced risk of RTIs lasting > 3 days by 43% (RR=0.57)
- Lowered number of days (median) with respiratory symptoms (LGG group: 0 days; placebo group: 4 days)

In the second study, 571 children (mean age 4-5 y/o) were randomized to LGG (100-200 million CFU daily) in fermented milk product or placebo milk product for 7 months.[24] Compared with the placebo group, the children in the LGG group had:

- Significantly fewer days (geometric mean) of absence from day care due to illness (LGG group: 4.9 days; placebo group: 5.8 days).
- 17% relative reduction in the number of children suffering from RTIs with complications
- 19% relative reduction in antibiotic treatments for RTIs

Preventing nosocomial infections. A study investigated the effect of LGG for prevention of nosocomial infections in a pediatric setting: 742 hospitalized children (mean age 10-11 y/o) were randomized to LGG (1 billion CFU daily) in fermented milk product or placebo milk product for the duration of the hospitalization.[25] Compared with placebo, LGG significantly reduced risk for:

- GI infections by 60% (RR=0.40) and episodes of GI infections lasting > 2 days by 60% (RR=0.40)
- RTIs by 62% (RR=0.38) and episodes of RTIs lasting > 3 days by 60% (RR=0.40)
- Vomiting episodes by 50% (RR=0.50)
- Diarrheal episodes by 76% (RR=0.24)

Reducing risks of acute otitis media and antibiotic use. A study randomized 81 infants (those requiring formula before age of 2 months) to formula containing LGG (10 billion CFU daily) plus BB-12 (10 billion CFU daily) or placebo until the age of 12 months.[26] Compared with placebo, LGG plus BB-12:

- Significantly reduced the risk of early acute otitis media by 56% (RR=0.44) and need for antibiotic treatment by 48% (RR=0.52) during the first 7 months of life
- Significantly reduced the incidence of recurrent RTIs by 49% (RR=0.51) during the first 12 months of life

Reducing risks of diarrhea. Another study randomized 90 healthy infants (age < 8 months) in a residential care setting to BB-12 (> 100 million CFU daily) or placebo.[27] The mean duration of monitoring was 20-21 weeks. The study found that:

- Fewer infants (28.3%) receiving BB-12 than those receiving placebo (38.6%) experienced acute diarrhea
- The mean number of days with diarrhea was significantly lower in the infants receiving BB-12 (1.15 days) than those receiving placebo (2.3 days)
- The relative risk of diarrhea (as incidence per child-year) in the BB-12 group was 0.54

In another study, 559 children (mean age 1.6 y/o) administered for acute watery diarrhea (57% of whom tested positive for rotavirus) were randomized to oral rehydration solution (ORS) alone, ORS + LGG (20 billion CFU daily), or ORS + LGG (2 trillion CFU daily) for ≥7 days or until diarrhea stopped and the children were rehydrated.[28] Compared with the ORS only group, both ORS + LGG groups had:

- Significant reduction in the daily frequency of diarrhea from fourth day onwards
- Significantly shorter mean diarrhea duration (by ~2 days)
- Significantly shorter hospital stay (by ~3.5 days)
- No significant difference within the 2 intervention groups

Reducing risks of antibiotic-associated diarrhea (AAD). A study investigated the incidence of AAD when co-administered with an oral antibiotic in 202 children (6 months to 10 years of age) with acute infectious disorders.[29] Children were

randomized to LGG (10-20 billion CFU daily) or placebo. By the tenth day, 25 placebo-treated children—but only 7 LGG-treated children—had diarrhea (≥ 2 liquid stools per day).

A similar study investigated the incidence of AAD in 119 children receiving oral antimicrobial agents for acute respiratory infections.[30] Children (mean age 4.5 y/o) were randomized to LGG (40 billion CFU daily) or placebo during the antimicrobial treatment. During the first 2 weeks after starting the antimicrobial treatment, 5% in the LGG group and 16% in the placebo group had diarrheal episodes (≥ 3 loose stools per day for a minimum of 2 consecutive days).

Reducing risks of atopic eczema via prenatal supplementation or infant formula. In a study of 62 pregnant women with a personal history of atopic eczema and a family history of atopy, subjects were given LGG (20 billion CFU daily) or placebo from 4 weeks before their due dates and throughout breastfeeding.[31] The infants' clinical status was assessed until 24 months of age. During the first 2 years, 47% of infants whose mothers were given placebo developed atopic eczema, whereas only15% of the infants whose mothers had taken probiotics developed atopic eczema. The LGG treatment decreased the risk of atopic eczema by 68% (RR=0.32).

In another study, 27 infants (mean age 4.6 months) with atopic eczema were randomized to a hydrolyzed whey formula containing LGG (300 million CFU daily), BB-12 (1 billion CFU daily), or placebo for 2 months.[32] SCORAD (SCORing Atopic Dermatitis) was calculated to assess the extent and severity of atopic eczema. The study found that:

- Median SCORAD score (16 at baseline) was significantly reduced to 1 in the LGG group and 0 in the BB-12 group, compared with 13.4 in the placebo group
- Concentration of serum sCD4 was significantly decreased in the LGG and BB-12 group but not the placebo group; changes between the 3 groups were statistically significant

A third study investigated the effect of viable and heat-inactivated LGG in 35 infants (mean age 5.5 months) with atopic eczema and allergy to cow's milk.[33] Infants were randomized to viable LGG (30 billion CFU/kg body weight daily), heat-inactivated LGG, or placebo formula for a mean duration of 7.5 weeks. Infants receiving viable LGG had greater improvements in SCORAD score than those receiving placebo. (Infants receiving heat-inactivated LGG experienced adverse GI symptoms; thus recruitment was prematurely terminated.)

SUMMARY

LGG and BB-12 are 2 of the safest, most extensively studied probiotic strains available. These strains have clinical evidence supporting their use in pediatric populations. Research with LGG and BB-12 includes:

- RTIs[22-26]
- Acute otitis media[26]
- GI infections and diarrhea[25,27-30]
- Need for antibiotic treatments[24,26]
- AAD[29,30]
- Atopic eczema[31-33]

LGG and BB-12 may provide a useful application in clinical practice as a recommendation for parents and pregnant mothers looking for a safe and effective daily probiotic supplement to support healthy immune function, GI health, and the establishment of a healthy gut microbiota in their children.

References

1. Monto AS. Epidemiology of viral respiratory infections. *Am J Med*. 2002;112 Suppl 6A:4S-12S.
2. Vesa S, Kleemola M, Blomqvist S, et al. Epidemiology of documented viral respiratory infections and acute otitis media in a cohort of children followed from two to twenty-four months of age. *Pediatr Infect Dis J*. 2001;20:574-581.
3. Alho OP, Koivu M, Sorri M, Rantakallio P. The occurrence of acute otitis media in infants. A life-table analysis. *Int J Pediatr Otorhinolaryngol*. 1991;21:7-14.
4. McFarland LV. Antibiotic-associated diarrhea: epidemiology, trends and treatment. *Future Microbiol*. 2008;3:563-578.
5. Glass RI, Lew JF, Gangarosa RE, LeBaron CW, Ho MS. Estimates of morbidity and mortality rates for diarrheal diseases in American children. *J Pediatr*.1991;118:S27-33.
6. Wald ER, Guerra N, Byers C. Frequency and severity of infections in day care: three-year follow-up. *J Pediatr*. 1991;118:509-514.
7. Welliver RC, McLaughlin S. Unique epidemiology of nosocomial infection in a children's hospital. *Am J Dis Child*. 1984;138:131-135.
8. Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70:338-351.
9. Penders J, Thijs C, van den Brandt PA, et al. Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study. *Gut*. 2007;56:661-667.
10. Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev*. 2011;242:233-246.
11. Young VB. The intestinal microbiota in health and disease. *Curr OpinGastroenterol*. 2012;28:63-69.
12. Li M, Wang M, Donovan SM. Early development of the gut microbiome and immune-mediated childhood disorders. *Semin Reprod Med*. 2014;32:74-86.
13. Matamoros S, Gras-Leguen C, Le Vacon F, Potel G, de La Cochetiere MF. Development of intestinal microbiota in infants and its impact on health. *Trends Microbiol*. 2013;21:167-173.
14. Adlerberth I, Wold AE. Establishment of the gut microbiota in Western infants. *Acta Paediatr*. 2009;98:229-238.
15. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy*. 2008;38:629-633.
16. Cardwell CR, Stene LC, Joner G, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia*. 2008;51:726-735.
17. Droste JH, Wieringa MH, Weyler JJ, et al. Does the use of antibiotics in early childhood increase the risk of asthma and allergic disease? *Clin Exp Allergy*.2000;30:1547-1553.
18. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol*. 2010;105:2687-2692.
19. Marild K, Ye W, Lebwohl B, et al. Antibiotic exposure and the development of coeliac disease: a nationwide case-control study. *BMC Gastroenterol*. 2013;13:109.
20. Bailey LC, Forrest CB, Zhang P, et al. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatr*. 2014;168:1063-1069.
21. Bermudez-Brito M, Plaza-Diaz J, Munoz-Quezada S, Gomez-Llorente C, Gil A. Probiotic mechanisms of action. *Ann Nutr Metab*. 2012;61:160-174.

22. Taipale T, Pienihakkinen K, Isolauri E, et al. *Bifidobacterium animalis* subsp. *lactis* BB-12 in reducing the risk of infections in infancy. *Br J Nutr*. 2011;105:409-416.
23. Hojsak I, Snovak N, Abdovic S, et al. *Lactobacillus* GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. *Clin Nutr*. 2010;29:312-316.
24. Hatakka K, Savilahti E, Ponka A, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ*. 2001;322:1327.
25. Hojsak I, Abdovic S, Szajewska H, et al. *Lactobacillus* GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. *Pediatrics*. 2010;125:e1171-117726.
26. Rautava S, Salminen S, Isolauri E. Specific probiotics in reducing the risk of acute infections in infancy—a randomised, double-blind, placebo-controlled study. *Br J Nutr*. 2009;101:1722-1726.
27. Chouraqui JP, Van Egroo LD, Fichot MC. Acidified milk formula supplemented with *Bifidobacterium lactis*: impact on infant diarrhea in residential care settings. *J Pediatr Gastroenterol Nutr*. 2004;38:288-292.
28. Basu S, Paul DK, Ganguly S, Chatterjee M, Chandra PK. Efficacy of high-dose *Lactobacillus rhamnosus* GG in controlling acute watery diarrhea in Indian children: a randomized controlled trial. *J Clin Gastroenterol*. 2009;43:208-213.
29. Vanderhoof JA, Whitney DB, Antonson DL, et al. *Lactobacillus* GG in the prevention of antibiotic-associated diarrhea in children. *J Pediatr*. 1999;135:564-568.
30. Arvola T, Laiho K, Torkkeli S, et al. Prophylactic *Lactobacillus* GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. *Pediatrics*. 1999;104:e64.
31. Rautava S, Kalliomaki M, Isolauri E. Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant. *J Allergy Clin Immunol*. 2002;109:119-121.
32. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. *Clin Exp Allergy*. 2000;30:1604-1610.
33. Kirjavainen PV, Salminen SJ, Isolauri E. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. *J Pediatr Gastroenterol Nutr*. 2003;36:223-227.

Table 2. **Summary of Randomized Controlled Trials of LGG and/or BB-12 in Infants or Children**

	Study Population	N	Probiotic Species (Daily Dosage)	Duration	Outcome (Compared with Placebo Group)
Taipale et al.[22]	Infants 1-2 mo	109	BB-12 (10 billion CFU)	6-7 mo	Significant reduction in the occurrence of RTIs (RR=0.69; p=0.014)
Hojsak et al.[23]	Children (mean age 4-5 y/o) attending day care	281	LGG (1 billion CFU)	3 mo	Significantly reduced risk of: • Upper RTIs (RR=0.66) • RTIs lasting > 3 d (RR=0.57) Fewer days with respiratory symptoms
Hatakka et al.[24]	Children (1-6 y/o) attending day care	571	LGG (100-200 million CFU)	7 mo	• Fewer absences from day care due to illness • 17% relative reduction in RTIs • 19% relative reduction in antibiotic treatments
Hojsak et al.[25]	Hospitalized children (excluding respiratory and GI infections)	742	LGG (1 billion CFU)	Duration of hospitalization	Significantly reduced risk of: • GI infections (RR=0.4) • Episodes of GI infections lasting > 2 d (RR=0.4) • RTIs (RR=0.38) • Episodes of RTIs lasting > 3 d (RR=0.4) • Vomiting episodes (RR=0.5) • Diarrheal episodes (RR=0.24)
Rautava et al.[26]	Infants requiring formula before age of 2 mo	81	LGG (10 billion CFU) plus BB-12 (10 billion CFU)	Until the age of 12 mo	Significantly reduced risk of: • Acute otitis media (RR=0.44) and need for antibiotic treatment (RR=0.52) during first 7 mo • Recurrent RTIs (RR=0.51) during first 12 mo of life
Chouraqui et al.[27]	Healthy infants (age < 8 mo)	90	BB-12 (>100 million CFU)	20-21 wks (mean)	• Mean number of days with diarrhea was significantly lower (p=0.0002) • Risk of diarrhea (as incidence per child-year) was reduced (RR=0.54; p<0.001)
Basu et al.[28]	Children (mean age 1.6 y/o) hospitalized for acute watery diarrhea	559	LGG (20 billion CFU) or LGG (2 trillion CFU)	≥ 7 d or until diarrhea stopped	• Significantly reduced risk of daily frequency of diarrhea from 4th day onwards • Significantly shorter mean duration of diarrhea and hospital stay • No significant difference between the 2 LGG doses
Vanderhoof et al.[29]	Children (6 mo-10 y/o) on oral antibiotic for acute infectious disorders	202	LGG (10-20 billion CFU)	Varied	Fewer cases of AAD (25 in placebo group, but only 7 in LGG group)
Arvola et al.[30]	Children (mean age 4.5 y/o) on oral antimicrobials for acute RTIs	119	LGG (40 billion CFU)	Varied	Fewer cases of AAD during the first 2 wks after start of antimicrobial treatment (16% in placebo group, but only 5% in LGG group)
Rautava et al.[31]	Pregnant women with a history of atopic eczema	62	LGG (20 billion CFU)	4 wks before birth and throughout breastfeeding	Significant reduction in the risk of atopic eczema during the first 2 y of life (RR=0.32; p=0.0098)
Isolauri et al.[32]	Infants (mean age 4.6 mo) with atopic eczema	27	LGG (300 million CFU) or BB-12 (1 billion CFU)	2 mo	Significant reduction in extent and severity of atopic eczema as per SCORAD scores and serum sCD4 levels
Kirjavainen et al.[33]	Infants (mean age 5.5 mo) with atopic eczema	35	LGG (30 billion CFU/kg body weight)	7.5 wks (mean)	Significant reduction in the extent and severity of atopic eczema as per SCORAD scores