Lactobacillus rhamnosus GG
The Ideal Probiotic for Infants
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The Role of Microbiota in Infant Development

The Intestinal Microbiota is a Critical Driver for Overall Health

The human microbiota consists of all the microorganisms that live inside and on the human body. There are just as many of these microorganisms as human cells in each of us, however the types (diversity) and quantities (abundance) of these microbes are varied, meaning that each person’s microbiota is unique, like their fingerprints. The largest concentration of these microorganisms lives in the intestines. The intestinal, or gut, microbiota directs a variety of established, well-known processes that

Gut Microbiota and Vital Functions

Figure 1. Gut health is about more than digestive health. The intestinal microbiota is vital to our overall health and essential to baby’s healthy development.
contribute to human health including gut barrier protection, immune modulation, neuroendocrine communication, and the digestion and absorption, as well as the production, of nutrients.

The gut microbiota is vital to overall health throughout life and impacts many physiological functions through communication with many organs, mainly the liver and brain. Disruptions to the gut microbiota-liver axis can affect metabolic functions like energy and nutrient supply as well as vitamin synthesis, potentially resulting in the development of certain diseases, such as obesity or non-alcoholic fatty liver disease. Additionally, the gut and the brain are continually communicating with one another to modulate central nervous system functions like mood and anxiety, intestinal functions such as normal gut motility, and modulation and maturation of the immune system, which begins very early in life, therefore, it is important to have a healthy gut microbiota early in life.

Although humans are exposed to microbes in utero, major colonization for the human microbiota, including the gastrointestinal tract, largely begins during birth. The microbiota established in a newborn infant is predominantly Lactobacilli and Bifidobacteria and after one year of age begins to stabilize, resembling that of a young adult by age three. During childhood and adulthood, the microbiota is easily influenced by diet, environment, and medication, however the greatest impact can be made when our microbiota is first developing, during fetal development and early infancy.
Early Infancy is a Critical Period for Intestinal Microbial Development

A healthy gut begins with the introduction and colonization of the right microbes and this foundation is laid over a short period of time during fetal development, birth, and early infancy. This brief period is considered a “critical window” because the developing immune system is easily influenced during this period. The intestinal microbiota heavily impacts the developing immune system\(^\text{17}\) and helps set the stage for our overall health for the rest of our lives. By the time an infant reaches two years old they are fully colonized with more than 1000 bacterial species, so this short period when the microbiota and the immune system are developing is important.\(^\text{17}\)

During this critical window, four factors promote optimal microbial colonization:\(^\text{11,12}\)

- A healthy pregnancy
- A full-term, vaginal birth
- Cautious use of prenatal and postnatal antibiotics
- Predominant breastfeeding during the first year of life.
Factors that Impact Optimal Microbial Colonization

1. Pregnancy
2. Delivery
3. Antibiotics
4. Feeding

Figure 2. Four important factors impact microbial colonization
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A Healthy Pregnancy

The first factor for proper microbial colonization is a healthy pregnancy. During the first trimester, the microbiota of a pregnant mother is similar to that of a healthy, non-pregnant woman, but later undergoes compositional changes that significantly contribute to the metabolic, hormonal, and immunological changes that occur during pregnancy. The general microbial changes listed in Figure 3 for each microbial region: the mouth, gut, placenta, and vagina, are representative of a healthy pregnancy.

The microbiota in these regions is influenced by factors such as mom’s pre-pregnancy diet as well as her diet during pregnancy. There is some evidence that bacterial infections, such as periodontal disease and bacterial vaginosis, may be correlated with, or perhaps even induce, certain pregnancy complications such as preeclampsia, eclampsia, placental abruption, and preterm birth.
Figure 3. Mom’s microbiota changes during a healthy pregnancy to support fetal development and microbial colonization. Adapted from Nuriel-Ohayon, et al., Frontiers in Microbiology, 2016.
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Full-Term, Vaginal Birth

Delivery Mode

The second element for optimal bacterial colonization is a full-term, vaginal delivery. Although microbial exposure begins in the placenta during fetal development, the major microbial seeding event occurs during birth, when the infant is coated in and ingests large quantities of microbes that will colonize their intestinal tract. Vaginally-delivered infants are exposed to a completely different set of microbes than those that are born via C-section. An infant born vaginally will be colonized with mom’s vaginal microbiota, which is ideal for optimal microbial colonization, while infants born by C-section are primarily seeded with mom’s skin microbiota, therefore, the microbiota of a baby born by C-section is distinctly different than that of a baby born vaginally. For example, infants born by C-section have fewer Bifidobacterium, which are dominant in healthy, breast-fed infants. This is a growing concern as C-sections are common in developed countries. In the United States 32% of babies are delivered by C-section.
**Gestation Period**

Infants born prematurely have been shown to have more potentially pathogenic bacteria, such as *C. difficile* and *Klebsiella pneumoniae*, than full-term infants.\textsuperscript{11,25} In contrast, full-term infants have been shown to have more diverse gut microbiotas with more common and beneficial genera, such as the previously mentioned *Bifidobacterium*.\textsuperscript{25-27}

To paint a parallel that might highlight the importance of this period, consider the critical timing of exposure to certain factors with regard to the developing embryo.\textsuperscript{28} The neonatal period is an extension of prenatal development in that timing is critical with regard to exposure to the right microbes.

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**Figure 4.** Delivery mode and gestation period are important factors in optimal infant and microbial colonization

**Delivery Mode**

- **Cesarean**
  - *Bifidobacterium* ↓
  - > 30% in developed countries!

- **Vaginal**
  - Required for proper seeding
  - *Bifidobacterium* ↑

**Gestation Period**

**Preterm**

- *Enterobacteriaceae* ↑
- *Clostridium difficile*
- *Staphylococcus*
- *Klebsiella pneumoniae*

**Term**

- *Bifidobacterium*
- *Lactobacillus*
- *Streptococcus*
Cautious Use of Prenatal and Postnatal Antibiotics

Prenatal
The third factor for ideal microbial colonization is the cautious use of both prenatal and postnatal antibiotics. Antibiotics have proven to be beneficial, even life-saving in many situations, and pregnancy is no exception. Antibiotic Stewardship is a coordinated program that promotes the appropriate use of antibiotics, improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms. For example, vaginal infections and periodontal disease have been shown to lead to more pre-term deliveries. Therefore, antibiotics would be warranted and not considered unnecessary in this situation. While beneficial, these antibiotics will likely affect the vertical transmission of microbes during birth, interrupting microbial seeding, and ultimately, optimal colonization in the infant. Furthermore, up to 30% of pregnant women in the United States test positive for Group B Streptococcal (GBS) infections, and many of these women receive prophylactic antibiotics to prevent a potentially serious infection in their newborn. According to the CDC, 30% of women reported using antibiotics prior to or during pregnancy, which may have an impact on optimal microbial seeding during the critical window.
Postnatal
Antibiotics are commonly prescribed during infancy and early childhood. In fact, in the United States, the average toddler will receive three separate courses of antibiotics by the time they are two years old.\textsuperscript{30} Statistics show that half of all outpatient antibiotics are unnecessary, regardless of the patient’s age.\textsuperscript{31} This is noteworthy because antibiotics can change the composition of the microbiota regardless of age, especially with repeated use. Even one round of antibiotics can lead to a significant reduction in the diversity of certain communities that persists up to two years.\textsuperscript{32} Taking antibiotics during infancy leads to dysbiosis, which disrupts the important microbial colonization and can lead to long-term consequences such as obesity, dysregulation of the immune system, inflammation, allergy, and asthma.\textsuperscript{33}

**Antibiotic Stewardship** is a coordinated program that promotes the appropriate use of antibiotics, improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms.
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Predominant Breastfeeding

The fourth element for optimal microbial colonization is the prioritization and maximization of breastfeeding for as long as possible. The American Academy of Pediatrics recommends exclusive breastfeeding during the first six months of life, followed by continued breastfeeding as new foods are introduced for the remainder of the first year, however, this is not always possible. The composition of breast milk changes over the course of lactation, with regard to lactose and immunological factors, to support the growth of the infant. While there is some evidence that the microbiome of breast milk also changes during lactation, more data is needed in order to validate this. It is accepted, however, that during pregnancy, maternal prenatal hormones initiate the migration of microbes via macrophages from the intestinal tract to the breastmilk, helping to colonize the infant’s gut microbiota during early infancy. Additionally, breastmilk contains Human Milk Oligosaccharides (HMOs), which are natural prebiotics that promote the growth of beneficial bacteria such as Bifidobacterium and Fructo/Galacto Oligosaccharides (FOS/GOS).

Figure 5. Breastfeeding promotes optimal colonization
promote the growth of *Bifidobacteria* and other commensal bacteria.\textsuperscript{11} In an effort to better mimic human breast milk, formulas may contain added probiotics and oligosaccharides, such as galactooligosaccharides (GOS) or fructooligosaccharides (FOS), which have clinically proven benefits,\textsuperscript{37-44} however they cannot compare to native microbes and HMOs. Furthermore, breastmilk contains immunoglobulins that passively provide immunity for the infant during this critical time when the infants own immune system is maturing.\textsuperscript{45}

These four factors are important for the introduction and colonization of the right microbes during this critical window for the ideal development of the microbiota, especially the intestinal microbiota, which will help shape the overall health of the infant for the rest of their life.
Additional Factors for Optimal Colonization

Two important, less defined, factors for optimal colonization are genetics and environment. Some individuals are born with a genetic predisposition to develop certain conditions, such as allergies, but this factor is beyond the scope of this booklet. When it comes to environment, parents often isolate their newborns isolated, and attempt to keep the home sterile. This is in contrast to, the Hygiene Hypothesis which states that a lack of exposure to beneficial microbes and potentially infectious agents early in life increases our susceptibility to allergic diseases by suppressing the natural development of the immune system.\textsuperscript{46}

Consequences of Improper Microbial Colonization

Insufficient microbial colonization of the intestinal tract can result in episodic or short-term consequences such as digestive discomfort, colic, infectious diarrhea, eczema, and food allergy, as well as long-term or life-long consequences including atopic diseases, autoimmune diseases, neuropsychiatric disorders, and overall health.\textsuperscript{47-49}
Probiotics May Help Shape a Healthy Microbiota and Influence Immune Development

All the benefits that a healthy, intestinal microbiota promotes during the “critical window,” and ultimately helps to modulate immune responses later in life, cannot be completely replaced. However, probiotics may help benefit the microbiota during this important time when potential challenges, such as antibiotic exposure or formula feeding, are unavoidable.
The Role of Microbiota in Infant Development

How the Intestinal Microbiota Helps Shape the Developing Immune System

Additional Resources:

**Microbial changes during pregnancy, birth, and infancy**
This review discusses how the microbiome influences, and is influenced by, pregnancy, fetal development, and infant development. Compositional changes at a variety of body-specific microbiome sites are mentioned for each of these stages of development. The importance of early microbial colonization is discussed, as well as how mode of delivery, feeding regime, weaning, and antibiotic exposure influence colonization.

**Building a beneficial microbiome from birth**
This review describes the effect of the microbiome and the role of microbial metabolites in helping to shape newborn health and development. The structure and function of the gut microbiota during early life is discussed, as well as certain factors that help influence microbial composition. The influence of breastmilk and the role of human milk oligosaccharides on the infant microbiota is also discussed.

**Asthma and the microbiome: defining the critical window in early life**
Asthma is a chronic inflammatory, atopic disease of the lungs with growing prevalence. Research suggests that environmental factors play a role in etiology of this disorder. This review discusses how exposure to the right microbes early in life contributes to the prevention of asthma and introduces the idea that the first 100 days of life, or the “critical window,” is the ideal time to utilize microbes as prophylactic treatments in the prevention of asthma. Mouse-model and human studies are highlighted throughout.
**Lactobacillus GG**

*Lactobacillus* GG is a human derived probiotic strain and is well-established to be both safe and effective in infants. With over 1000 scientific studies and over 200 human clinical trials, *Lactobacillus rhamnosus* GG (Lactobacillus GG, LGG™) has been more extensively studied than any other probiotic strain. *Lactobacillus GG* was identified in 1983 by Professors Goldin and Gorbach at Tufts University. Isolated from a healthy human intestinal microbiota, the “GG” strain was selected for high cellular adhesion *in vitro*, survival in acidic conditions, and anti-pathogenic activity. *In vivo* studies have also shown persistence of *Lactobacillus* GG in the human gastrointestinal tract.

**Mechanisms of Action**

Competition for binding sites and resources contributes to the ability of *Lactobacillus* GG to prevent the adhesion and colonization of pathogens as well as translocation of intestinal bacteria. One subset of *Lactobacillus* GG-specific proteins is responsible for its ability to adhere to the epithelial cells that line the intestines. These proteins are structural components of the pili; hair-like projections that physically attach the bacterial cell to specific sites on epithelial cells (Figure 6). It is through this attachment...
that the immune system is enhanced.\textsuperscript{53,54} Production of acetic and lactic acid, short chain fatty acids, and a bacteriocin, a protein that inhibits related microbes, contributes to the pathogen-inhibiting environment created by \textit{Lactobacillus GG}.\textsuperscript{55}

\textbf{\textit{Lactobacillus GG: Proven Safe in Infants}}

\textit{Lactobacillus GG} is the most clinically studied probiotic strain in the world, including in infants, and is even the standard of care in many neonatal intensive care units.\textsuperscript{56} \textit{Lactobacillus GG} has been shown to colonize the intestinal tract, even at low doses,\textsuperscript{57-62} and has also been proven to be safe at doses as high as 100-200 billion CFU/d.\textsuperscript{63-68} \textit{Lactobacillus GG} has been safely used for very low birth weight (VLBW) infants (\textless 1500 g) at a Level 3 neonatal intensive care unit of Turku University Hospital, Turku, Finland.\textsuperscript{56} Over the twelve-year period, from 1997 to 2008, all enterally fed infants (n=644) were supplemented with \textit{Lactobacillus GG} once a day during their hospital stay. No incidence of septicemia connected to \textit{Lactobacillus GG} was found in the retrospective study.\textsuperscript{56}

Additionally, with respect to pre-term, low-birth weight infants, \textit{Lactobacillus GG} has been the subject of nine clinical trials.\textsuperscript{57,60,69-75} In two of these, clinicians sought to establish a regimen for \textit{Lactobacillus GG} use to address necrotizing enterocolitis. In the study by Manzoni and colleagues, \textit{Lactobacillus GG} (6 billion CFU/d) was administered in combination with bovine lactoferrin to 238 very low birth weight neonates.\textsuperscript{69} Mortality as well as the incidence of NEC was reduced in
the lactoferrin plus *Lactobacillus* GG cohort as compared to placebo. A significant reduction in NEC was also demonstrated by Uberos and co-workers in a study of over 250 very low birth weight newborns in response to *Lactobacillus* GG (1 billion CFU/d).57 There are still several unknowns regarding optimal probiotic use in the NICU including but not limited to appropriate doses and timing, however these studies confirm the safe use of the strain even in the most vulnerable populations.

**Epidemiological Support**

The safety of *Lactobacillus* GG is supported by surveillance studies that evaluated potential increases in clinical infections with increased probiotic consumption. Such studies showed that during a nine-year period, despite a notable increase in *Lactobacillus* GG consumption (~10-fold) in Finland, the number of infections involving *Lactobacillus* species reported to Helsinki health authorities remained at a constant background level of 10-20 cases per year.76

Additionally, Whelan and Myers collected safety data from all case reports, and published randomized and non-randomized trials, of subjects receiving nutritional support supplemented with probiotics.77 Altogether, 72 articles fulfilled the inclusion criteria, and in those articles, 32 out of 4131 patients reported adverse events (0.77%), all of which were caused by the most commonly used probiotics; *Saccharomyces boulardii* (27 cases) or *Lactobacillus* GG (5 cases). The risk factors included the presence of central venous catheters and disorders associated with increased bacterial translocation.

The infections reported in the infant population receiving *Lactobacillus* GG all involved hospitalized patients. Supplementation was prescribed
in an attempt to treat complications resulting from the underlying hospitalization.\textsuperscript{78,79} Definitive strain identification from the sickened patients was not obtained. It is possible that something changed in the infants’ health status making them more prone to infection, not that the probiotic itself translocated to the blood.

Surveillance of adverse events associated with probiotic use necessitates that the clinical isolate be identified to the strain level to be confirmed as the consumed probiotic strain. Lactobacilli, including \textit{Lactobacillus rhamnosus} are ubiquitous and the origin of the infectious agent may not be the supplemented probiotic. As there are numerous strains of Lactobacilli which can be identified, it is important to note that the relationship between the clinical isolate and the strain of Lactobacilli consumed by the subject should be confirmed by appropriate molecular methods.

\textit{Lactobacillus GG} is Included in a Widely Available Infant Formula and Generally Recognized as Safe (GRAS)

\textit{Lactobacillus} GG serves as a prototypic strain of probiotic that has been used in food products and supplements in both Europe and the United States for over 25 years. Of special note, infant formula containing \textit{Lactobacillus} GG has been on the market for several years in Europe and the United States with no reported safety concerns. \textit{Lactobacillus rhamnosus} species has achieved Qualified Presumption of Safety (QPS) –status from the Scientific Committee of European Food Safety Authority and according to U.S. Food and Drug Administration (FDA) the use of \textit{Lactobacillus} GG in infant formulas contains no risk and is Generally Recognized As Safe (GRAS).\textsuperscript{34} No health risks of \textit{Lactobacillus} GG consumption have been identified even when consumed in excess.
Antibiotic Susceptibility

In the unlikely event of a clinical infection, *Lactobacillus GG* is sensitive to antibiotics from each of the common classes: inhibitors of cell wall synthesis, protein synthesis and nucleic acid synthesis. *Lactobacillus GG* naturally carries resistant genes for certain antibiotics on its circular chromosome, however does not carry plasmids that can spread transferable genes. Thus, antibiotic resistance genes cannot be transferred. The complete genome sequence of *Lactobacillus GG* is documented, MCBI RefSeq: NC_013198.1. The fully annotated sequence was published in 2009.
LACTOBACILLUS GG


References, cont’d


Lactobacillus GG 
Clinical Support

*Lactobacillus rhamnosus* GG has been extensively studied in infants for a variety of outcomes including immune and gastrointestinal benefits. *Lactobacillus* GG helps train the immune system in early infancy to help reduce the incidence and severity of atopic conditions. Additionally, by helping to balance the gastrointestinal microbiota, *Lactobacillus* GG promotes digestive health.

### Healthy Immune Development

*Lactobacillus* GG Helps Reduce the Incidence and Severity of Atopic Dermatitis in High Risk Populations

Over the past several decades, the prevalence of ‘modern day maladies,’ such as atopic diseases like eczema, have drastically increased, according to the Centers for Disease Control and Prevention (CDC). Currently, this increase is most remarkable in westernized regions, however the trend is also becoming visible in developing areas. While some children quickly outgrow atopic diseases, for many, these illnesses persist into adulthood and can result in life-long struggles. Data collected over the last two decades indicates that a lack of optimal microbial colonization during the critical window, promotes the risk of atopic disease, highlighting the importance of a healthy human microbiota very early during infancy.¹

When administered prenatally and during infancy, *Lactobacillus* GG has been shown to reduce the incidence and severity of atopic conditions, such as atopic dermatitis, in high risk infants. Clinical studies often utilize the SCORing Atopic Dermatitis (SCORAD) scale to evaluate the presence
and severity of eczema. Two notable studies showed a reduction in SCORAD symptom scores of infants with eczema in response to the inclusion of *Lactobacillus* GG in combination with extensively hydrolyzed whey formula (EHWF). In a study by Isolauri and colleagues, by two months, *Lactobacillus* GG (LGG™+EHWF) reduced the severity of eczema as compared to EHWF (average SCORAD scores of 1 vs. 13.4, respectively; Figure A).

**Figure A:**

*Lactobacillus* GG Improves Severity of Eczema in Infants

*Lactobacillus* GG has been shown to improve the symptoms of eczema in infants, measured by the standardized symptom score scale, SCORAD.

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**N=27**  
**Dose:** $3 \times 10^2$ CFU  
**Duration:** 2 Months  
**Mean Age:** 4-6 Months
The Isolauri lab went on to study *Lactobacillus* GG and its benefits in additional clinical trials. Mothers who met high-risk criteria for allergy were given *Lactobacillus* GG during their last trimester, followed by postnatal administration to their infants for six months. The babies were followed for seven years and the results consistently showed a reduction in the incidence of eczema (Figure B).4-6

**Figure B:**
*Lactobacillus GG Reduces Incidence of Eczema in High Risk Children*

*Lactobacillus GG* has been proven to reduce the incidence of eczema when supplementation begins during the critical window of microbial development.

Additionally, by three months of age the total number of immunoglobulin (Ig) G-secreting cells in the *Lactobacillus* GG group exceeded those in the placebo group, and by twelve months of age for IgG-, IgA-, and IgG-secreting cells, revealing a stimulation of the immune system.7 This study highlights the importance of the early, critical window for microbial development during infancy to help properly train the immune system.
While supplementation with *Lactobacillus* GG later during infancy may help to reduce the severity of eczema, administration during the critical window, even for only a few months, may have lasting immune benefits on the risk of atopic diseases, throughout the individual’s life.

Supportive of the above findings, Majamaa and associates studied the effects of *Lactobacillus* GG on eczema in infants with suspected cow’s milk allergy. They found that for infants on a cow’s milk elimination diet, consuming EHWF + *Lactobacillus* GG resulted in significant improvements in SCORAD scores after one month of intervention, compared to control groups that consumed only EHWF, even at a much lower dose than the Isolauri lab investigated (0.5 billion cfu/gm of formula).

Additional support for the immune benefits of *Lactobacillus* GG come from Nermes and colleagues, who investigated the effects of probiotic supplementation on humoral immunity. Hydrolyzed casein formula with or without *Lactobacillus* GG (about 3 billion CFU/d) was administered to full-term infants with atopic eczema for three months. Although SCORAD scores were not significantly different between the two groups, blood, fecal, and skin samples, collected periodically throughout the study, revealed fewer Ig-secreting cells in probiotic group infants compared to placebo group infants potentially indicating the attenuation of an overly stimulated immune system, strengthened gut barrier function, and enhanced pathogen/antigen exclusion.

Taken together, these findings support the efficacy of administration of *Lactobacillus* GG early during infancy to help promote healthy immune responses later in childhood and life, as demonstrated by reduced incidence of atopic eczema in high risk infants, as well as reduced severity of eczema in infants already effected.
**Lactobacillus GG Helps Infants Acquire Tolerance to Cow’s Milk Allergy**

Cow’s milk allergy (CMA) is the most common food allergy in early childhood. CMA is typically a non-IgE-mediated immunological reaction to the cow’s milk proteins (CMP) casein and whey, while IgE-mediated CMA is less common.⁹ Infants with CMA display a variety of symptoms, including skin rash, respiratory issues, vomiting, diarrhea, gas, bloating.

Extensively hydrolyzed casein formula (EHCF) is a well-known regimen for infants diagnosed with CMA. However, studies show that when *Lactobacillus* GG is added to EHCF, babies acquire tolerance for CMP earlier and more completely.¹⁰,¹¹ Berni Canani and colleagues administered *Lactobacillus* GG or placebo to infants with diagnosed CMA for a year, followed by food challenges at six and twelve months. They found that more infants supplemented with *Lactobacillus* GG achieved dairy tolerance, at both the six and twelve month timepoints, than those who received placebo, meaning that *Lactobacillus* GG was more effectively able to attenuate the increased intestinal permeability observed in infants with CMP allergy (Figure C).¹⁰ *Lactobacillus* GG creates complex responses in the intestinal mucosa, reflected by the up- and down-regulation of several genes involved in immune response, inflammation, cell-cell signaling, signal transcription, and signal transduction.¹⁰

Supporting these findings, Baldassarre and colleagues found that for infants with hematochezia due to suspected cow’s milk allergy, both rectal bleeding and fecal calprotectin levels were significantly decreased after four weeks in infants fed extensively hydrolyzed casein formula (EHCF) supplemented with *Lactobacillus* GG (~1 million CFU/g), compared to control group infants fed only EHCF.¹² After the four week study, none of
the infants in the *Lactobacillus* GG group (EHCF + LGG™) had blood in their stools, compared to 35% of those in the EHCF-only group (EHCF - LGG™). This indicates that *Lactobacillus* GG helps decrease blood loss and may aid in the recovery of the intestinal mucosa in infants with cow’s milk allergy.

Additional studies in infants, measuring fecal immune markers such as calprotectin, IgA, TNF-α, and IFN-γ, indicate the efficacy of *Lactobacillus* GG (5 billion CFU/d) in both boosting the immune response to food antigens and reducing inflammation in the gut.13-15 Taken together, the clinical findings support the potential for *Lactobacillus* GG to help resolve an allergy to CMP when beginning supplementation during infancy.

**Figure C:**
*Lactobacillus* GG Drives Faster Resolution of Cow’s Milk Allergy

Infants who receive *Lactobacillus* GG supplementation achieve milk tolerance faster and more completely than those given placebo.
The Link Between Digestion, Food Allergies, and Colic

Infantile colic is defined by crying that lasts for three or more hours a day, for three or more days a week, for at least three weeks.\(^\text{16}\) While the root cause of colic is not well understood, one hypothesis suggests that the disorder may stem from gastrointestinal dysfunction and allergy issues, such as food allergy. Findings from Partty and associates\(^\text{17,18}\) support the use of \textit{Lactobacillus} GG to help reduce the incidence of infantile colic. In one of their studies, premature infants were supplemented with \textit{Lactobacillus} GG for the first two months of life resulting in fewer infants classified as “excessive criers” in the intervention group compared to control group infants (19\% vs. 47\%, respectively; Figure D).\(^\text{18}\) This study indicates that \textit{Lactobacillus} GG may help reduce the occurrence of colic, likely by reducing one of the presumed root causes of colic, namely gastrointestinal disorders and/or food allergies.

**Figure D:**
\textit{Lactobacillus} GG Helps Reduce Crying Time in Preterm Infants

\textit{Lactobacillus} GG may alleviate symptoms associated with fussing and crying in preterm infants.

- N=94
- Dose: 1-2 Billion CFU
- Duration: 2 Months
- Mean Age: Preterm Infants (23-36 weeks GA)

In another study by the same investigators, full term infants already diagnosed with colic were treated with either *Lactobacillus* GG (4.5 billion CFU/d) or placebo for four weeks. They found that *Lactobacillus* GG did not significantly alter the amount of crying each day\(^\text{17}\) however, parents had the perception that their babies cried less.

*Lactobacillus* GG may be a good prophylactic approach for infantile colic by preventing the gastrointestinal discomfort and allergic problems that theoretically lead to colic. It is worth noting that even though the window of colic is relatively short, peaking between six and eight weeks of age, findings by Savino and associates indicate that susceptibility to psychological disorders in childhood may be increased in those who had suffered from infantile colic\(^\text{19}\) (see Emerging Science).
Lactobacillus GG
Clinical Support

Gastrointestinal Benefits

*Lactobacillus* GG Helps Reduce the Incidence and Duration of Diarrhea in Infants

Diarrheal disease is a worldwide problem and of particular concern in developing countries. According to the CDC, 1 in 9 child deaths worldwide are due to diarrheal disease. Acute gastroenteritis (AGE) causes inflammation of the gastrointestinal tract, affecting the stomach lining and the small intestine resulting in loose or liquid stools and/or increased frequency of evacuation, with or without fever or vomiting. AGE is caused by a range of factors including viruses, bacteria, and parasites. Viruses are the most common cause of AGE, with rotavirus being the most prevalent viral pathogen worldwide. According to the CDC, by the age of five most children will have had a rotavirus infection regardless of where they live.

While supplementing with *Lactobacillus* GG during early infancy helps modulate the immune system and contributes to healthy development, supplementation at any point during infancy helps alleviate dysbiosis and has been clinically proven to reduce the incidence and duration of acute diarrheal infections,\(^{20-28}\) including rotavirus\(^{29-34}\) and nosocomial diarrhea,\(^{28}\) as well as antibiotic-associated side effects.\(^{27}\) These findings are supported by many clinical trials in older populations demonstrating similar results.\(^{35-44}\) Additionally, *Lactobacillus* GG has been shown to increase the IgA-specific antibody-secreting cell response to rotavirus in infants, leading to a rotavirus IgA seroconversion.\(^{45,46}\) These findings indicate that in addition to strengthening the epithelial barrier which contributes to pathogen exclusion and helps keep infants healthy, *Lactobacillus* GG also boosts the adaptive immune response to rotavirus.
Recommendations for the Use of LGG™ for Digestive Benefits

“If probiotics for preventing nosocomial diarrhea in children are considered, the working group recommends using L. rhamnosus GG (at least 1 billion CFU per day, for the duration of hospital stay).”

European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)

“It has been confirmed that different probiotic strains, including LGG™, are useful in reducing the severity and duration of acute infectious diarrhea in children.”

World Gastroenterology Organisation

“The use of Lactobacillus GG may be considered in the management of children with AGE as an adjunct to rehydration therapy.”

ESPGHAN
Szajewska, H., et al. JPGN. 2014
Additional Resources:

**Prevention and management of cow’s milk allergy in non-exclusively breastfed infants**


This review discusses the prevention and management of cow’s milk allergy in infants that are not exclusively breastfed. While breastfeeding is described as the most ideal feeding regimen for infants, the review also discusses the efficacy of hydrolyzed infant formulas, as well as additional alternatives to cow’s milk-based formulas, such as rice hydrolysates and soy-based formulas. The potential benefits of both probiotics and prebiotics are also discussed.

**Probiotics for the prevention of necrotizing enterocolitis in very low-birth-weight infants: a meta-analysis and systematic review.**


This meta-analysis reviewed 23 recent randomized controlled trials to assess the efficacy of probiotic supplementation in both preventing necrotizing enterocolitis (NEC) and death in very-low-birth weight (VLBW) infants. They conclude that probiotic supplementation led to significant reductions in the incidence of both NEC (stage 2 and higher) and mortality in VLBW infants.
The Gut Microbiota, Autism, and ADHD

According to the CDC, the estimated prevalence of Autism Spectrum Disorders (ASD) in 1970 was 1 in 2,000 children, however today that figure is 1 in 68. The underlying cause for this increase is debated. Nevertheless, similar to the research that indicates a connection between the gut microbiome, digestive health, and gastrointestinal disease, there is also data to indicate a strong gut-brain connection. Scientists now appreciate the impact that commensal bacteria from the gut have on the function of the brain. Partty and associates investigated the effect of *Lactobacillus* GG on the diagnosis of ADHD and/or Asperger’s Syndrome by the age of 13. Pregnant mothers supplemented with *Lactobacillus* GG (10 billion CFU/d) for the four weeks prior to their due date and their newborn infants continued the same intervention for six months. Neuropsychiatric diagnoses were reported and assessed at follow-up visits when the children reached 13 years of age. Compared to the placebo group, infants treated with *Lactobacillus* GG were significantly less likely to be diagnosed with ADHD or Asperger’s Syndrome at age 13 (Figure E).

Although only one study investigated using *Lactobacillus* GG in reducing the incidence of ADHD and/or Asperger’s Syndrome so far, this is one of the first gut-brain clinical trials to be published in infants and the only clinical trial to investigate the prevention of these disorders using probiotics.
Supplementation with *Lactobacillus GG* during the critical window may help reduce the risk of certain neuropsychiatric disorders later in life.

**Figure E:**
By Age 13, ADHD or Asperger’s Syndrome were Significantly Less Prevalent in Those Who Received *Lactobacillus GG* During Infancy

The safety and efficacy of *Lactobacillus GG* in infants has been investigated with thousands of infants and toddlers, in over 90 clinical trials, using doses ranging from 14 million-200 billion CFU/d. The most clinically studied probiotic strain in the world, *Lactobacillus GG* has been shown to help properly train the immune system. The strain-specific ability of *Lactobacillus GG* to adhere in the intestine also helps inhibit the colonization of pathogens through competitive exclusion and antimicrobial secretion. With the potential to reduce the incidence and severity of atopic diseases, food allergies, and gastroenteritis, the administration of *Lactobacillus GG* can begin prenatally and continue in newborns to help infants avoid or minimize both digestive and immune conditions, not only during infancy but throughout their lives.
**Lactobacillus GG Clinical Support**

**References**


