Study summaries BB-12®

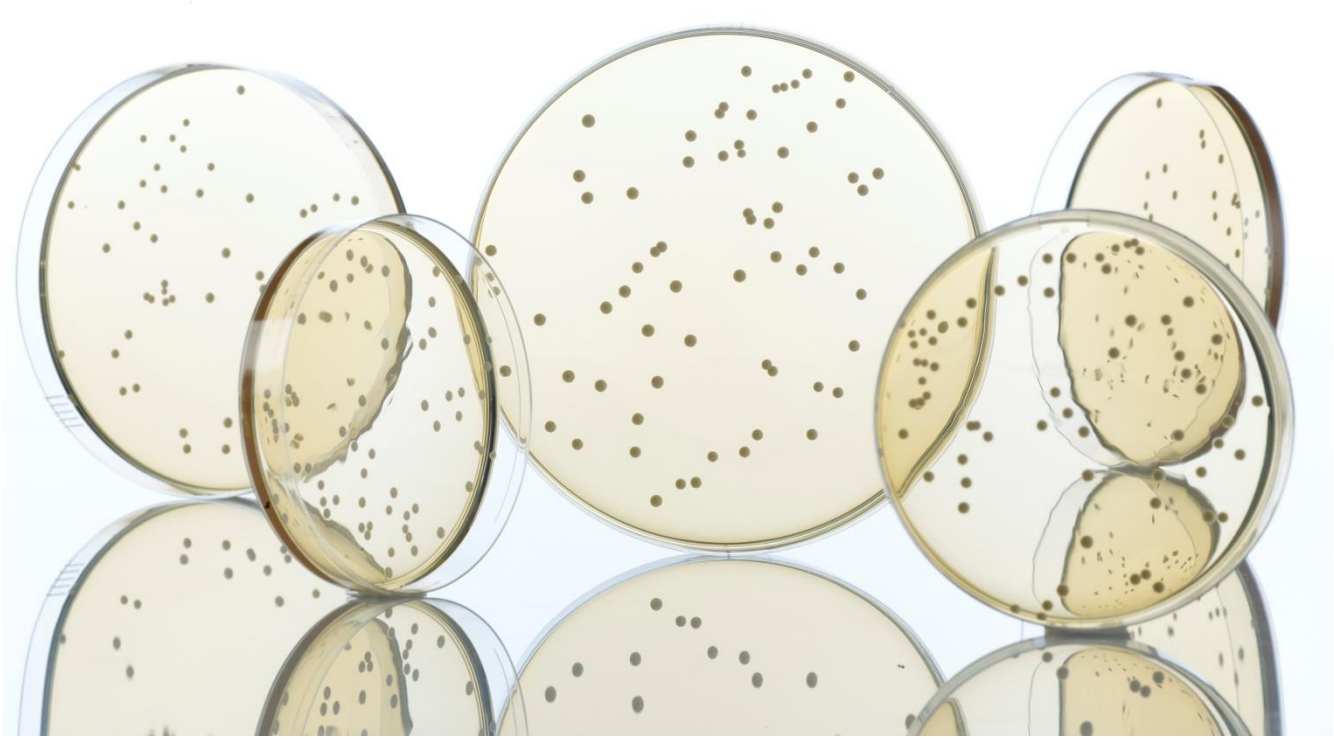
This binder contains summaries of clinical studies performed with with *Bifidobacterium* BB-12® - alone or in combination with other strains.

Clinical studies are performed within Infant & Children's Nutrition – including studies in pre-term infants and pregnant women.

February 2019

Chr. Hansen A/S

Human Health & Nutrition



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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and L. rhamnosus LGG®
Dosage CFU/day: 1 x 10^9 of each

Larnkjær, A., et al. "Effect of probiotics on thymus size and markers of infection in late infancy: a randomized controlled trial". *Pediatric Research*, (January), 1–6 (2020).

Abstract: BACKGROUND: Probiotics are known to stimulate the immune system but the effect on thymus size in late infancy is unknown. We examined the effect of probiotics on thymus size and C-reactive protein (CRP) in healthy Danish infants starting daycare. We further examined associations between thymus size, CRP and recent infections. METHODS: The study included 186 children randomized to a combination of Lactobacillus rhamnosus, LGG® and Bifidobacterium animalis spp. lactis, BB-12® or placebo for 6 months. Thymus size, assessed as thymus index (TI) and thymus weight index (TWI), was measured by ultrasound at baseline and at endpoint. Blood samples were drawn to measure CRP. Infections were parent-reported. RESULTS: There was no significant difference in thymus size between the probiotic group and placebo ($p \geq 0.248$) but TWI tended to be higher in the probiotic group corresponding to 5% higher than placebo ($p = 0.068$) in an adjusted model. There was no effect of probiotics on CRP ($p = 0.331$). At the endpoint, thymus size was inversely associated with CRP ($p \leq 0.040$), diarrhea ($p \leq 0.050$), and TI was also associated with the absence from daycare due to respiratory or gastrointestinal infections ($p = 0.010$). CONCLUSION: The probiotic intervention had no effect on thymus size or CRP in Danish children at the age of starting daycare.

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Research field: Infant and Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and L. rhamnosus LGG®
Dosage CFU/day: 10 billion total

Castro-Mejía, J. L., et al. "Restitution of gut microbiota in Ugandan children administered with probiotics (Lactobacillus rhamnosus GG and Bifidobacterium animalis subsp. lactis BB-12) during treatment for severe acute malnutrition". *Gut Microbes*, *00*(00), 1–13 (2020).

Abstract: Severe acute malnutrition (SAM) is a major challenge in low-income countries and gut microbiota (GM) dysbiosis may play a role in its etiology. Here, we determined the GM evolution during rehabilitation from SAM and the impact of probiotics (Lactobacillus rhamnosus GG and Bifidobacterium animalis subsp. lactis BB-12) supplementation. The GM (16S rRNA gene amplicon sequencing) of children admitted to hospital with SAM showed distinct composition over admission (e.g. Klebsiella spp., and Enterobacteriaceae spp.), discharge (e.g. Clostridiaceae spp., Veilonella dispar) and follow-up (e.g. Lactobacillus ruminis, Blautia spp., Faecalibacterium prausnitzii), reaching similar β- and α-diversity as healthy individuals. Children with diarrhea had reduced distribution of Bacteroidaceae, Lachnospiraceae, increased Enterobacteriaceae and Moraxellaceae, and lower α-diversity. Children suffering from edematous SAM had diminished proportion of Prevotellaceae, Lachnospiraceae, Ruminoccaceae and a higher α-diversity when compared to non-edematous SAM. Supplementation of probiotics did not influence β-diversity upon discharge or follow-up, but it increased ($p < .05$) the number of observed species [SE: > 4.5]. Children where the probiotic species were detected had lower cumulative incidence ($p < .001$) of diarrhea during the follow-up period compared to children receiving placebo and children receiving probiotics, but where the probiotics were not detected. The GM of children with non-edematous and edematous SAM differ in composition, which might have implications for future GM targeted treatments. Probiotics treatment reduced the cumulative incidence of diarrhea during the outpatient phase, with the strongest effect in children where the administered probiotics could be detected in the GM.

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Research field: Maternal Health and Mental Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and L. rhamnosus LGG®
Dosage CFU/day: minimum of 6.5 x 10^9

Dawe, J. P., et al. "Probiotics and Maternal Mental Health: A Randomised Controlled Trial among Pregnant Women with Obesity". *Scientific Reports*, *10*(1), 1–11 (2020).

Abstract: Poor maternal mental health has been associated with a myriad of pregnancy and child health complications. Obesity in pregnancy is known to increase one's risk of experiencing poor maternal mental health and associated physical and mental health complications. Probiotics may represent a novel approach to intervene in poor mental health and obesity. We conducted this pre-specified secondary analysis of the Healthy Mums and Babies (HUMBA) randomised controlled trial to investigate whether probiotics would improve maternal mental health outcomes up to 36 weeks of pregnancy. Two-hundred-and-thirty pregnant women with obesity (BMI ≥ 30.0 kg/m2) were recruited and randomised to receive probiotic (Lactobacillus rhamnosus GG and Bifidobacterium lactis BB12, minimum 6.5 × 109 CFU) or placebo capsules. Depression, anxiety, and functional health and well-being were assessed at baseline (120−176 weeks' gestation) and 36 weeks of pregnancy. Depression scores remained stable and did not differ between the probiotic (M = 7.18, SD = 3.80) and placebo groups (M = 6.76, SD = 4.65) at 36 weeks (p-values > 0.05). Anxiety and physical well-being scores worsened over time irrespective of group allocation, and mental well-being scores did not differ between the two groups at 36 weeks. Probiotics did not improve mental health outcomes in this multi-ethnic cohort of pregnant women with obesity.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU: 10^9 of each strain

Schmidt et al. "Probiotics in late infancy reduce the incidence of eczema : A randomized controlled trial". *Pediatr Allergy Immunol*, *30*(3), 1–6, (2019).

Abstract: Abstract Background: Allergic diseases are common and represent a considerable health and economic burden worldwide. We aimed to examine the effect of a combination of two probiotic strains administered in late infancy and early childhood on the development of allergic diseases and sensitization. Methods: In this double-blind, placebo-controlled intervention trial, participants were randomized to receive a daily mixture of Lactobacillus rhamnosus and Bifidobacterium animalis subsp lactis or placebo—starting prior to attending day care. The intervention period was 6 months, and the parents answered web-based questionnaires on allergic symptoms and doctor's diagnosed allergic disease monthly. IgE was measured at baseline and follow-up. Results: A total of 290 participants were randomized: 144 in the probiotic group and 146 in the placebo group. Mean age at intervention start was 10.1 months. At follow- up (mean age 16.1 months), the incidence of eczema was 4.2% in the probiotic group and 11.5% in the placebo group (P = 0.036). The incidence of asthma and conjunctivitis did not differ between groups, and no children presented with rhinitis. Sensitization was equal in the two groups at intervention start (7.5% and 9.5%, respectively), and two children in each group were sensitized during the intervention. Conclusions: We observed a significantly lower incidence of eczema in the probiotic group compared to the placebo group. The probiotics were administered in late infancy— prior to attending day care—suggesting a broader window of opportunity using probiotics in the prevention of eczema. The incidence of asthma, rhinitis, conjunctivitis, and sensitization did not differ.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day:

Nabukeera-Barungi et al. "Thymus gland size during recovery from complicated severe acute malnutrition: a prospective study of the role of probiotics". Paediatrics and International Child Health, 39(2), 95–103, (2019).

Abstract: BACKGROUND: Children with severe acute malnutrition (SAM) are prone to infections due to immune dysfunction including severe thymus atrophy which recovers during nutritional rehabilitation. AIM: To investigate predictors of thymus size recovery, including probiotics during nutritional rehabilitation of children admitted with complicated SAM. METHODS: In this prospective study nested in a randomized controlled trial, children 6-59 months admitted with SAM received standard care and either probiotics or placebo during hospitalization until 8 weeks post-discharge. Thymus size was measured using ultrasound at admission, discharge, 8 weeks post-discharge and among 27 community controls. Predictors of thymus size recovery were assessed using linear regression. RESULTS: Among 388 children with SAM, mean (SD) thymus size was 1.06 cm2 (0.41), 1.24 cm2 (0.48), 2.85 cm2 (1.07) and 4.2 cm2 (0.93) at admission, discharge, follow-up and in the healthy controls respectively ($p < 0.05$).Probiotics did not affect thymus recovery. During both inpatient therapeutic care (ITC) and outpatient therapeutic care (OTC), thymus recovery correlated positively with anthropometry but negatively with caregiver-perceived illness severity and Haemoglobin <8 g/dl. Negative predictors of thymus recovery during ITC included grade 3 oedema (beta -0.13, 95%CI -0.25; -0.01), dermatosis (beta -0.21, 95%CI -0.41; -0.01), C-reactive protein (CRP) >15mg/L (beta -0.13, 95%CI -0.25; -0.02) and neutrophils (beta -0.01, 95%CI -0.02; -0.002). During OTC, HIV negatively predicted thymus recovery. CONCLUSION: Children with SAM failed to regain thymus size at 8 weeks post-discharge. Probiotics did not predict thymus recovery during nutritional rehabilitation. More research is needed to find interventions which can accelerate immune recovery. ABBREVIATIONS: ART, Antiretroviral therapy; BB-12, Bifidobacterium animalis subsp. Lactis; CRP, C-reactive protein; ITC, inpatient therapeutic care; LGG, Lactobacillus rhamnosus; MNU, Mwanamugimu Nutrition Unit; MUAC, mid-upper arm circumference; OTC, outpatient therapeutic care; PCR, Polymerised chain reaction; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; VAS, visual analogue score; WHO, World Health Organization; WHZ, weight-for-height score.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU/day: 6.5 x 10^9

Okesene-Gafa et al, "Effect of antenatal dietary interventions in maternal obesity on pregnancy weight-gain and birthweight: Healthy Mums and Babies (HUMBA) randomized trial". *American Journal of Obstetrics and Gynecology*, *221*(2), 152.e1-152.e13 (2019).

Abstract: Background: Pregnancy interventions that improve maternal and infant outcomes are urgently needed in populations with high rates of obesity. We undertook the Healthy Mums and Babies (HUMBA) randomized controlled trial to assess the effect of dietary interventions and or probiotics in a multiethnic population of pregnant women with obesity, living in an area of high deprivation. Objectives: To determine whether a culturally tailored dietary intervention and or daily probiotic capsules in pregnant women with obesity reduces the co-primary outcomes of (1) excessive gestational weight gain (mean >0.27 kg/week) and (2) birthweight. Study Design: We conducted a 2 × 2 factorial, randomized controlled trial in women without diabetes at pregnancy booking, body mass index ≥30 kg/m 2 , and a singleton pregnancy. At 12 +0 to 17 +6 weeks' gestation, eligible women were randomized to a dietary intervention (4 tailored educational sessions at ≤28 weeks' gestation by a community health worker trained in key aspects of pregnancy nutrition plus text messaging until birth) or to routine dietary advice; and to daily capsules containing either (Lactobacillus rhamnosus GG and Bifidobacterium lactis BB12, minimum 6.5 × 10 9 colony forming units), or placebo, until birth. Analysis was by intention to treat with adjustment for maternal baseline body mass index. Infant outcomes were additionally adjusted for ethnicity, sex, and gestational age at birth. Results: In total, 230 women were recruited between April 2015 and June 2017 (dietary intervention N = 116 vs routine dietary advice N = 114; probiotics N = 115 vs placebo N = 115). Baseline characteristics and demographic variables were similar across all groups. There was no significant difference between intervention groups, for the co-primary outcomes of (1) proportion of women with excessive gestational weight gain (dietary intervention vs routine advice: 79/107 [73.8%] vs 90/110 [81.8%], adjusted relative risk [relative risk, 0.92; 95% confidence interval, 0.80–1.05]; probiotics versus placebo: 89/108 [82.4%] and 80/109 [73.4%], relative risk, 1.14, 95% confidence interval, 0.99–1.31) or (2) birthweight (dietary intervention vs routine advice: 3575 vs 3612 g, adjusted mean difference, −24 g, 95% confidence interval, −146 to 97; probiotics vs placebo: 3685 vs 3504 g, adjusted mean difference, 107 g, 95% confidence interval, −14 to 228). Total maternal weight gain, a secondary outcome, was lower with dietary intervention compared with routine dietary advice (9.7 vs 11.4 kg, adjusted mean difference, −1.76, 95% confidence interval, −3.55 to 0.03). There were no significant differences between intervention groups in other secondary maternal or neonatal outcomes. Conclusion: Although dietary education and or probiotics did not alter rates of excessive gestational weight gain or birthweight in this multiethnic, high-deprivation population of pregnant women with obesity, dietary education was associated with a modest reduction in total weight gain with potential future benefit for the health of mothers and their offspring if sustained.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU/day: 2 x 10^9

Adler Sørensen et al. "Probiotics and the immunological response to infant vaccinations; a double-blind randomized controlled trial". *Clinical Microbiology and Infection*, *25*(4), 511.e1-511.e7, (2019).

Abstract:
Objectives: To examine the effect of a combination of probiotics on the antibody response to pneumococcal and pertussis vaccination in healthy Danish children, aged 8–14 months, at the time of starting day care. Moreover, the cytokine response to lipopolysaccharide of whole blood was assessed. Methods: A total of 290 children were randomly allocated to receive a combination of Bifidobacterium animalis ssp. lactis and Lactobacillus rhamnosus GG daily for a 6-month intervention period, and blood samples were drawn at the start and end of the study. Specific antibody response towards Streptococcus pneumoniae serotypes and Bordetella pertussis toxin, as well as endotoxin-induced interleukin-6 (IL-6) and interferon-γ (IFN-γ) production in blood were analysed by Luminex and ELISA. Results: There was no significant difference between the average individual changes from baseline to end of study in antibody concentrations for S. pneumoniae for both the probiotics (340.4% ± 11.2%) and the placebo group (382.9% ± 10.4%) (p 0.525), nor for B. pertussis toxin in the two groups (probiotics 190.1% ± 12.6% versus placebo 238.8% ± 1.1%, p 0.340). The average individual change in IL-6 concentration was significantly lower in the probiotics versus the placebo group (2.9% ± 10.3% versus 33.7% ± 9.0%, p 0.024), whereas there was no difference in IFN-γ concentration (0.0% ± 0.2% versus −0.2% ± 0.1%, p 0.279). Conclusions: The probiotic intervention did not affect the antibody response against S. pneumoniae and B. pertussis toxin in healthy Danish children.

Research field: Infant and Children´s Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12®
Dosage CFU/day: 1 × 10^9 cfu BB-12® per day

Nocerino et al. *Bifidobacterium animalis* subsp.*lactis* BB-12 is effective in the treatment of infant colic: result of a randomized controlled trial. *Alimentary Pharmacology & Therapeutics*, (December), 1–11, (2019)

Abstract
OBJECTIVES AND STUDY. Infant colic (IC) is a very common affecting up to 20-40% of infants aged <3 m, with a typical peak at about 6 wks of age. The pathophysiology is still poorly defined, but alterations in gut microbiota structure and function seem to be involved. This suggests the potential role of probiotics as therapeutic strategy. We aimed to evaluate the potential efficacy of *Bifidobacterium animalis* subsp.*lactis* BB-12 (BB-12) in babies with IC. Main study outcome was the rate of infants with a reduction of ≥50% of mean daily crying duration at 28 days after intervention. Secondary outcomes were the mean number of crying episodes, occurrence of infectious episodes, number of bowel movements and stool consistency. Gut microbiota structure and function (butyrate production) and fecal level of human beta defensin 2 (HBD-2), cathelicidin (LL-37), secretory IgA (sIgA) and calprotectin (CLP) were also evaluated.
METHODS. A double-blind RCT on otherwise healthy exclusively breastfed infants aged ≤ 7 wks, with IC were performed. Infants were randomly allocated to 2 groups (group A, BB-12 or group B, placebo) according to the randomization list. Study products were provided in drops packed in identical boxes with the same color, weight, smell and taste. Each subject assumed orally 6 drops/day of the assigned product for 28 consecutive days. Patient's parents were provided with a diary to report daily the number and duration of crying episodes, number of bowel movements and stool consistency. All subjects were clinically examined weekly and parents' diary completeness were checked. At baseline and at the end of treatment, a stool sample was collected from all study subjects to assess gut microbiota structure (16sRNA), butyrate production (HPLC-MS), HBD-2, LL-37, sIgA, CLP (ELISA).
RESULTS. 80 infants were randomized, 40 per group; 8 subjects were lost to follow up, and 72 subjects completed the study: 35 in BB-12 group and 37 in placebo group. At baseline, main demographic and clinical features of the 2 study groups were similar. The rate of infants with reduction of ≥50% of duration of crying was significantly higher in infants treated with BB-12 compared to placebo (80% vs 32.5% respectively, $p<0.05$). The mean number of crying episodes significantly decreased in both groups, but with a significant higher effect in BB-12 group
(-4.77±3.43 vs -2.31±2.28 respectively, $p<0.05$). Mean daily stool frequency decreased in both groups but the effect was significant higher in the BB-12 group; stool consistency was similar between the 2 groups. A significant increase in Bifidobacterium abundance, butyrate production, HBD-2, LL-37, sIgA, associated with a decrease in CLP level was observed in BB-12 group. ($p<0.05$).
CONCLUSIONS. The results of this study demonstrate that the oral daily supplementation with BB-12 is effective in managing IC. The effect could derive from multiple immune and non-immune mechanisms associated with a possible modulation of gut microbiota. This RCT studied specific well characterized probiotic strain, dose, and age group. The findings cannot be extrapolated for other probiotic strains.

Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and E. faecium L3
Dosage CFU/day: 2 billion of each strain

Di Pierro, Francesco et al. "Use of a Probiotic Mixture Containing Bifidobacterium Animalis Subsp. Lactis BB12 and Enterococcus Faecium L3 in Atopic Children." Minerva Pediatrica 70.5 (2018): 418–424.

Abstract: BACKGROUND Imbalance of the human gut microbiota in childhood, mainly due to low gut biodiversity and a low bifidobacterial load, has been suggested as a risk factor for atopy. Administration of Enterococcus faecium L3 in infants has been shown to increase the gut bifidobacterial count. The aim was to verify if a mixture of Bifidobacterium animalis subsp. lactis BB12 and E. faecium L3 could reduce the signs, symptoms and need for drugs in atopic children. METHODS We retrospectively analyzed, and compared with controls, clinical outcomes following use of BB12 and L3 strains when administered 3 months before or during the development of signs and symptoms of atopy. RESULTS When administered in the 3 months before the development of atopy, the BB12 and L3 strains significantly reduced ($p<0.001$) rhinitis, watery eyes and cough/bronchospasm. However, reduced efficacy was observed when the mixture was given during the 3 months of atopy. The mixture of strains also significantly reduced the use of oral anti-histamines, inhaled corticosteroids (in the same children in two different years) and oral corticosteroids (in different children in the same year). CONCLUSIONS When administered as a prophylactic, the mixture of BB12 and L3 (iNatal Ped®) statistically decreases the signs and symptoms of atopy and reduces the use of drugs. Administration of the same probiotics as treatment after the appearance of atopy is less effective.

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Research field: Infant and Children´s Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12® and Lactobacillus acidophilus LA-5 and L. rhamnosus LGG®
Dosage CFU/day: 5×10^{10} cfu of LGG and Bb-12 and 5×10^{9} cfu of La-5 per day

Simpson, Melanie Rae et al. "Breastfeeding-Associated Microbiota in Human Milk Following Supplementation with Lactobacillus Rhamnosus GG, Lactobacillus Acidophilus La-5, and Bifidobacterium Animalis Ssp Lactis Bb-12." Journal of Dairy Science 101.2 (2018): 889–899.

Abstract: Breastfeeding is one of the major factors affecting the early development of the infant gut microbiota, and weaning is associated with a shift in the gut microbiota toward a more adult composition. Through breastfeeding, infants receive bioactive components that shape their microbiota while also being exposed to the breast milk and breast surface microbial communities. Recent studies have suggested the possibility of an entero-mammary route of microbial transfer, opening the possibility of infant gut microbiota modulation through maternal probiotic supplementation. In this study, we have analyzed breast milk samples collected at 10 d and 3 mo postpartum from women participating in the Probiotics in the Prevention of Allergy among Children in Trondheim placebo controlled trial. Women who were randomized to the probiotic arm of the Probiotics in the Prevention of Allergy among Children in Trondheim trial received a fermented milk supplemented with Lactobacillus rhamnosus GG, Lactobacillus acidophilus La-5, and Bifidobacterium animalis ssp. lactis Bb-12, consuming this daily from 4 wk before their expected due date until 3 mo after birth. In total, 472 breast milk samples were assessed for the administered bacteria using quantitative real-time PCR and the microbiota transferred during breastfeeding was analyzed using 16S ribosomal RNA gene sequencing of 142 samples. We found that breastfeeding is unlikely to be a significant source of L. rhamnosus GG, L. acidophilus La-5, and B. animalis ssp. lactis Bb-12 for infants in the probiotic arm of the trial. Furthermore, maternal supplementation did not significantly affect the overall composition of the breast milk microbiota transferred during breastfeeding. We also present a descriptive analysis of this microbiota, which was largely dominated by Streptococcus and Staphylococcus genera at both 10 d and 3 mo postpartum. Samples collected at 3 mo postpartum had a statistically significant lower presence and relative abundance of the Staphylococcus genus. These samples also had a greater number of observed species and diversity, including more operational taxonomic units from the Rothia, Veillonella, Granulicatella, and Methylbacterium genera.

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Research field: Infant and Children´s Nutrition
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12®, Bifidobacterium longum subsp. infantis BB-02 and Streptococcus thermophilus TH-4
Dosage CFU/day: 350 x 10^6, 300x10^6 and 350x10^6 CFU, respectively

Plummer, Erica L. et al. "Gut Microbiota of Preterm Infants Supplemented with Probiotics: Sub-Study of the ProPrems Trial." Bmc Microbiology 18.1 (2018): 184.

Abstract: Background: The ProPrems trial, a multi-center, double-blind, placebo-controlled randomized trial, previously reported a 54% reduction in necrotizing enterocolitis (NEC) of Bell stage 2 or more from 4.4 to 2.0% in 1099 infants born before 32 completed weeks' gestation and weighing < 1500 g, receiving probiotic supplementation (with Bifidobacterium longum subsp. infantis BB-02, Streptococcus thermophilus TH-4 and Bifidobacterium animalis subsp. lactis BB-12). This sub-study investigated the effect of probiotic supplementation on the gut microbiota in a cohort of very preterm infants in ProPrems. Results: Bifidobacterium was found in higher abundance in infants who received the probiotics (AOR 17.22; 95% CI, 3.49–84.99, p < 0.001) as compared to the placebo group, and Enterococcus was reduced in infants receiving the probiotic during the supplementation period (AOR 0.27; 95% CI, 0.09–0.82, p = 0.02). Conclusion: Probiotic supplementation with BB-02, TH-4 and BB-12 from soon after birth increased the abundance of Bifidobacterium in the gut microbiota of very preterm infants. Increased abundance of Bifidobacterium soon after birth may be associated with reducing the risk of NEC in very preterm infants.

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Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU/day:

Tan, Tina P. et al. "Safety of Bifidobacterium Animalis Subsp Lactis (B. Lactis) Strain BB-12-Supplemented Yogurt in Healthy Children." Journal of Pediatric Gastroenterology and Nutrition 64.2 (2017): 302–309.

Abstract: OBJECTIVES: Probiotics are live microorganisms that may provide health benefits to the individual when consumed in sufficient quantities. For studies conducted on health or disease endpoints on probiotics in the United States, the Food and Administration has required those studies to be conducted as investigational new drugs. This phase I, double-blinded, randomized, controlled safety study represents the first requirement of this pathway. The purpose of the study was to determine the safety of Bifidobacterium animalis subsp. lactis (B lactis) strain BB-12 (BB-12)-supplemented yogurt when consumed by a generally healthy group of children. The secondary aim was to assess the effect of BB-12-supplemented yogurt on the gut microbiota of the children.
METHODS: Sixty children ages 1 to 5 years were randomly assigned to consume 4 ounces of either BB-12-supplemented yogurt or nonsupplemented control yogurt daily for 10 days. The primary outcome was to assess safety and tolerability, as determined by the number of reported adverse events.
RESULTS: A total of 186 nonserious adverse events were reported, with no significant differences between the control and BB-12 groups. No significant changes due to probiotic treatment were observed in the gut microbiota of the study cohort.
CONCLUSIONS: BB-12-supplemented yogurt is safe and well-tolerated when consumed by healthy children. The present study will form the basis for future randomized clinical trials investigating the potential effects of BB-12-supplemented yogurt in different disease states.

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Research field: Infant and children´s nutrition and Immune Health
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12® and L. rhamnosus, LGG® **and** Lactobacillus acidophilus La-5.
Dosage CFU/day: 5x10^{10} CFU/day of each strain

Schei et al. "Early Gut Mycobiota and Mother-Offspring Transfer." Microbiome 5.1 (2017): 107

Abstract: BACKGROUND: The fungi in the gastrointestinal tract, the gut mycobiota, are now recognised as a significant part of the gut microbiota, and they may be important to human health. In contrast to the adult gut mycobiota, the establishment of the early gut mycobiota has never been described, and there is little knowledge about the fungal transfer from mother to offspring.
METHODS: In a prospective cohort, we followed 298 pairs of healthy mothers and offspring from 36 weeks of gestation until 2 years of age (1516 samples) and explored the gut mycobiota in maternal and offspring samples. Half of the pregnant mothers were randomised into drinking probiotic milk during and after pregnancy. The probiotic bacteria included Lactobacillus rhamnosus GG (LGG), Bifidobacterium animalis subsp. lactis Bb-12 and Lactobacillus acidophilus La-5. We quantified the fungal abundance of all the samples using qPCR of the fungal internal transcribed spacer (ITS)1 segment, and we sequenced the 18S rRNA gene ITS1 region of 90 high-quantity samples using the MiSeq platform (Illumina).
RESULTS: The gut mycobiota was detected in most of the mothers and the majority of the offspring. The offspring showed increased odds of having detectable faecal fungal DNA if the mother had detectable fungal DNA as well (OR = 1.54, p = 0.04). The fungal alpha diversity in the offspring gut increased from its lowest at 10 days after birth, which was the earliest sampling point. The fungal diversity and fungal species showed a succession towards the maternal mycobiota as the child aged, with Debaryomyces hansenii being the most abundant species during breast-feeding and Saccharomyces cerevisiae as the most abundant after weaning. Probiotic consumption increased the gut mycobiota abundance in pregnant mothers (p = 0.01).
CONCLUSION: This study provides the first insight into the early fungal establishment and the succession of fungal species in the gut mycobiota. The results support the idea that the fungal host phenotype is transferred from mother to offspring.

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Research field: Infant and children´s nutrition and Immune Health
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12® and L. rhamnosus, LGG®
Dosage CFU/day: 10^9 CFU/day

Groele et al. Effects of Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 on beta-cell function in children with newly diagnosed type 1 diabetes: protocol of a randomised controlled trial. Bmj Open 7.10 (2017):

Abstract: INTRODUCTION: Recent evidence has demonstrated that, among other factors, dysbiosis (imbalances in the composition and function of the gut microbiota) may be relevant in the development of type 1 diabetes (T1D). Thus, gut microbiota may be a target for improving outcomes in subjects with T1D. The aim of the study is to examine the effects of Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 on beta-cell function in children with newly diagnosed T1D.
METHODS AND ANALYSIS: A total of 96 children aged 8 to 17 years with newly diagnosed T1D, confirmed by clinical history and the presence of at least one positive autoantibody, will be enrolled in a double-blind, randomised, placebo-controlled trial in which they will receive L. rhamnosus GG and B. lactis Bb12 at a dose of 109 colony-forming units or an identically appearing placebo, orally, once daily, for 6 months. The follow-up will be for 12 months. The primary outcome measures will be the area under the curve of the C-peptide level during 2-hour responses to a mixed meal.
ETHICS AND DISSEMINATION: The Bioethics Committee approved the study protocol. The findings of this trial will be submitted to a peer-reviewed paediatric journal. Abstracts will be submitted to relevant national and international conferences.
TRIAL REGISTRATION NUMBER: NCT03032354; Pre-results.

Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12® and L. rhamnosus, LGG®
Dosage CFU/day:

Rø et al. Reduced Th22 cell proportion and prevention of atopic dermatitis in infants following maternal probiotic supplementation. Clin Exp Allergy. 2017 Aug;47(8):1014-1021

Abstract: BACKGROUND: In the randomized, controlled study Probiotics in the Prevention of Allergy among Children in Trondheim (ProPACT), maternal probiotic supplementation reduced the incidence of atopic dermatitis (AD) in the offspring. In the current study, we hypothesized that the effect was mediated by a shift in the T helper (Th) cells in the children.
OBJECTIVE: To examine whether Th cell proportions were affected by maternal probiotic supplementation and thus could mediate the preventive effect of probiotics on AD.
METHODS: A total of 415 pregnant women were randomized to ingest a combination of Lactobacillus rhamnosus GG (LGG), Bifidobacterium animalis subsp. lactis Bb-12 (Bb-12) and Lactobacillus acidophilus La-5 (La-5) or placebo, and their offspring were assessed for AD during the first 2 years of life. Peripheral blood collected at 3 months of age was analysed for regulatory T cells (n=140) and Th subsets (n=77) including Th1, Th2, Th9, Th17 and Th22.
RESULTS: The proportion of Th22 cells was reduced in children in the probiotic group compared to the placebo group (median 0.038% vs 0.064%, P=.009). The difference between the probiotic and placebo groups was also observed in the children who did not develop AD during the 2-year follow-up. The proportion of Th22 cells was increased in children who developed AD compared to the children who did not develop AD (0.090% vs 0.044%, P<.001). Mediation analysis indicated that the preventive effect of probiotics was partially mediated through the reduction in Th22 cells.
CONCLUSION: Perinatal maternal probiotic supplementation with a combination of LGG, Bb-12 and La-5 reduced the proportion of Th22 cells in 3-month-old children. This may partially explain the preventive effect of probiotics on AD.

Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: Bifidobacterium, Bb-12®
Dosage CFU/day:

Xinias et al. Innovative Dietary Intervention Answers to Baby Colic. Pediatr Gastroenterol Hepatol Nutr. 2017 Jun;20(2):100-106.

Abstract: PURPOSE: The purpose of this paper is to evaluate the efficacy of a lactose-reduced synbiotic partial whey hydrolysate in formula fed infants presenting with colic and the impact of this dietary intervention in mean crying time and quality of life. METHODS: Forty infants with infantile colic were treated during one month with parental reassurance and the intervention formula (partial whey hydrolysate, reduced lactose, Bifidobacterium lactis BB12 and galacto-oligosaccharides) and were compared to a control group of 20 infants with infantile colic treated with parental reassurance and a standard infant formula. Parents completed a quality of life (QoL) questionnaire assessing the burden of infantile colic. Wilcoxon test, t-test and Mann-Whitney test were used to compare QoL scores before and after intervention as well as between the intervention and control group. RESULTS: At inclusion, duration of crying did not differ between both groups. Crying duration decreased with 2.7 hours (from 3.2 to 0.5 hours) in the intervention group while duration of crying decreased only with 1.2 hours in the control group ($p<0.001$). Stool composition became looser in the intervention group, but defecation frequency did not change. The median scores of the QoL questionnaire improved significantly in the intervention group for all parameters. In the control group, parameters improved significantly also but not for the parent-child and social interaction. The score changes were significantly greater in the intervention than in the control group.
CONCLUSION: The intervention formula (partial whey hydrolysate, synbiotic, reduced lactose) significantly reduced the duration of crying and improved QoL of the parents and infants.

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Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: Bifidobacterium, BB-12® and L. rhamnosus, LGG®
Product formulation:

Laursen et al. Administration of two probiotic strains during early childhood does not affect the endogenous gut microbiota composition despite probiotic proliferation. BMC Microbiol. 2017 Aug 17;17(1):175.

Abstract: BACKGROUND: Probiotics are increasingly applied to prevent and treat a range of infectious, immune related and gastrointestinal diseases. Despite this, the mechanisms behind the putative effects of probiotics are poorly understood. One of the suggested modes of probiotic action is modulation of the endogenous gut microbiota, however probiotic intervention studies in adults have failed to show significant effects on gut microbiota composition. The gut microbiota of young children is known to be unstable and more responsive to external factors than that of adults. Therefore, potential effects of probiotic intervention on gut microbiota may be easier detectable in early life. We thus investigated the effects of a 6 month placebo-controlled probiotic intervention with Bifidobacterium animalis subsp. lactis (BB-12®) and Lactobacillus rhamnosus (LGG®) on gut microbiota composition and diversity in more than 200 Danish infants (N = 290 enrolled; N = 201 all samples analyzed), as assessed by 16S rRNA amplicon sequencing. Further, we evaluated probiotic presence and proliferation by use of specific quantitative polymerase chain reaction (qPCR).
RESULTS: Probiotic administration did not significantly alter gut microbiota community structure or diversity as compared to placebo. The probiotic strains were detected in 91.3% of the fecal samples from children receiving probiotics and in 1% of the placebo treated children. Baseline gut microbiota was not found to predict the ability of probiotics to establish in the gut after the 6 month intervention. Within the probiotics group, proliferation of the strains LGG® and BB-12® in the gut was detected in 44.7% and 83.5% of the participants, respectively. A sub-analysis of the gut microbiota including only individuals with detected growth of the probiotics LGG® or BB-12® and comparing these to placebo revealed no differences in community structure or diversity.
CONCLUSION: Six months of probiotic administration during early life did not change gut microbiota community structure or diversity, despite active proliferation of the administered probiotic strains. Therefore, alteration of the healthy infant gut microbiota is not likely to be a prominent mechanism by which these specific probiotics works to exert beneficial effects on host health.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. rhamnosus, LGG®
Dosage CFU/day: 5 billion each
Product formulation:
Sachet (maltodextrin with or without probiotics)
Reference number: 1739

Grenov, et al. Effect of Probiotics on Diarrhea in Children With Severe Acute Malnutrition: A Randomized Controlled Study in Uganda. J.Pediatr.Gastroenterol.Nutr. 2017;[Epub ahead of print]

Abstract: OBJECTIVES: To assess the effect of probiotics on diarrhea during in- and outpatient treatment of children with severe acute malnutrition (SAM). METHODS: A randomized, double-blind, placebo-controlled study was conducted involving 400 children admitted with SAM. Patients received one daily dose of a blend of Bifidobacterium animalis subsp. lactis (BB-12) and Lactobacillus rhamnosus (LGG) (10 billion colony-forming units, 50:50) or placebo during hospitalization followed by an 8-12 week outpatient treatment period, depending on patients' recovery rate. All outcomes were reported for in- and outpatient treatment separately. The primary outcome was number of days with diarrhea during hospitalization. Secondary outcomes included other diarrhea outcomes, pneumonia, weight gain, and recovery. RESULTS: There was no difference in number of days with diarrhea between the probiotic (n = 200) and placebo (n = 200) groups during inpatient treatment (adjusted difference +0.2 days, 95% CI -0.8 to 1.2, p = 0.69), however during outpatient treatment, probiotics reduced days with diarrhea (adjusted difference -2.2 days 95% CI -3.5 to -0.3, p = 0.025). There were no effects of probiotics on diarrhea incidence and severity or pneumonia, weight gain or recovery during in- or outpatient treatment. Twenty-six patients died in the probiotic versus 20 in the placebo group (p = 0.38). CONCLUSION: BB-12 and LGG had no effect on diarrhea in children with SAM during hospitalization, but reduced the number of days with diarrhea in outpatient treatment by 26%. Probiotics may have a role in follow-up of hospitalized children with SAM or in community based treatment of malnourished children, but further studies are needed to confirm this.This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. http://creativecommons.org/licenses/by-nc-nd/4.0.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® , L. rhamnosus, LGG® ,Lactobacillus paracasei ST11 and Bifidobacterium longum BL999
Dosage CFU/day:

Lundelin, Krista et al. "Long-Term Safety and Efficacy of Perinatal Probiotic Intervention: Evidence from a Follow-up Study of Four Randomized, Double-Blind, Placebo-Controlled Trials." Pediatric Allergy and Immunology 28.2 (2017): 170–175

Abstract: BACKGROUND: Societies worldwide are faced with a progressive increase in immune-mediated health problems such as allergic, autoimmune, and inflammatory diseases, as well as obesity. Perinatal administration of specific probiotic bacteria is an attractive approach in reducing the risk of these conditions, but long-term efficacy and safety data are lacking. The aim here was to evaluate the clinical benefit and long-term safety of specific probiotics administered during the perinatal period.
METHODS: The probiotic strains used were Lactobacillus rhamnosus GG, Bifidobacterium lactis Bb-12, Lactobacillus paracasei ST11, and Bifidobacterium longum BL999. The children involved have subsequently undergone prospective long-term follow-up. In addition to physical examination, data were collected by structured questionnaires on non-communicable diseases and continued probiotic use, and growth data from welfare clinics and school nurses.
RESULTS: Altogether 303 mother-infant pairs were included in the analysis. Seventy-six of 163 (47%) children receiving perinatal probiotics had developed allergic disease compared with 79 of 140 (56%) receiving placebo (OR 0.67, 95% confidence intervals [CI] 0.43-1.06, p = 0.09). Fifty-nine of 133 (44%) children receiving L. rhamnosus GG perinatally had developed allergic disease, OR 0.62, 95% CI 0.38-0.99, p = 0.047, as compared to placebo. We found no differences in growth or non-communicable disease prevalence between children receiving perinatally probiotics or placebo.
CONCLUSIONS: Perinatal probiotic administration is safe in long-term follow-up. Children receiving L. rhamnosus GG perinatally tended to have decreased allergy prevalence.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU/day: 10^9 CFU

Hojsak et al. "Bifidobacterium Animalis Subsp Lactis in Prevention of Common Infections in Healthy Children Attending Day Care Centers - Randomized, Double Blind, Placebo-Controlled Study." Clinical Nutrition 35.3 (2016): 587–591

Abstract: Background & aims: The aim of our study was to investigate the role of Bifidobacterium animalis subsp. lactis (BB-12®) in the prevention of common (gastrointestinal and respiratory) infections in healthy children who attend day care centers. Methods: We conducted a randomized, double-blind, placebo-controlled trial in 210 children who attend day care centers. They were randomly allocated to receive placebo (Placebo group, n = 106) or BB-12®at a dose of 109colony-forming units (CFU) (Intervention group, n = 104) during the 3-month intervention period. Results: Intention to treat analysis was used. There were overall 99 infections in Placebo group and 97 in Intervention group (incidence rate ratio = 1.0014, p = 0.992, Poisson regression model). Overall 65 children (61.3%) in Placebo group and 67 (64.4%) in Intervention group had common infections (p = 0.642). Mean number of infections per child was 0.93 (range 0-3) in Placebo group and 0.93 (range 0-3) in Intervention group (p = 0.898). There was no difference in secondary (duration of symptoms, number of children with gastrointestinal and respiratory tract infections, absence from day care center due to infections, use of antibiotics) and exploratory (type of gastrointestinal and respiratory tract infection) endpoints between groups. Conclusion: Results of performed study show that BB-12®has no effect on the prevention of gastrointestinal and respiratory tract infections in healthy children who attend day care centers.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU/day: -
Product formulation: -
Reference number: 1626

Murakami, et al. Intestinal microbiota in neonates requiring urgent surgery: assessing the role of probiotics using fecal DNA sequencing. Pediatr.Surg.Int. 2016;32(1):37-43

Abstract: PURPOSE: To assess the impact of urgent surgery on neonates and the value of an orally administered probiotic preparation of Bifidobacterium animalis subsp. lactis LKM512 (LKM) using fecal DNA sequencing to analyze intestinal microbiota. METHODS: Subjects for this study were 13 neonates born at our institution. Surgical cases required surgery within 3 days of birth. Groups studied were surgical cases administered LKM (n = 4; LKM+), surgical cases not administered have surgery and were not administered LKM (n = 2; CS), and normal healthy neonates (n = 3; CN). Stool specimens (20 mg) were collected five times (after birth, and on days 3, 7, 10, and 14 after surgery in surgical cases, and after birth, and on days 4, 8, 11, and 15 of life in controls). RESULTS: Clinical data were similar for LKM+ and LKM-. Enterobacteriaceae, Streptococcaceae, Staphylococcaceae and Bifidobacteriaceae were identified in the descending order of abundance in CS stool. Streptococcaceae, Staphylococcaceae, Enterococcaceae and Bifidobacteriaceae were identified in the descending order of abundance in LKM+ stool. Bifidobacteriaceae, Enterobacteriaceae, Staphylococcaceae and Streptococcaceae were identified in the descending order of abundance in LKM- stool. Unexpectedly, Bifidobacteriaceae was significantly more abundant in LKM- than LKM+ ($p < 0.05$). CONCLUSION: Surgical stress appears to affect intestinal microbiota considerably. Probiotic administration in neonates requires clarification.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU/day: 10 billion CFU/day
Product formulation: Other, tablet in a pacifier
Reference number: 1602

Taipale, et al. Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in early childhood. Pediatr.Res. 2016;79(1):65-69

Abstract: BACKGROUND: Specific probiotic bacteria have proven to be effective in the prevention and treatment of infectious diseases in early life in at-risk populations. The impact of administration of Bifidobacterium animalis subsp. lactis BB-12 (BB-12) on the risk of acute infectious diseases was studied in healthy children. METHODS: In this double-blind, placebo-controlled study, 109 one-month-old infants were assigned randomly to a probiotic group receiving a BB-12-containing tablet (n=55) or a placebo (n=54). Test tablets were administered to the infants twice a day (daily dose of BB-12 10 billion CFU) until the age of two years with a novel slow-release pacifier or a spoon. Breastfeeding habits, pacifier use, dietary habits, medications and all signs and symptoms of acute infections were registered in diaries by parents and in questionnaires by trained professionals. RESULTS: The infants receiving BB-12 were reported to have experienced fewer respiratory tract infections (87% vs. 100%; RR 0.87; 95% CI 0.76, 1.00; P=0.033) than the controls. No significant differences between the groups were observed in reported gastrointestinal symptoms, otitis media or fever. The baseline characteristics of the two groups were similar, as was the duration of breastfeeding. CONCLUSION: Administration of BB-12 in early childhood may reduce respiratory tract infections.Pediatric Research (2015); doi:10.1038/pr.2015.174.

Research field: Infant and Children's nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®
Dosage CFU: $5x10^9$ cfu/ day

Ringel-Kulka, Tamar et al. "Randomized, Double-Blind, Placebo-Controlled Study of Synbiotic Yogurt Effect on the Health of Children." Journal of Pediatrics 166.6 (2015)

Abstract: Objective To assess the effects of daily consumption of a synbiotic yogurt drink on the health, growth, and quality of life of healthy children 12-48 months of age in out-of-home child care. Study design Healthy children attending child care centers were enrolled in a prospective, double-blind, placebo-controlled clinical trial. The intervention was a yogurt drink containing Streptococcus thermophilus, Lactobacillus bulgaricus, and Bifidobacterium animalis subspecies lactis (BB-12) (5 × 109 cfu/100 mL serving), and 1 g of inulin (synbiotic group) vs a similar nonsynbiotic-containing acidified milk drink (placebo group) once daily for 16 weeks. The end points were days of diarrhea, fever, vomiting, symptoms of upper respiratory tract infection, use of antibiotics, physician visits, child care absenteeism, parental work absenteeism, and quality of life (PedsQL 4.0; Mapi Research Trust, Lyon, France). Results Compared with placebo (n = 73), children receiving synbiotic (n = 76) had significantly fewer days of reported fever (1.85 vs 1.95, P

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Research field: Infant and Children's nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. acidophilus, LA-5® and LGG
Dosage CFU/day:

Simpson, Melanie Rae et al. "Perinatal Probiotic Supplementation in the Prevention of Allergy Related Disease: 6 Year Follow up of a Randomised Controlled Trial." Bmc Dermatology 15.1 (2015): 13

Abstract: BACKGROUND Perinatal probiotics supplementation has been shown to be effective in the primary prevention of atopic dermatitis (AD) in early childhood, although the long term effects of probiotics on AD and other allergic diseases is less certain. We have previously reported a significant reduction in the cumulative incidence of AD at 2 years after maternal probiotic supplementation. In this study we present the effects of perinatal probiotics given to women from a general population on allergy related diseases in their offspring at 6 years. METHODS Four hundred and fifteen pregnant women were randomised to receive probiotic or placebo milk in a double-blinded trial from 36 week gestation until 3 months postpartum. Probiotic milk contained Lactobacillus rhamnosos GG, L. acidophilus La-5 and Bifidobacterium animalis subsp. lactis Bb-12. At 6 years, children were re-assessed for AD, atopic sensitisation, asthma and allergic rhinoconjunctivitis (ARC). RESULTS At 6 years, 81 and 82 children were assessed for AD in the probiotic and placebo groups, respectively. In a multiple imputation analysis, there was as trend towards a lower cumulative incidence of AD in the probiotic group compared to the placebo group (OR 0.64, 95 % CI 0.39-1.07, p = 0.086; NNT = 10). This finding was statistically significantly in the complete case analysis (OR 0.48, 95 % CI 0.25-0.92, p = 0.027, NNT = 6). The prevalence of asthma and atopic sensitisation, and the cumulative incidence of ARC were not significantly affected by the probiotic regime at 6 years of age. CONCLUSIONS Maternal probiotic ingestion alone may be sufficient for long term reduction in the cumulative incidence of AD, but not other allergy related diseases. TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT00159523.

Research field: Infant and Children's nutrition and Oral Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. acidophilus, LA-5®
Dosage CFU/day: 1 million of each strain

Product formulation: Other / ice cream
Reference number: 1586

Ashwin, et al. Effect of Probiotic Containing Ice-cream on Salivary Mutans Streptococci (SMS) Levels in Children of 6-12 Years of Age: A Randomized Controlled Double Blind Study with Six-months Follow Up. J.Clin.Diagn.Res. 2015;9(2):6-9

Abstract: INTRODUCTION: To evaluate the caries risk based on the salivary levels of streptococcus mutans in children of 6-12 years of age group before and after consuming probiotic ice-cream containing Bifidobacterium lactis Bb-12 and Lactobacillus acidophilus La-5. MATERIALS AND METHODS: A double blind, placebo controlled trial was carried out in 60 children aged between 6 to 12 years with zero decayed, missing, and filled teeth (DMFT). They were randomly divided into two equal groups. Saliva sample were collected before the consumption of ice-cream and Streptococcus mutans count was calculated and recorded as baseline data. For the next seven days both the groups were given ice creams marked as A and B. Saliva samples were collected after ice-cream consumption at the end of study period and also after a washout period of 30 days and again after six months. Samples were inoculated and colonies were counted. RESULTS: On statistical evaluation by students paired t-test, probiotic ice-cream brought significant reduction in the Streptococcus mutans count after seven days of ice-cream ingestion ($p<0.001$) and also after 30 d of washout period ($p<0.001$). There was no significant reduction ($p=0.076$) by normal ice-cream consumption. After six months of the study period in both the groups the salivary levels of Streptococcus mutans was similar to the baseline. CONCLUSION: Probiotic ice-cream containing Bifidobacterium lactis Bb-12 and Lactobacillus acidophilus La-5 can cause reduction in caries causative organism. The dosage of the probiotic organisms for the long term or synergetic effect on the oral health are still needed to be explored.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. acidophilus LA-5 and L. rhamnosus LGG
Dosage CFU/day: 1 billion LA-5 + 10 billion BB-12 and LGG each

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Product formulation: Fermented milk
Reference number: 1601

Dotterud, et al. Does Maternal Perinatal Probiotic Supplementation Alter the Intestinal Microbiota of Mother and Child? J.Pediatr.Gastroenterol.Nutr. 2015;61(2):200-207

Abstract: OBJECTIVES Maternal probiotic supplementation has been shown to prevent the development of atopic dermatitis in the offspring. We aimed to investigate whether probiotics in pregnant and breast-feeding mothers altered the colonization pattern and the diversity of the mothers' and children's intestinal microbiota. METHODS In a randomized, double-blind trial, women received probiotic milk or placebo from 36 weeks of gestation up to 3 months postnatally while breast-feeding. The probiotic milk contained Lactobacillus rhamnosus GG, L acidophilus La-5, and Bifidobacterium animalis subsp. lactis Bb-12. Stool samples were collected from the mothers at 30 to 36 weeks of gestation and 3 months after birth, and from the child at age 10 days, 3 months, 1 year, and 2 years, and bacteria were analyzed by quantitative polymerase chain reaction. Additionally, stool samples from 3-month-old and 2-year-old children were characterized using 16S ribosomal RNA gene deep sequencing to estimate the bacterial classes and genera, and the α- and β-diversity. RESULTS Three months after birth, both the prevalence and the relative abundance of the administered probiotic bacteria were significantly increased among the mothers in the probiotic group compared with among those in the placebo group. Only the Lactobacillus rhamnosus GG bacteria colonized the children at 10 days and at 3 months of age. There were no significant differences in the abundance of the administered probiotic bacteria between the groups at 1 and 2 years of age. For the bacterial classes and genera, and α- and β-diversity, there were no significant differences between the groups. CONCLUSIONS Different probiotic bacteria seem to have different ability to transfer from the mother to the child. We found no evidence that the probiotics altered the microbial composition or α- and β-diversity of the children.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. acidophilus, LA-5® and L. rhamnosus, LGG®

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Dosage CFU/day: NA
Product formulation: Fermented milk
Reference number: 1570

Fox, et al. Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study. BMJ Open 2015;5:1-6

Abstract: OBJECTIVE: To estimate the efficacy of a probiotic yogurt compared to a pasteurised yogurt for the prevention of antibiotic-associated diarrhoea in children. DESIGN AND SETTING: This was a multisite, randomised, double-blind, placebo-controlled clinical trial conducted between September 2009 and 2012. The study was conducted through general practices and pharmacies in Launceston, Tasmania, Australia. PARTICIPANTS AND INTERVENTIONS: Children (aged 1-12 years) prescribed antibiotics, were randomised to receive 200 g/day of either yogurt (probiotic) containing Lactobacillus rhamnosus GG (LGG), Bifidobacterium lactis (Bb-12) and Lactobacillus acidophilus (La-5) or a pasteurised yogurt (placebo) for the same duration as their antibiotic treatment. OUTCOMES: Stool frequency and consistency were recorded for the duration of treatment plus 1 week. Primary outcome was stool frequency and consistency, classified at different levels of diarrhoea severity. Due to the small number of cases of diarrhoea, comparisons between groups were made using Fisher's exact analysis. RESULTS: 72 children commenced and 70 children (36 placebo and 34 probiotic) completed the trial. There were no incidents of severe diarrhoea (stool consistency >/=6, >/=3 stools/day for >/=2 consecutive days) in the probiotic group and six in the placebo group (Fisher's exact p=0.025). There was also only one episode of minor diarrhoea (stool consistency >/=5, >/=2 stools/day for >/=2 days in the probiotic group compared to 21 in the placebo group (Fisher's exact p<0.001). The probiotic group reported fewer adverse events (1 had abdominal pain, 1 vomited and 1 had headache) than the placebo group (6 had abdominal pain, 4 had loss of appetite and 1 had nausea). CONCLUSIONS: A yogurt combination of LGG, La-5 and Bb-12 is an effective method for reducing the incidence of antibiotic-associated diarrhoea in children. TRIAL REGISTRATION NUMBER: Australian New Zealand Clinical Trials Registry ACTRN12609000281291.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and S. thermophiles, TH-4® and Lactobacillus paracasei ssp.paracasei CRL-431
Dosage CFU/day: CRL-431 (1,75x10^9CFU), BB-12 (1,75x10^9 CFU), TH-4 (1,50x10^9 CFU) daily

Valsecchi, C. et al. "Evaluation of the Effects of a Probiotic Supplementation with Respect to Placebo on Intestinal Microflora and Secretory IgA Production, during Antibiotic Therapy, in Children Affected by Recurrent Airway Infections and Skin Symptoms." Journal of Biological Regulators and Homeostatic Agents 28.1 (2014): 117–124

Abstract: Antibiotic therapy, especially in pediatric patients, is often associated with significant modifications of the gut microflora, which can lead to intestinal dysbiosis and influence intestinal physiology and immune system functionality. Herein we report the results from a double blind controlled clinical trial in 77 pediatric patients affected by recurrent airway infections, receiving antibiotic therapy with amoxicillin and clavulanic acid. A group was treated with an oral probiotic preparation composed of Lactobacillus paracasei ssp.paracasei CRL-431, Bifidobacterium BB-12, Streptococcus thermophilus TH-4 and a fructooligosaccharide (FOS) during and after antibiotic therapy for seven days, while the other group received placebo. The study revealed a reduction in the Clostridia population, with a contemporary increase in Bifidobacteria and Lactobacilli in fecal samples in the probiotic group and an increase in the Enterobacteria population in the placebo group. Moreover, there was a decreasing trend in secretory IgA production in the probiotic group. Some relevant, but not statistically significant probiotic supplementation effects were identified.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and S. thermophiles, TH-4®
Dosage CFU/day: 1 billion BB-12® and 0.1 billion TH-4®
Product formulation: NA
Reference number: 1532

Ivakhnenko, Nian'kovskii. Effect of probiotics on the dynamics of gastrointestinal symptoms of food allergy to cow's milk protein in infants. Georgian Med.News. 2013;(219)(219):46-52

Abstract: The problem of food allergy to cow's milk protein in children is highly important. The aim of this study was to estimate the effect of Bifidobacterium lactis BB-12 (1small ha, Cyrillic109 CFU) and Streptococcus thermophilus TH-4 (1small ha, Cyrillic108 CFU) administration on gastrointestinal symptoms of cow's milk allergy in infants. We conducted an open randomized prospective clinical study. 60 infants aged of 3-12 months with the diagnosis of atopic dermatitis and allergy to cow's milk protein were enrolled. Children were divided into 2 groups, one of which received probiotics during 4 weeks. Results were estimated after 4 and 8 weeks of study. We found significant impact on reducing the frequency of constipation in infants who received the probiotics in complex treatment. After 4 weeks of treatment constipation was absent in 85.71% infants who received probiotics as compared to 48.15% in the control group (small er, Cyrillic=0.02), after 8 weeks the same numbers were 92.86% vs. 62.96% accordingly (p=0.04). Significant differences between the groups were also determined by the incidences of infantile colic through 4 and 8 weeks and on diarrhea through 8 weeks of studies. It is possible to draw a conclusion that administration of probiotics in addition to elimination diet and base treatment to infants with atopic dermatitis and cow's milk allergy improves clinical symptoms of the disease and decreases gastrointestinal clinical manifestations of cow's milk allergy.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and S. thermophilus TH-4 and B. infantis BB-02
Dosage CFU/day: 1 billion
Product formulation: Other (powder)
Reference number: 1502

Jacobs, et al. Probiotic Effects on Late-onset Sepsis in Very Preterm Infants: A Randomized Controlled Trial. Pediatrics 2013;132(6):1055-1062

Abstract: BACKGROUND AND OBJECTIVE:Late-onset sepsis frequently complicates prematurity, contributing to morbidity and mortality. Probiotics may reduce mortality and necrotizing enterocolitis (NEC) in preterm infants, with unclear effect on late-onset sepsis. This study aimed to determine the effect of administering a specific combination of probiotics to very preterm infants on culture-proven late-onset sepsis.METHODS:A prospective multicenter, double-blinded, placebo-controlled, randomized trial compared daily administration of a probiotic combination (Bifidobacterium infantis, Streptococcus thermophilus, and Bifidobacterium lactis, containing 1 x 109 total organisms) with placebo (maltodextrin) in infants born before 32 completed weeks' gestation weighing <1500 g. The primary outcome was at least 1 episode of definite late-onset sepsis.RESULTS:Between October 2007 and November 2011, 1099 very preterm infants from Australia and New Zealand were randomized. Rates of definite late-onset sepsis (16.2%), NEC of Bell stage 2 or more (4.4%), and mortality (5.1%) were low in controls, with high breast milk feeding rates (96.9%). No significant difference in definite late-onset sepsis or all-cause mortality was found, but this probiotic combination reduced NEC of Bell stage 2 or more (2.0% versus 4.4%; relative risk 0.46, 95% confidence interval 0.23 to 0.93, P = .03; number needed to treat 43, 95% confidence interval 23 to 333).CONCLUSIONS:The probiotics B infantis, S thermophilus, and B lactis significantly reduced NEC of Bell stage 2 or more in very preterm infants, but not definite late-onset sepsis or mortality. Treatment with this combination of probiotics appears to be safe.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: 0,1 Billion
Product formulation: Milk powder
Reference number: 1395

Holscher, et al. Bifidobacterium lactis Bb12 Enhances Intestinal Antibody Response in Formula-Fed Infants: A Randomized, Double-Blind, Controlled Trial. JPEN J.Parenter.Enteral Nutr. 2012;36(1 Suppl):106S-17S

Abstract: Background: Addition of probiotics to infant formula may positively affect immune function in nonexclusively breastfed infants. This study aimed to investigate the effect of infant starter formula containing the probiotic Bifidobacterium animalis subspecies lactis (Bb12) on intestinal immunity and inflammation. Methods: Six-week-old healthy, full-term infants (n = 172) were enrolled in a prospective, randomized, double-blind, controlled clinical trial with 2 groups studied in parallel to a breastfed comparison group. Formula-fed (FF) infants were randomized to partially hydrolyzed whey formula (CON) or the same formula containing 10(6) colony-forming units (CFU) Bb12/g (PRO) for 6 weeks. Fecal secretory IgA (sIgA), calprotectin, lactate, and stool pH were assessed at baseline, 2 weeks, and 6 weeks. Anti-poliovirus-specific IgA and anti-rotavirus-specific IgA were assessed at 2 and 6 weeks. Results: Among vaginally delivered FF infants, PRO consumption increased (P < .05) fecal sIgA compared to CON. Anti-poliovirus-specific IgA concentration increased (P < .05) in all infants consuming PRO, whereas anti-rotavirus-specific IgA tended to increase (P = .056) with PRO consumption in cesarean-delivered infants. Anthropometrics and tolerance did not differ significantly between FF infants. Conclusions: Infants consuming formula with Bb12 produced feces with detectable presence of Bb12 and augmented sIgA concentration. Furthermore, cesarean-delivered infants consuming Bb12 had heightened immune response, as evidenced by increased anti-rotavirus- and anti-poliovirus-specific IgA following immunization. These results demonstrate that negative immune-related effects of not breastfeeding and cesarean delivery can be mitigated by including Bb12 in infant formula, thereby providing infants a safe, dietary, immune-modulating bacterial introduction.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: 10 billion
Product formulation: Other
Reference number: 1213

Taipale, et al. Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in infancy. Br.J.Nutr. 2011;105:409-16

Abstract: The impact of controlled administration of Bifidobacterium animalis subsp. lactis BB-12 (BB-12) on the risk of acute infectious diseases was studied in healthy newborn infants. In this double-blind, placebo-controlled study, 109 newborn 1-month-old infants were assigned randomly to a probiotic group receiving a BB-12-containing tablet (n 55) or to a control group receiving a control tablet (n 54). Test tablets were administered to the infants twice a day (daily dose of BB-12 10 billion colony-forming units) from the age of 1-2 months to 8 months with a novel slow-release pacifier or a spoon. Breastfeeding habits, pacifier use, dietary habits, medications and all signs and symptoms of acute infections were registered. At the age of 8 months, faecal samples were collected for BB-12 determination (quantitative PCR method). The baseline characteristics of the two groups were similar, as was the duration of exclusive breastfeeding. BB-12 was recovered (detection limit log 5) in the faeces of 62 % of the infants receiving the BB-12 tablet. The daily duration of pacifier sucking was not associated with the occurrence of acute otitis media. No significant differences between the groups were observed in reported gastrointestinal symptoms, otitis media or use of antibiotics. However, the infants receiving BB-12 were reported to have experienced fewer respiratory infections (65 v. 94 %; risk ratio 0.69; 95 % CI 0.53, 0.89; P = 0.014) than the control infants. Controlled administration of BB-12 in early childhood may reduce respiratory infections.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. paracasei subsp. paracasei L. casei 431
Dosage CFU/day: 1 billion
Product formulation: Milk powder
Reference number: 1253

Vlieger, et al. Tolerance and safety of Lactobacillus paracasei ssp. paracasei in combination with Bifidobacterium animalis ssp. lactis in a prebiotic-containing infant formula: a randomised controlled trial. Br.J.Nutr. 2009;102:869-875

Abstract: The addition of probiotics to infant formula has been shown to be an efficient way to increase the number of beneficial bacteria in the intestine in order to promote a gut flora resembling that of breast-fed infants. The objective of the present study was to evaluate the safety and tolerance of a combination of two probiotic strains in early infancy. A group of 126 newborns were randomised to receive a prebiotic-containing starter formula supplemented with Lactobacillus paracasei ssp. paracasei and Bifidobacterium animalis ssp. lactis or the same formula without probiotics for the first 3 months of life. A total of eighty infants continued the study until they were aged 6 months. Growth measurements were taken monthly at healthy baby clinics. Diaries were used to monitor behaviour, infections, use of antibiotics, as well as stool characteristics. Normal growth occurred in all infants and no statistically significant differences were detected between the probiotics group and the control group for gain in weight, length and head circumference. Infants in the probiotics group produced softer and more frequent stools during the first 3 months of life. No differences were found in crying and sleeping hours, number of parent-diagnosed infections, antibiotic use, visits to the general practitioner and number of adverse events. The use of a prebiotic-containing starter formula supplemented with L. paracasei ssp. paracasei and B. animalis ssp. lactis in early infancy is safe, well tolerated and has no adverse effects on growth and infant behaviour.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion of each
Product formulation: Milk powder
Reference number: 0494

Rautava, et al. Specific probiotics in reducing the risk of acute infections in infancy--a randomised, double-blind, placebo-controlled study. Br.J.Nutr. 2009;101(11):1722-1726

Abstract: A randomised, double-blind, placebo-controlled study was conducted to determine whether probiotics might be effective in reducing the risk of infections in infancy. Infants requiring formula before the age of 2 months were recruited from community well-baby clinics. Infant formula supplemented with the probiotics Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb-12 or placebo was administered daily until the age of 12 months. Incidence of early infections (before the age of 7 months) and incidence of recurrent (three or more) infections during the first year of life were recorded as the main outcome measures of the study. During the first 7 months of life, seven out of thirty-two (22 %) infants receiving probiotics and twenty out of forty (50 %) infants receiving placebo experienced acute otitis media (risk ratio (RR) 0.44 (95 % CI 0.21, 0.90); P = 0.014) and antibiotics were prescribed for ten out of thirty-two (31 %) infants receiving probiotics and twenty-four out of forty (60 %) infants receiving placebo (RR 0.52 (95 % CI 0.29, 0.92); P = 0.015). During the first year of life, nine out of thirty-two (28 %) infants receiving probiotics and twenty-two out of forty (55 %) infants receiving placebo encountered recurrent respiratory infections (RR 0.51 (95 % CI 0.27, 0.95); P = 0.022). These data suggest that probiotics may offer a safe means of reducing the risk of early acute otitis media and antibiotic use and the risk of recurrent respiratory infections during the first year of life. Further clinical trials are warranted.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion BB-12 and 10 billion LGG
Product formulation: Milk powder
Reference number: 0509

Rautava, et al. Specific probiotics in enhancing maturation of IgA responses in formula-fed infants. Pediatr.Res. 2006;60:221-224

Abstract: The first months of life represent a critical period for the maturation of the infant's immune system and, thus, a window of opportunity for measures to reduce the risk of disease. We hypothesized that specific probiotics might promote mucosal immunologic maturation in formula-fed infants. The numbers of cow's milk-specific and total IgA-secreting cells were measured at 3, 7, and 12 mo of age in a double-blind placebo-controlled study of 72 infants with early artificial feeding. The infants consumed infant formula supplemented with specific probiotics (Lactobacillus GG and Bifidobacterium lactis Bb-12) or placebo during the first year of life. Further analyses of the serum concentrations of the IgA-inducing cytokine TGF-beta2 and the soluble innate microbial receptor sCD14 were conducted. The numbers of cow's milk-specific IgA secreting cells were significantly higher in infants receiving probiotics compared with those receiving placebo ($p = 0.045$, ANOVA for repeated measures). At 12 mo of age, the serum concentrations of sCD14 were 1479 pg/mL [95% confidence interval (CI) 1373-1592] in infants receiving probiotics and 1291 pg/mL (95% CI 1152-1445) in infants receiving placebo ($p = 0.046$). Administration of the probiotics Lactobacillus GG and Bifidobacterium lactis Bb-12 at the time of introduction of cow's milk in the infant's diet results in cow's milk-specific IgA antibody responsiveness that may be the result of increased production of sCD14.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and S. thermophilus TH-4
Dosage CFU/day: Approx. 1 and 10 billion
Product formulation: Milk powder
Reference number: 0719

Mao, et al. Effect of a lactose-free milk formula supplemented with bifidobacteria and streptococci on the recovery from acute diarrhoea. Asia Pac.J.Clin.Nutr. 2008;17:30-34

Abstract: Probiotics have been proposed for the management and prevention of acute diarrhoea in infants. A double-blind, randomised, placebo controlled study was carried out in 224 Chinese infants 6 to 36 months of age with severe acute diarrhoea and free from moderate or severe malnutrition. After oral or parenteral rehydration, they were allocated to one of three groups: a lactose-free formula (Control); the same formula but with viable 10(8)CFU B. lactis Bb12 and 5x10(7)CFU St. thermophilus TH4 per gram of powder and, the same formula with the same microorganisms, but with 10(9)CFU/g and 5x10(8)CFU, respectively. Anthropometric parameters, duration of the diarrhoea and rotavirus shedding were evaluated. Eighty seven percent of the episodes were associated with rotavirus infection. The duration of the diarrhoea was not influenced by the intake of probiotics. However, a decrease of rotavirus shedding was observed in infants fed the formula with 10(9) Bb12/g, a finding of probable epidemiological importance in the transmission of this agent.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: Approx. 0.1 billion
Product formulation: Milk powder
Reference number: 0437

Chouraqui, et al. Acidified milk formula supplemented with bifidobacterium lactis: impact on infant diarrhea in residential care settings. J.Pediatr.Gastroenterol.Nutr. 2004;38:288-292

Abstract: OBJECTIVES: Probiotics may be useful in preventing acute infectious diarrhea. Bifidobacteria are particularly attractive as probiotics agent because they constitute the predominant colonic flora of breastfed infants and are thought to play a role in the decreased incidence of diarrhea in breastfed infants. METHODS: This was a multicenter, double-blind, controlled study to evaluate the efficacy of a milk formula supplemented with viable Bifidobacterium lactis strain Bb 12 (BbF) in the prevention of acute diarrhea in infants younger than 8 months living in residential nurseries or foster care centers. RESULTS: Ninety healthy children received either the BbF or a conventional formula (CF) daily. The mean duration of the stay in the residential center was similar (137 v 148 days). At enrollment, there were no differences between the two groups with respect to age (3.7 +/- 2.1 months), gender, anthropometric data, history of allergy or gastrointestinal disease, frequency of breast-feeding in the neonatal period or timing of introduction of solid food. Altogether, 28.3% of the BbF infants had diarrhea during the study compared with 38.7% of controls (NS). There was a statistically insignificant trend for shorter episodes of diarrhea in the BbF group (5.1 +/- 3.3 days v 7 +/- 5.5 days, NS). The number of days with diarrhea was 1.15 +/- 2.5 in the BbF group with a daily probability of diarrhea of 0.84 versus 2.3 +/- 4.5 days and 1.55, respectively, in the CF group (P = 0.0002 and 0.0014). Feeding infants with the BbF reduced their risk of getting diarrhea by a factor of 1.9 (range, 1.33-2.6). Analysis of the cumulative incidence of diarrheal episodes showed a trend that the first onset of diarrhea occurred later in the BbF group. CONCLUSION: These results provide some evidence that viable Bifidobacterium lactis strain Bb 12, added to an acidified infant formula, has some protective effect against acute diarrhea in healthy children.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and S. thermophilus TH-4
Dosage CFU/day: Mean daily consumption of BB-12 was 41 million per kg bodyweight of child in the high supplementation group and 3.7 million in the low supplemented group.
Product formulation: Milk powder
Reference number: 0435

Saavedra, et al. Long-term consumption of infant formulas containing live probiotic bacteria: tolerance and safety. Am.J.Clin.Nutr. 2004;79:261-267

Abstract: BACKGROUND: Nonpathogenic live bacteria are consumed as food by many children, particularly in the form of yogurt. The tolerance and safety of long-term consumption of specific types and strains of probiotic bacteria are not well documented. OBJECTIVE: The goal was to evaluate tolerance to formulas containing 2 levels of probiotic supplementation and effects on growth, general clinical status, and intestinal health in free-living healthy infants. DESIGN: This was a prospective, double-blind, randomized, placebo-controlled study of healthy infants aged 3-24 mo. Infants were assigned to receive a standard milk-based formula containing 1 x 10(7) colony-forming units (CFU)/g each of Bifidobacterium lactis and Streptococcus thermophilus, formula containing 1 x 10(6) CFU/g each of B. lactis and S. thermophilus, or unsupplemented formula. Clinical outcomes included formula intake, gastrointestinal tolerance, anthropometric measures, daycare attendance, and history of illness. RESULTS: One hundred eighteen infants aged (+/- SD) 7.0 +/- 2.9 mo at enrollment consumed formula for 210 +/- 127 d. There were no significant differences in age, sex, formula consumption, or length of study between groups. The supplemented formulas were well accepted and were associated with a lower frequency of reported colic or irritability ($P < 0.001$) and a lower frequency of antibiotic use ($P < 0.001$) than was the unsupplemented formula. There were no significant differences between groups in growth, health care attention seeking, daycare absenteeism, or other health variables. CONCLUSION: Long-term consumption of formulas supplemented with B. lactis and S. thermophilus was well tolerated and safe and resulted in adequate growth, reduced reporting of colic or irritability, and a lower frequency of antibiotic use.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: ≥ 12 billion
Product formulation: Milk powder
Reference number: 0411

Nopchinda, et al. Effect of bifidobacterium Bb12 with or without Streptococcus thermophilus supplemented formula on nutritional status. J.Med.Assoc.Thai. 2002;85(Suppl 4):1225-1231

Abstract: Acute diarrhea is a common cause of infant morbidity and mortality. Probiotic supplemented infant formula is one of the effective methods for prevention of rotavirus diarrhea. Other benefits of the probiotics supplemented formula were evaluated by monitoring the growth of the children. A double-blind, placebo-controlled trial was done in 148 children aged 6-36 months. They were divided into 3 groups: the Bb12 group, 51 children received infant formula with Bifidobacteria Bb12 supplement; the Bb12+ST group, 54 children received infant formula with Bb12 and Streptococcus thermophilus supplement; and the control group, 43 children received infant formula without supplement. The mean weight Z-score according to WHO reference standard of the Bbl2 group was -1.8 +/- 0.12, the Bb12+ST group was -1.4 +/- 0.11 and the control group was -1.8 +/- 0.13 at entry. The mean weight Z-score of children after 6 month showed that the children in the Bbl2+ST group had the highest increase in weight which was increased from -1.4 +/- 0.11 to -0.9 +/- 0.12 compared to the Z-score of the Bb12 group which had increased from -1.8 +/- 0.12 to -1.2 +/- 0.13 and in the control group from -1.8 +/- 0.13 to -1.7 +/- 0.25. In terms of the mean height Z-score, the Bb12 group was -2.7 +/- 0.14 to -1.7 +/- 0.16 which was higher than the Bb12+ST group (- 2.2 +/- 0.13 to -1.7 +/- 0.13) but was not different from the control group. However, the mean weight/height Z-score of the Bbl2+ST group had approached the reference standard (Bb12 group -0.1 +/- 0.11 to -0.1 +/- 0.13, Bb12+ST group -0.1 +/- 0.10 to 0.3 +/- 0.17, control group -0.4 +/- 0.12 to -0.1 +/- 0.16). Data showed that children who received the probiotics supplement formula had better growth during the 6 month period.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 30-80 billion
Product formulation: Milk powder
Reference number: 0388

Isolauri, et al. Probiotics in the management of atopic eczema. Clin.Exp.Allergy 2000;30(11):1604-1610

Abstract: BACKGROUND: Over the last two decades the incidence of allergic diseases has increased in industrialized countries, and consequently new approaches have to be explored. OBJECTIVE: The potential of probiotics to control allergic inflammation at an early age was assessed in a randomized double-blind placebo-controlled study. METHODS: A total of 27 infants, mean age 4.6 months, who manifested atopic eczema during exclusive breast-feeding and who have had no exposure to any infant or substitute formula were weaned to probiotic-supplemented, Bifidobacterium lactis Bb-12 or Lactobacillus strain GG (ATCC 53103), extensively hydrolysed whey formulas or to the same formula without probiotics. The extent and severity of atopic eczema, the growth and nutrition of infants, and concentrations of circulating cytokines/chemokines and soluble cell surface adhesion molecules in serum and methyl-histamine and eosinophilic protein X in urine were determined. RESULTS: The SCORAD score reflecting the extent and severity of atopic eczema was 16 (7-25) during breast-feeding, median (interquartile range). After 2 months, a significant improvement in skin condition occurred in patients given probiotic-supplemented formulas, as compared to the unsupplemented group; chi(2) = 12.27, P = 0.002. SCORAD decreased in the Bifidobacterium lactis Bb-12 group to 0 (0-3.8), and in the Lactobacillus GG group to 1 (0.1-8.7), vs unsupplemented 13.4 (4.5-18.2), median (interquartile range), in parallel with a reduction in the concentration of soluble CD4 in serum and eosinophilic protein X in urine. CONCLUSION: The results provide the first clinical demonstration of specific probiotic strains modifying the changes related to allergic inflammation. The data further indicate that probiotics may counteract inflammatory responses beyond the intestinal milieu. The combined effects of these probiotic strains will guide infants through the weaning period, when sensitization to newly encountered antigens is initiated. The probiotic approach may thus offer a new direction in the search for future foods for allergy treatment and prevention strategies.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: NA
Product formulation: Milk powder
Reference number: 0413

Phuapradit, et al. Reduction of rotavirus infection in children receiving bifidobacteria-supplemented formula. J.Med.Assoc.Thai. 1999;82 Suppl 1:S43

Abstract: This study was conducted at Pakkred Babies Home, Bangkok, Thailand; with the hypothesis that children receiving probiotic-supplemented milk-based formula may be protected from developing diarrheal diseases. Salivary rotavirus-specific IgA antibody was used as an indicator of rotavirus infection. One hundred and seventy-five children, aged 6-36 months, were enrolled in the study. They were divided into 3 groups according to the type of formula given. There were 81 episodes of diarrhea during an 8-month study period, most of which were caused by bacterial enteropathogens. Ninety-seven pairs of salivary samples were adequate for the analysis of rotavirus antibody. Among 23 children receiving milk-based follow-up formula and serving as control group, 30.4 per cent of them had > or = 4-fold increase in the antibody titre, indicating subclinical rotavirus infection. The majority of children in the other 2 study groups, receiving the same formula supplemented with either Bifidobacterium Bb12 alone or together with Streptococcus thermophilus, had no significant change in the antibody titres between the two time points. The results of this study support our hypothesis that children receiving bifidobacteria-supplemented milk-based formula may be protected against symptomatic rotavirus infection.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: 1 billion
Product formulation: Milk powder
Reference number: 0332

Fukushima, et al. Effect of a probiotic formula on intestinal immunoglobulin A production in healthy children. Int.J.Food Microbiol. 1998;42:39-44

Abstract: The anti-infectious effect of probiotics has recently been reported and one mechanism may be the non-specific stimulation of immunity. This study was performed to elucidate the influence of a probiotic formula on intestinal microflora and local immunity in healthy children. A follow-up formula containing viable bifidobacteria was given to seven healthy Japanese children (15 to 31 months old) for 21 days. During intake of the formula, the administered strain was detected in feces from five subjects (71%) and total fecal bifidobacteria slightly increased. Fecal levels of total IgA and anti-poliovirus IgA during intake of the formula were significantly higher than those before intake ($P < 0.05$). The increase in local IgA levels resulting from ingestion of the probiotic formula may contribute to enhancement of the mucosal resistance against gastrointestinal infections.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: > 0.6 billion
Product formulation: Milk powder
Reference number: 0285

Fukushima, et al. Effect of follow-up formula containing bifidobacteria (NAN BF) on fecal flora and fecal metabolites in healthy children. Bioscience Microflora 1997;16:65-72

Abstract: 7 healthy children age 15-31 months received follow-up formulas with BB-12 for 21 days. The effect on fecal flora and metabolic products were studied. BB-12 was detected in fecal samples in 71% of the subjects. Fecal bifidobacteria tended to increase, while clostridia decreased ($P<0.05$). Fecal putrefactive products were significantly reduced ($P<0.01$), and acetic acid increased ($P<0.05$). The formulas was well-accepted by all children. Results suggest that the formula with BB-12 is beneficial in improving the intestinal flora and maintaining the healthy intestinal condition of children during and after weaning.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12
Dosage CFU/day: Approx. 0.1 billion
Product formulation: Milk powder
Reference number: 0221

Langhendries, et al. Effect of a fermented infant formula containing viable bifidobacteria on the fecal flora composition and pH of healthy full-term infants. J.Pediatr.Gastroenterol.Nutr. 1995;21:177-181

Abstract: We assessed the growth, tolerance, and acceptability as well as fecal flora composition and stool pH of 20 healthy full-term infants fed with a fermented whey-adapted infant formula containing viable bifidobacteria (10(6)/g of powder) during the first 2 months of life. This fermented infant formula, first biologically acidified by Streptococcus thermophilus and Lactobacillus helveticus, was compared to a whey-adapted, nonacidified, low-phosphate infant formula in a double-blind, randomized controlled study. The results were compared to a control group (n = 14) of fully breast-fed infants. The fermented whey-adapted formula containing viable bifidobacteria induced a prevalence of colonization with bifidobacteria at 1 month of age similar to that of breast-fed infants (12/20 versus 8/14) but significantly higher than in the group fed the standard infant formula (4/20). The mean bacterial count of bifidobacteria was similar in all colonized infants; however, fecal pH was significantly lower in the breast-fed infants than in the nonacidified bottle-fed infants. This kind of infant formula was well tolerated and promoted a normal growth during the first 2 months.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and S. thermophilus TH-4
Dosage CFU/day: >10 billion
Product formulation: Milk powder
Reference number: 0200

Saavedra, et al. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. Lancet 1994;344(8929):1046-1049

Abstract: Acute diarrhoea is a serious cause of infant morbidity and mortality, and the development of preventive measures remains an important goal. Bifidobacteria (which constitute the predominant intestinal flora of breastfed infants), as well as other lactic-acid-producing organisms such as Streptococcus thermophilus, are thought to have a protective effect against acute diarrhoeal disease. However, their efficacy has not been assessed in controlled trials. In a double-blind, placebo-controlled trial, infants aged 5-24 months who were admitted to a chronic medical care hospital were randomised to receive a standard infant formula or the same formula supplemented with Bifidobacterium bifidum and S thermophilus. Patients were evaluated daily for occurrence of diarrhoea, and faecal samples, obtained weekly, were analysed for rotavirus antigen by enzyme immunoassay. Faecal samples were also obtained during an episode of diarrhoea for virological and bacteriological analyses. 55 subjects were evaluated for a total of 4447 patient-days during 17 months. 8 (31%) of the 26 patients who received the control formula and 2 (7%) of 29 who received the supplemented formula developed diarrhoea during the course of the study ($p = 0.035$, Fisher's exact test, two-tailed). 10 (39%) of the subjects who received the control formula and 3 (10%) of those who received the supplemented formula shed rotavirus at some time during the study ($p = 0.025$). The supplementation of infant formula with B bifidum and S thermophilus can reduce the incidence of acute diarrhoea and rotavirus shedding in infants admitted to hospital.

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Study summaries LGG®

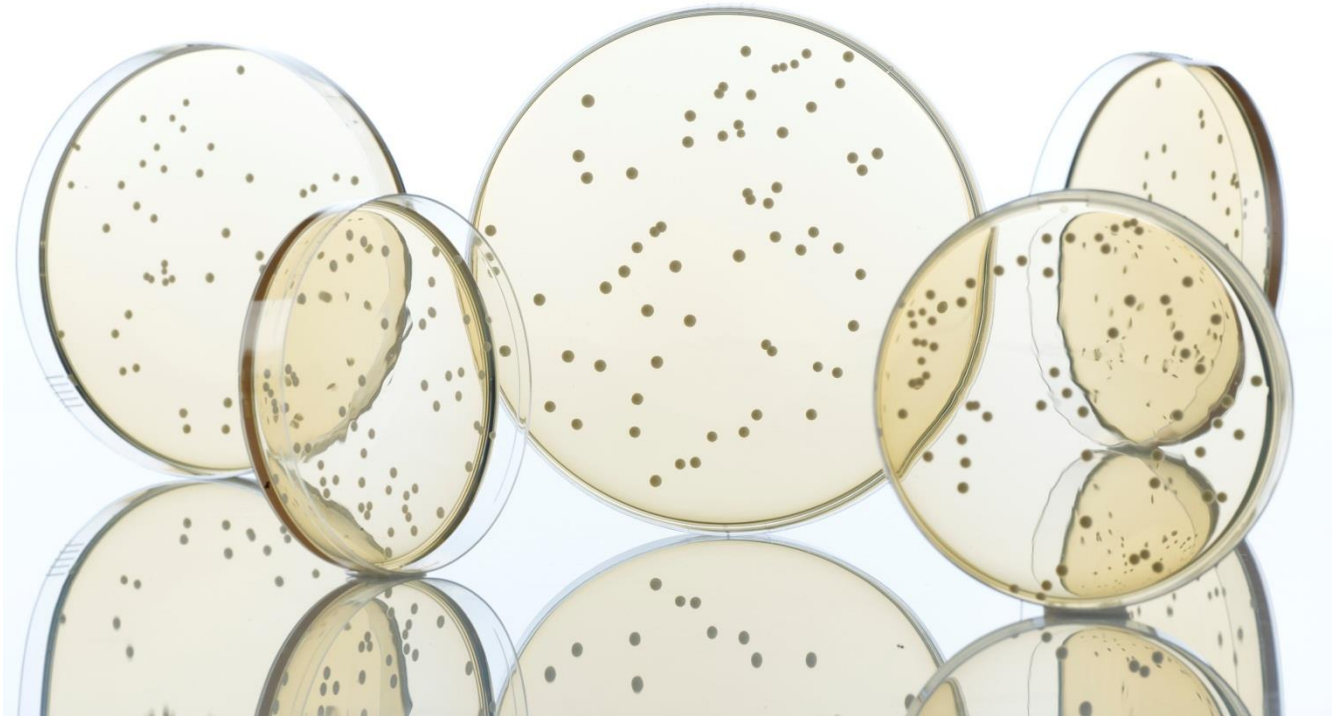
This binder contains summaries of clinical studies performed with Lactobacillus rhamnosus, LGG® - alone or in combination with other strains.

Clinical studies are performed within Infant & Children's Nutrition – including studies in pre-term infants and pregnant women.

February 2020

Chr. Hansen A/S

Human Health & Nutrition



Research field: Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day:

Groah et al, "*Intravesical Lactobacillus rhamnosus GG is safe and well tolerated in adults and children with neurogenic lower urinary tract dysfunction: first-in-human trial*". Therapeutic Advances in Urology, *11*, 1–13, (2019).

Abstract: Background: Urinary symptoms are common for people with neurogenic lower urinary tract dysfunction (NLUTD). No nonprescription approach has been proven safe and effective for self-management of urinary symptoms. Our objective was to describe the safety and tolerability of Lactobacillus rhamnosus GG (LGG®) instilled intravesically for self-management of inflammatory urinary symptoms in adults and children with NLUTD due to spinal cord injury or disease (SCI/D) and who use intermittent catheterization (IC). Methods: A total of 103 individuals with SCI/D enrolled in an 18-month study consisting of three 6-month stages: baseline (weekly observation of urinary symptoms); intervention (self-instilled intravesical LGG® in response to more cloudy or foul-smelling urine); and washout (weekly observation of urinary symptoms). Urinary symptoms were assessed using the Urinary Symptom Questionnaire for people with neurogenic bladder using intermittent catheters (USQNB-IC). Safety was based on serious adverse events and adverse events (S/ AEs) and trends in symptoms. Tolerability was defined as the independence of AE experience and willingness to use/pay for this intervention. Results: A total of 74 (77%) adults and 6 (86%) of children completed the study, of whom 64 instilled LGG® for a total of 357 instillations (range 1–41 per person). There were 59 S/AEs, 44% (26/59) of which were categorized as infectious genitourinary. There was no statistical relationship between S/AEs and use or dose of the intervention. Conclusions: One or two doses of self-instilled intravesical LGG® in response to more cloudy or foul-smelling urine was safe and well tolerated among this sample of adults and children with SCI/D who have NLUTD and use IC. Keywords:

Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day:

Paparo et al, "*Randomized controlled trial on the influence of dietary intervention on epigenetic mechanisms in children with cow's milk allergy: the EPICMA study*". *Scientific Reports*, *9*(1), 1–10, (2019).

Abstract: Epigenetic mechanisms could drive the disease course of cow's milk allergy (CMA) and formula choice could modulate these pathways. We compared the effect of two different dietary approaches on epigenetic mechanisms in CMA children. Randomized controlled trial on IgE-mediated CMA children receiving a 12-month treatment with extensively hydrolyzed casein formula containing the probiotic L.rhamnosus GG (EHCF + LGG) or with soy formula (SF). At the baseline, after 6 and 12 months of treatment FoxP3 methylation rate and its expression in CD4+ T cells were assessed. At same study points IL-4, IL-5, IL-10, and IFN-γ methylation rate, expression and serum concentration, miRNAs expression were also investigated. 20 children (10/group) were evaluated. Baseline demographic, clinical and epigenetic features were similar in the two study groups. At 6 and 12 months, EHCF + LGG group showed a significant increase in FoxP3 demethylation rate compared to SF group. At the same study points, EHCF + LGG group presented a higher increase in IL-4 and IL-5 and a higher reduction in IL-10 and IFN-γ DNA methylation rate compared to SF group. A different modulation of miR-155, -146a, -128 and -193a expression was observed in EHCF + LGG vs. SF. Dietary intervention could exert a different epigenetic modulation on the immune system in CMA children.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU: 10^9 of each strain

Schmidt et al. "Probiotics in late infancy reduce the incidence of eczema : A randomized controlled trial". *Pediatr Allergy Immunol*, *30*(3), 1–6, (2019).

Abstract: Abstract Background: Allergic diseases are common and represent a considerable health and economic burden worldwide. We aimed to examine the effect of a combination of two probiotic strains administered in late infancy and early childhood on the development of allergic diseases and sensitization. Methods: In this double-blind, placebo-controlled intervention trial, participants were randomized to receive a daily mixture of Lactobacillus rhamnosus and Bifidobacterium animalis subsp lactis or placebo—starting prior to attending day care. The intervention period was 6 months, and the parents answered web-based questionnaires on allergic symptoms and doctor's diagnosed allergic disease monthly. IgE was measured at baseline and follow-up. Results: A total of 290 participants were randomized: 144 in the probiotic group and 146 in the placebo group. Mean age at intervention start was 10.1 months. At follow- up (mean age 16.1 months), the incidence of eczema was 4.2% in the probiotic group and 11.5% in the placebo group (P = 0.036). The incidence of asthma and conjunctivitis did not differ between groups, and no children presented with rhinitis. Sensitization was equal in the two groups at intervention start (7.5% and 9.5%, respectively), and two children in each group were sensitized during the intervention. Conclusions: We observed a significantly lower incidence of eczema in the probiotic group compared to the placebo group. The probiotics were administered in late infancy— prior to attending day care—suggesting a broader window of opportunity using probiotics in the prevention of eczema. The incidence of asthma, rhinitis, conjunctivitis, and sensitization did not differ.

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Research field: Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion

Bianchini et al, "Effects of probiotic administration on immune responses of children and adolescents with type 1 diabetes to a quadrivalent inactivated influenza vaccine". *Human Vaccines & Immunotherapeutics*, *0*(00), 1–9, (2019).

Abstract: This study was planned to evaluate whether a 3-month treatment with Lactobacillus rhamnosus GG (LGG) can modify immune system functions in children and adolescents with type 1 diabetes (T1D), leading to an increased immune response to an injectable quadrivalent inactivated influenza vaccine (QIV). A total of 87 pediatric patients with T1D were screened, although 34 patients in the Probiotic group and 30 in the Control group accepted to be vaccinated with QIV and completed the study. Vaccine immunogenicity and safety and the inflammatory cytokine response were studied. Results showed that QIV was immunogenic and safe in T1D pediatric patients and pre-administration of LGG for three months did not substantially modify the QIV humoral immunity. The combination of QIV and LGG reduced inflammatory responses (i.e., IFN-γ, IL17A, IL-17F, IL-6, and TNF-α) from activated PBMCs of pediatric patients with T1D, without dampening the production of seroprotective antibodies. In conclu- sion, QIV is associated with an adequate immunogenicity in children and adolescents with T1D in presence of a good safety profile. Although a systematic administration of LGG did not result in an improvement of humoral responses to an influenza vaccine, the probiotic did induce important anti- inflammatory effects.

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Research field: Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day:

Nabukeera-Barungi et al. "Thymus gland size during recovery from complicated severe acute malnutrition: a prospective study of the role of probiotics". Paediatrics and International Child Health, 39(2), 95–103, (2019).

Abstract: BACKGROUND: Children with severe acute malnutrition (SAM) are prone to infections due to immune dysfunction including severe thymus atrophy which recovers during nutritional rehabilitation. AIM: To investigate predictors of thymus size recovery, including probiotics during nutritional rehabilitation of children admitted with complicated SAM. METHODS: In this prospective study nested in a randomized controlled trial, children 6-59 months admitted with SAM received standard care and either probiotics or placebo during hospitalization until 8 weeks post-discharge. Thymus size was measured using ultrasound at admission, discharge, 8 weeks post-discharge and among 27 community controls. Predictors of thymus size recovery were assessed using linear regression. RESULTS: Among 388 children with SAM, mean (SD) thymus size was 1.06 cm2 (0.41), 1.24 cm2 (0.48), 2.85 cm2 (1.07) and 4.2 cm2 (0.93) at admission, discharge, follow-up and in the healthy controls respectively ($p < 0.05$).Probiotics did not affect thymus recovery. During both inpatient therapeutic care (ITC) and outpatient therapeutic care (OTC), thymus recovery correlated positively with anthropometry but negatively with caregiver-perceived illness severity and Haemoglobin <8 g/dl. Negative predictors of thymus recovery during ITC included grade 3 oedema (beta -0.13, 95%CI -0.25; -0.01), dermatosis (beta -0.21, 95%CI -0.41; -0.01), C-reactive protein (CRP) >15mg/L (beta -0.13, 95%CI -0.25; -0.02) and neutrophils (beta -0.01, 95%CI -0.02; -0.002). During OTC, HIV negatively predicted thymus recovery. CONCLUSION: Children with SAM failed to regain thymus size at 8 weeks post-discharge. Probiotics did not predict thymus recovery during nutritional rehabilitation. More research is needed to find interventions which can accelerate immune recovery. ABBREVIATIONS: ART, Antiretroviral therapy; BB-12, Bifidobacterium animalis subsp. Lactis; CRP, C-reactive protein; ITC, inpatient therapeutic care; LGG, Lactobacillus rhamnosus; MNU, Mwanamugimu Nutrition Unit; MUAC, mid-upper arm circumference; OTC, outpatient therapeutic care; PCR, Polymerised chain reaction; RUTF, ready-to-use therapeutic food; SAM, severe acute malnutrition; VAS, visual analogue score; WHO, World Health Organization; WHZ, weight-for-height score.

Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU/day: 2 x 10^9

Adler Sørensen et al. "Probiotics and the immunological response to infant vaccinations; a double-blind randomized controlled trial". *Clinical Microbiology and Infection*, *25*(4), 511.e1-511.e7, (2019).

Abstract: CONTEXT/OBJECTIVE Manipulation of the microbiome is an emerging approach to promote health. We conducted a Phase Ia safety study of a single bladder instillation of probiotics in asymptomatic patients with neuropathic bladder to determine the tolerability and safety of a single Lactobacillus instillation. DESIGN Phase Ia safety study. SETTING Outpatient rehabilitation clinic at a rehabilitation hospital (adults) and urology clinic at a free-standing children's hospital (children). PARTICIPANTS Ten patients with neuropathic bladder were included: five children with spina bifida and five adults with spinal cord injury. INTERVENTIONS A single Lactobacillus rhamnosus GG (Culturelle, 20 billion live organisms) instillation. OUTCOME MEASURES After the instillation, participants self-monitored symptoms using the Urinary Symptoms Questionnaire for People with Neuropathic Bladder using Intermittent Catheterization daily for one week. Repeat urinalysis, urine culture, and 16S bacterial rRNA-based microbiome analyses were performed 7-10 days after instillation. RESULTS Probiotic instillation was well-tolerated. One child had upper respiratory tract symptoms during the trial, and two had transient cloudy urine. No adults reported any symptoms following instillation. Lactobacillus did not grow on culture post-instillation. There were differences in beta diversity of the urine microbiome in children vs. adults with neuropathic bladder ($P < 0.0156$). Lactobacillus was present in the pre-instillation urinary microbiomes all of the adults and 4 out of 5 of the pediatric subjects, and identified in 4 out of 5 of both the adult and pediatric subjects' post-instillation urinary microbiomes. CONCLUSION Intravesical instillation of Culturelle probiotic may be safe and well-tolerated in patients with neuropathic bladder.

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Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 10 billion colony-forming units of LGG per day

Cabana et al. A Pilot Analysis of Early *Lactobacillus rhamnosus* GG for Infant Colic Prevention. Journal of pediatric gastroenterology and nutrition, (2018).

Abstract: We conducted a secondary analysis of data from a trial of Lactobacillus rhamnosus GG (LGG) supplementation as a pilot study to assess whether LGG prevents infant colic. For the first 6 months of life, infants received a daily dose of 10 billion colony-forming units of LGG or a control (n=184). We compared the likelihood of a diagnosis of colic before 4 months of age, based on parent reported symptoms or a physician diagnosis of colic. Out of the 184 infants, 18 (9.8%) had colic. There were no differences between the two groups in the percentage of infants with colic based on symptoms (control 5.4% vs. LGG 9.8%; p=0.19); physician diagnosis (control 3.2% vs. LGG 7.6%; p=0.26); or either symptoms or diagnosis combined (control 6.5% vs. LGG 13.0%; p=0.13). In this pilot study, early infant LGG supplementation does not appear to prevent the later development of colic.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12®.
Dosage CFU: 10^9 of each strain

Fjeldhøj et al. "Probiotics and carriage of Streptococcus pneumoniae serotypes in Danish children, a double-blind randomized controlled trial". *Scientific Reports*, *8*(1), 1–9, (2018).

Abstract: We conducted a secondary analysis of data from a trial of Lactobacillus rhamnosus GG (LGG) supplementation as a pilot study to assess whether LGG prevents infant colic. For the first 6 months of life, infants received a daily dose of 10 billion colony-forming units of LGG or a control (n=184). We compared the likelihood of a diagnosis of colic before 4 months of age, based on parent reported symptoms or a physician diagnosis of colic. Out of the 184 infants, 18 (9.8%) had colic. There were no differences between the two groups in the percentage of infants with colic based on symptoms (control 5.4% vs. LGG 9.8%; p=0.19); physician diagnosis (control 3.2% vs. LGG 7.6%; p=0.26); or either symptoms or diagnosis combined (control 6.5% vs. LGG 13.0%; p=0.13). In this pilot study, early infant LGG supplementation does not appear to prevent the later development of colic.

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Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and L. rhamnosus LC705 and B. breve Bb99 and Propionibacterium freudenreichii
Dosage CFU/day: $5x10^9$, $5x10^9$, $2x10^8$ and $2x10^9$ of each strain, respectively.

Korpela et al. "Probiotic Supplementation Restores Normal Microbiota Composition and Function in Antibiotic-Treated and in Caesarean-Born Infants." Microbiome, 6(1), 182, (2018)

Abstract:
Infants born by caesarean section or receiving antibiotics are at increased risk of developing metabolic, inflammatory and immunological diseases, potentially due to disruption of normal gut microbiota at a critical developmental time window. We investigated whether probiotic supplementation could ameliorate the effects of antibiotic use or caesarean birth on infant microbiota in a double blind, placebo-controlled randomized clinical trial. Mothers were given a multispecies probiotic, consisting of Bifidobacterium breve Bb99 (Bp99 2 × 108 cfu) Propionibacterium freundenreichii subsp. shermanii JS (2 × 109cfu), Lactobacillus rhamnosus Lc705 (5 × 109 cfu) and Lactobacillus rhamnosus GG (5 × 109 cfu) (N = 168 breastfed and 31 formula-fed), or placebo supplement (N = 201 breastfed and 22 formula-fed) during pregnancy, and the infants were given the same supplement. Faecal samples of the infants were collected at 3 months and analyzed using taxonomic, metagenomic and metaproteomic approaches. The probiotic supplement had a strong overall impact on the microbiota composition, but the effect depended on the infant's diet. Only breastfed infants showed the expected increase in bifidobacteria and reduction in Proteobacteria and Clostridia. In the placebo group, both birth mode and antibiotic use were significantly associated with altered microbiota composition and function, particularly reduced Bifidobacterium abundance. In the probiotic group, the effects of antibiotics and birth mode were either completely eliminated or reduced. The results indicate that it is possible to correct undesired changes in microbiota composition and function caused by antibiotic treatments or caesarean birth by supplementing infants with a probiotic mixture together with at least partial breastfeeding. clinicaltrials.gov NCT00298337.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and L. rhamnosus LC705 and B. breve Bb99 and Propionibacterium freudenreichii
Dosage CFU/day: LGG (5 × 10^9 CFU), LC705 (5 × 10^9 CFU), Bb99 (2 × 10^8 CFU) and Propionibacterium freudenreichii (2 × 10^9 CFU) - twice a day until delivery

Kallio et al. Perinatal probiotic intervention prevented allergic disease in a Caesarean-delivered subgroup at 13-year follow-up. Clinical & Experimental Allergy. 2018. October.

Abstract: BACKGROUND The long-term effects of probiotic intervention for primary prevention of allergic diseases are not well known. We previously reported less eczema until 10 years in our probiotic intervention trial. OBJECTIVE To investigate the effect of early probiotic intervention on the prevalence of allergic diseases up to 13 years of age. METHODS Pregnant women (n=1223) carrying a child at a high risk of allergy (at least one parent with allergic disease) were randomised to receive a mixture of probiotics (Lactobacillus rhamnosus GG and LC705, Bifidobacterium breve Bb99 and Propionibacterium freudenreichii) or placebo in a double-blind manner from 36 weeks of gestation until birth. Their infants received the same product for the first six months (registration number NCT00298337). At 13-year follow-up the participants were requested to return a questionnaire and to provide a blood sample. RESULTS A questionnaire was returned by 642 participants (63.1% of intention-to-treat infants) and 459 provided a blood sample. In the whole cohort there were no statistically significant differences in doctor-diagnosed allergic disease (55.2% and 59.0%, probiotic and placebo group, respectively) or allergic disease (47.9% and 51.6%) based on the ISAAC questionnaire data. Inhalant-specific IgE-sensitisation (>0.7 kU/L) was 59.3% in the probiotic group and 49.8% in the placebo group (p=0.040). In a post hoc analysis made in Caesarean-delivered subgroup allergy was reported in 41.5% of the probiotic group and 67.9% of the placebo group (p=0.006), and eczema in 18.9% and 37.5% respectively (p=0.031). In the whole cohort 8.5% of the probiotic group had suffered from wheezing attacks during the previous 12 months vs. 14.7% in the placebo group (p=0.013). There was no statistically significant differences discovered between the characteristics of the participating group and the dropout-group. CONCLUSIONS Probiotic intervention protected Caesarean-delivered subgroup from allergic disease and eczema, but not the total cohort. This article is protected by copyright. All rights reserved.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 2.5 to 5 × 10^9 CFU/day

Kane et al. Routine Supplementation of Lactobacillus rhamnosus GG and Risk of Necrotizing Enterocolitis in Very Low Birth Weight Infants. J Pediatr. 2018 Apr;195:73-79.

Abstract: Objective: To evaluate if routine supplementation of Lactobacillus rhamnosus GG ATCC 53103 (LGG) is associated with a decreased risk of necrotizing enterocolitis in very low birth weight (VLBW) infants. Study design: Retrospective observational cohort study of VLBW (<1500 g) infants at a single center from 2008 to 2016. LGG supplementation with Culturelle at a dose of 2.5 to 5 × 109CFU/day began in 2014. We used multivariable logistic regression to evaluate the association between LGG supplementation and necrotizing enterocolitis (modified Bell stage IIA or greater), after adjusting for potential confounders. We also compared changes in necrotizing enterocolitis incidence before and after implementation of LGG using a statistical process control chart. Results: We evaluated 640 VLBW infants with a median gestational age of 28.7 weeks (IQR 26.3-30.6); 78 (12%) developed necrotizing enterocolitis. The median age at first dose of LGG was 6 days (IQR 3-10), and duration of supplementation was 32 days (IQR 18-45). The incidence of necrotizing enterocolitis in the epoch before LGG implementation was 10.2% compared with 16.8% after implementation. In multivariable analysis, LGG supplementation was associated with a higher risk of necrotizing enterocolitis (aOR 2.10, 95 % CI 1.25-3.54, P =.005). We found no special cause variation in necrotizing enterocolitis after implementation of LGG supplementation. There were no episodes of Lactobacillus sepsis during 5558 infant days of LGG supplementation. Conclusions: In this study, routine LGG supplementation was not associated with a decreased risk of necrotizing enterocolitis. Our findings do not support the use of the most common probiotic preparation currently supplemented to VLBW infants in the US.

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Research field: Infant and Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day:

Berni Canani et al. Gut microbiota composition and butyrate production in children affected by non-IgE-mediated cow's milk allergy. Scientific Reports 8.1 (2018).

Abstract: Cow's milk allergy (CMA) is one of the earliest and most common food allergy and can be elicited by both IgE- or non-IgE-mediated mechanism. We previously described dysbiosis in children with IgE-mediated CMA and the effect of dietary treatment with extensively hydrolyzed casein formula (EHCF) alone or in combination with the probiotic Lactobacillus rhamnosus GG (LGG). On the contrary, the gut microbiota in non-IgE-mediated CMA remains uncharacterized. In this study we evaluated gut microbiota composition and fecal butyrate levels in children affected by non-IgE-mediated CMA. We found a gut microbiota dysbiosis in non-IgE-mediated CMA, driven by an enrichment of Bacteroides and Alistipes. Comparing these results with those previously obtained in children with IgE-mediated CMA, we demonstrated overlapping signatures in the gut microbiota dysbiosis of non-IgE-mediated and IgE-mediated CMA children, characterized by a progressive increase in Bacteroides from healthy to IgE-mediated CMA patients. EHCF containg LGG was more strongly associated with an effect on dysbiosis and on butyrate production if compared to what observed in children treated with EHCF alone. If longitudinal cohort studies in children with CMA will confirm these results, gut microbiota dysbiosis could be a relevant target for innovative therapeutic strategies in children with non-IgE-mediated CMA.

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Research field: Immune health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10^{10}

Lazarus et al. The effect of probiotics and zinc supplementation on the immune response to oral rotavirus vaccine: A randomized, factorial design, placebo-controlled study among Indian infants. Vaccine, Jan 4;36(2):273-279, (2018).

Abstract: BACKGROUND: Strategies are needed to improve oral rotavirus vaccine (RV), which provides suboptimal protection in developing countries. Probiotics and zinc supplementation could improve RV immunogenicity by altering the intestinal microbiota and immune function.
METHODS: Infants 5weeks old living in urban Vellore, India were enrolled in a randomized, double-blind, placebo-controlled trial with a 4-arm factorial design to assess the effects of daily zinc (5mg), probiotic (1010Lactobacillus rhamnosus GG) or placebo on the immunogenicity of two doses of RV (Rotarix®, GlaxoSmithKline Biologicals) given at 6 and 10weeks of age. Infants were eligible for participation if healthy, available for the study duration and without prior receipt of RV or oral poliovirus vaccine other than the birth dose. The primary outcome was seroconversion to rotavirus at 14weeks of age based on detection of VP6-specific IgA at ≥20U/ml in previously seronegative infants or a fourfold rise in concentration.
RESULTS: The study took place during July 2012 to February 2013. 620 infants were randomized equally between study arms and 551 (88.9%) completed per protocol. Seroconversion was recorded in 54/137 (39.4%), 42/136 (30.9%), 40/143 (28.0%), and 37/135 (27.4%) infants receiving (1) probiotic and zinc, (2) probiotic and placebo, (3) placebo and zinc, (4) two placebos. Seroconversion showed a modest improvement among infants receiving probiotic (difference between groups 1, 2 and 3, 4 was 7.5% (97.5% Confidence Interval (CI): -1.4%, 16.2%), p=0.066) but not zinc (difference between groups 1, 3 and 2, 4 was 4.4% (97.5% CI: -4.4%, 13.2%), p=0.272). 16 serious adverse events were recorded, none related to study interventions. CONCLUSIONS: Zinc or probiotic supplementation did not significantly improve the low immunogenicity of rotavirus vaccine given to infants in a poor urban community in India. A modest effect of combined supplementation deserves further investigation.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: $1x10^{10}$

Durack et al. "Delayed Gut Microbiota Development in High-Risk for Asthma Infants Is Temporarily Modifiable by Lactobacillus Supplementation." Nature Communications 9.1 (2018)

Abstract:
Gut microbiota dysbiosis and metabolic dysfunction in infancy precedes childhood atopy and asthma development. Here we examined gut microbiota maturation over the first year of life in infants at high risk for asthma (HR), and whether it is modifiable by early-life Lactobacillus supplementation. We performed a longitudinal comparison of stool samples collected from HR infants randomized to daily oral Lactobacillus rhamnosus GG (HRLGG) or placebo (HRP) for 6 months, and healthy (HC) infants. Meconium microbiota of HRP participants is distinct, follows a delayed developmental trajectory, and is primarily glycolytic and depleted of a range of anti-inflammatory lipids at 6 months of age. These deficits are partly rescued in HRLGG infants, but this effect was lost at 12 months of age, 6 months after cessation of supplementation. Thus we show that early-life gut microbial development is distinct, but plastic, in HR infants. Our findings offer a novel strategy for early-life preventative interventions.

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Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® and B. animalis subsp. lactis, BB-12® and L. acidophilus LA-5
Dosage CFU/day: 5×10^{10} of each strain

Schei, Kasper et al. "Early Gut Mycobiota and Mother-Offspring Transfer." Microbiome 5.1 (2017)

Abstract: The fungi in the gastrointestinal tract, the gut mycobiota, are now recognised as a significant part of the gut microbiota, and they may be important to human health. In contrast to the adult gut mycobiota, the establishment of the early gut mycobiota has never been described, and there is little knowledge about the fungal transfer from mother to offspring. In a prospective cohort, we followed 298 pairs of healthy mothers and offspring from 36 weeks of gestation until 2 years of age (1516 samples) and explored the gut mycobiota in maternal and offspring samples. Half of the pregnant mothers were randomised into drinking probiotic milk during and after pregnancy. The probiotic bacteria included Lactobacillus rhamnosus GG (LGG), Bifidobacterium animalis subsp. lactis Bb-12 and Lactobacillus acidophilus La-5. We quantified the fungal abundance of all the samples using qPCR of the fungal internal transcribed spacer (ITS)1 segment, and we sequenced the 18S rRNA gene ITS1 region of 90 high-quantity samples using the MiSeq platform (Illumina). The gut mycobiota was detected in most of the mothers and the majority of the offspring. The offspring showed increased odds of having detectable faecal fungal DNA if the mother had detectable fungal DNA as well (OR = 1.54, p = 0.04). The fungal alpha diversity in the offspring gut increased from its lowest at 10 days after birth, which was the earliest sampling point. The fungal diversity and fungal species showed a succession towards the maternal mycobiota as the child aged, with Debaryomyces hansenii being the most abundant species during breast-feeding and Saccharomyces cerevisiae as the most abundant after weaning. Probiotic consumption increased the gut mycobiota abundance in pregnant mothers (p = 0.01). This study provides the first insight into the early fungal establishment and the succession of fungal species in the gut mycobiota. The results support the idea that the fungal host phenotype is transferred from mother to offspring. Clinicaltrials.gov NCT00159523

Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® or L.acidophilus + B.bifidum
Dosage CFU/day: 1 billion

Narbona-López et al. "Probiotics to prevent necrotising enterocolitis and nosocomial infection in very low birth weight preterm infants". *British Journal of Nutrition*, *117*(7), 994 (2017)

Abstract: The aim of the study was to determine whether routine probiotic supplementation (RPS) with Lactobacillus rhamnosus GG (LGG) or Lactobacillus acidophilus +Lactobacillus bifidum is associated with reduced risk of necrotising enterocolitis (NEC)≥Stage II in preterm neonates born at ≤32 weeks' gestation. We conducted a retrospective cohort study on the effect of probiotic supplementation in very low birth weight infants in our neonatal unit by comparing two periods: before and after supplementation. The incidence of NEC≥Stage II, late-onset sepsis and all-cause mortality was compared for an equal period 'before' (Period I) and 'after' (Period II) RPS with LGG or L. acidophillus+L. bifidum. Multivariate logistic regression analysis was conducted to adjust for relevant confounders. The study population was composed of 261 neonates (Period I v. II: 134 v. 127) with comparable gestation duration and birth weights. In <32 weeks, we observed a significant reduction in NEC≥Stage II (11·3 v. 4·8 %), late-onset sepsis (16 v. 10·5 %) and mortality (19·4 v. 2·3 %). The benefits in neonates aged ≤27 weeks did not reach statistical significance. RPS with LGG or L. acidophillus+L. bifidum is associated with a reduced risk of NEC≥Stage II, late-onset sepsis and mortality in preterm neonates born at ≤32 weeks' gestation. [ABSTRACT FROM PUBLISHER]

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Research field: Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® and Bifidobacterium, BB-12®
Product formulation: 10^9

Laursen et al. Probiotics and Child Care Absence Due to Infections: A Randomized Controlled Trial. *Pediatrics*, *140*(2), (2017)

Abstract: OBJECTIVES The risk of infections is higher in children attending child care compared with children cared for at home. This study examined the effect of a combination of probiotics on absence from child care because of respiratory and gastrointestinal infections in healthy infants aged 8 to 14 months at the time of enrollment in child care. METHODS The ProbiComp study was a randomized, double-blind, placebo-controlled study. A total of 290 infants were randomly allocated to receive a placebo or a combination of Bifidobacterium animalis subsp lactis and Lactobacillus rhamnosus in a dose of 10(9) colony-forming units of each daily for a 6-month intervention period. Absence from child care, occurrence of infant symptoms of illness, and doctor visits were registered by the parents using daily and weekly Web-based questionnaires. RESULTS Median absence from child care was 11 days (interquartile range: 6-16). Intention-to-treat analysis showed no difference between the probiotics and placebo groups (P = .19). Additionally, there was no difference in any of the secondary outcomes between groups; the number of children with doctor-diagnosed upper or lower respiratory tract infections, the number of doctor visits, antibiotic treatments, occurrence and duration of diarrhea, and days with common cold symptoms, fever, vomiting, or caregivers' absence from work. CONCLUSIONS A daily administration of a combination of B animalis subsp lactis and L rhamnosus for 6 months did not reduce the number of days absent from child care in healthy infants at the time of enrollment in child care.

Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day:

Berni Canani et al. Extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. J Allergy Clin Immunol. 2017 Jun;139(6):1906-1913

Abstract: BACKGROUND: Children with cow's milk allergy (CMA) have an increased risk of other allergic manifestations (AMs).
OBJECTIVE: We performed a parallel-arm randomized controlled trial to test whether administration of an extensively hydrolyzed casein formula (EHCF) containing the probiotic Lactobacillus rhamnosus GG (LGG) can reduce the occurrence of other AMs in children with CMA.
METHODS: Children with IgE-mediated CMA were randomly allocated to the EHCF or EHCF+LGG groups and followed for 36 months. The main outcome was occurrence of at least 1 AM (eczema, urticaria, asthma, and rhinoconjunctivitis). The secondary outcome was tolerance acquisition, which was defined as the negativization of a double-blind food challenge results at 12, 24, and 36 months. AMs were diagnosed according to standardized criteria. Tolerance acquisition was evaluated every 12 months.
RESULTS: A total of 220 children (147 boys [67%]) with a median age of 5.0 months (interquartile range, 3.0-8.0 months) were randomized; 110 children were placed in the EHCF group, and 110 children were placed in the EHCF+LGG group. In the complete case analysis the absolute risk difference for the occurrence of at least 1 AM over 36 months was -0.23 (95% CI, -0.36 to -0.10; P < .001), and the absolute risk difference for the acquisition of cow's milk tolerance was 0.20 (95% CI, 0.05-0.35; P < .01) at 12 months, 0.24 (95% CI, 0.08-0.41; P < .01) at 24 months, and 0.27 (95% CI, 0.11-0.43; P < .001) at 36 months. In the sensitivity analysis the effect size of the main outcome was virtually unchanged when the occurrence of AMs was assigned to all 27 missing children.
CONCLUSIONS: EHCF+LGG reduces the incidence of other AMs and hastens

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® alone or in combination with B. animalis subsp. lactis, BB-12®, Lactobacillus paracasei ST11 and *Bifidobacterium longum* BL999
Dosage CFU/day: NA

Lundelin, et al. "Long-term safety and efficacy of perinatal probiotic intervention: evidence from a follow-up study of four randomized, double-blind, placebo-controlled trials. . Pediatric Allergy and Immunology, 28(2), 170–175 (2017).

Abstract: BACKGROUND: Societies worldwide are faced with a progressive increase in immune-mediated health problems such as allergic, autoimmune and inflammatory diseases, as well as obesity. Perinatal administration of specific probiotic bacteria is an attractive approach in reducing the risk of these conditions, but long-term efficacy and safety data are lacking. The aim here was to evaluate the clinical benefit and long-term safety of specific probiotics administered during the perinatal period. METHODS: The probiotic strains used were Lactobacillus rhamnosus GG, Bifidobacterium lactis Bb-12, Lactobacillus paracasei ST11 and Bifidobacterium longum BL999. The children involved have subsequently undergone prospective long-term follow-up. In addition to physical examination, data were collected by structured questionnaires on non-communicable diseases and continued probiotic use, and growth data from welfare clinics and school nurses. RESULTS: Altogether 303 mother-infant pairs were included in the analysis. Seventy-six out of 163 (47%) children receiving perinatal probiotics had developed allergic disease compared with 79 out of 140 (56%) receiving placebo (OR 0.67, 95% CI 0.43-1.06, p=0.09). Fifty-nine out of 133 (44%) children receiving Lactobacillus rhamnosus GG perinatally had developed allergic disease, OR 0.62, 95% CI 0.38-0.99, p=0.047, as compared to placebo. We found no differences in growth or non-communicable disease prevalence between children receiving perinatally probiotics or placebo. CONCLUSIONS: Perinatal probiotic administration is safe in long-term follow-up. Children receiving Lactobacillus rhamnosus GG perinatally tended to have decreased allergy prevalence. This article is protected by copyright. All rights reserved.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12®**,** L. rhamnosus, LGG®
Dosage CFU/day: 5 billion each
Product formulation: Sachets (maltodextrin with or without probiotics)
Reference number: 1739

Grenov, et al. "Effect of Probiotics on Diarrhea in Children With Severe Acute Malnutrition: A Randomized Controlled Study in Uganda". *Journal of Pediatric Gastroenterology and Nutrition*, *64*(3), 396–403, (2017).

Abstract: OBJECTIVES: To assess the effect of probiotics on diarrhea during in- and outpatient treatment of children with severe acute malnutrition (SAM). METHODS: A randomized, double-blind, placebo-controlled study was conducted involving 400 children admitted with SAM. Patients received one daily dose of a blend of Bifidobacterium animalis subsp. lactis (BB-12) and Lactobacillus rhamnosus (LGG) (10 billion colony-forming units, 50:50) or placebo during hospitalization followed by an 8-12 week outpatient treatment period, depending on patients' recovery rate. All outcomes were reported for in- and outpatient treatment separately. The primary outcome was number of days with diarrhea during hospitalization. Secondary outcomes included other diarrhea outcomes, pneumonia, weight gain, and recovery. RESULTS: There was no difference in number of days with diarrhea between the probiotic (n = 200) and placebo (n = 200) groups during inpatient treatment (adjusted difference +0.2 days, 95% CI -0.8 to 1.2, p = 0.69), however during outpatient treatment, probiotics reduced days with diarrhea (adjusted difference -2.2 days 95% CI -3.5 to -0.3, p = 0.025). There were no effects of probiotics on diarrhea incidence and severity or pneumonia, weight gain or recovery during in- or outpatient treatment. Twenty-six patients died in the probiotic versus 20 in the placebo group (p = 0.38). CONCLUSION: BB-12 and LGG had no effect on diarrhea in children with SAM during hospitalization, but reduced the number of days with diarrhea in outpatient treatment by 26%. Probiotics may have a role in follow-up of hospitalized children with SAM or in community based treatment of malnourished children, but further studies are needed to confirm this.

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Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 10 billion

Cabana et al. Early Probiotic Supplementation for Eczema and Asthma Prevention: A Randomized Controlled Trial. Pediatrics. 2017 Sep;140(3)

Abstract: OBJECTIVES: To determine if probiotic administration during the first 6 months of life decreases childhood asthma and eczema.
METHODS: We conducted a randomized, double-blind controlled trial of Lactobacillus rhamnosus GG (LGG) supplementation on the cumulative incidence of eczema (primary end point) and asthma and rhinitis (secondary end points) in high-risk infants. For the first 6 months of life, intervention infants (n = 92) received a daily dose of 10 billion colony-forming units of LGG and 225 mg of inulin (Amerifit Brands, Cromwell, CT), and control infants (n = 92) received 325 mg of inulin alone. We used survival analysis methods to estimate disease incidences in the presence or absence of LGG and to estimate the efficacy of LGG in delaying or preventing these diseases.
RESULTS: Infants were accrued over a 6-year period (median follow-up: 4.6 years; 95% retention rate at 2 years). At 2 years of age, the estimated cumulative incidence of eczema was 30.9% (95% confidence interval [CI], 21.4%-40.4%) in the control arm and 28.7% (95% CI, 19.4%-38.0%) in the LGG arm, for a hazard ratio of 0.95 (95% CI, 0.59-1.53) (log-rank P = .83). At 5 years of age, the cumulative incidence of asthma was 17.4% (95% CI, 7.6%-27.1%) in the control arm and 9.7% (95% CI, 2.7%-16.6%) in the LGG arm, for a hazard ratio of 0.88 (95% CI, 0.41-1.87) (log-rank P = .25).
CONCLUSIONS: For high-risk infants, early LGG supplementation for the first 6 months of life does not appear to prevent the development of eczema or asthma at 2 years of age.

Research field: Infant and children´s nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® and Bifidobacterium, BB-12®
Product formulation:

Laursen et al. Administration of two probiotic strains during early childhood does not affect the endogenous gut microbiota composition despite probiotic proliferation. BMC Microbiol. 2017 Aug 17;17(1):175.

Abstract: BACKGROUND: Probiotics are increasingly applied to prevent and treat a range of infectious, immune related and gastrointestinal diseases. Despite this, the mechanisms behind the putative effects of probiotics are poorly understood. One of the suggested modes of probiotic action is modulation of the endogenous gut microbiota, however probiotic intervention studies in adults have failed to show significant effects on gut microbiota composition. The gut microbiota of young children is known to be unstable and more responsive to external factors than that of adults. Therefore, potential effects of probiotic intervention on gut microbiota may be easier detectable in early life. We thus investigated the effects of a 6 month placebo-controlled probiotic intervention with Bifidobacterium animalis subsp. lactis (BB-12®) and Lactobacillus rhamnosus (LGG®) on gut microbiota composition and diversity in more than 200 Danish infants (N = 290 enrolled; N = 201 all samples analyzed), as assessed by 16S rRNA amplicon sequencing. Further, we evaluated probiotic presence and proliferation by use of specific quantitative polymerase chain reaction (qPCR).
RESULTS: Probiotic administration did not significantly alter gut microbiota community structure or diversity as compared to placebo. The probiotic strains were detected in 91.3% of the fecal samples from children receiving probiotics and in 1% of the placebo treated children. Baseline gut microbiota was not found to predict the ability of probiotics to establish in the gut after the 6 month intervention. Within the probiotics group, proliferation of the strains LGG® and BB-12® in the gut was detected in 44.7% and 83.5% of the participants, respectively. A sub-analysis of the gut microbiota including only individuals with detected growth of the probiotics LGG® or BB-12® and comparing these to placebo revealed no differences in community structure or diversity.
CONCLUSION: Six months of probiotic administration during early life did not change gut microbiota community structure or diversity, despite active proliferation of the administered probiotic strains. Therefore, alteration of the healthy infant gut microbiota is not likely to be a prominent mechanism by which these specific probiotics works to exert beneficial effects on host health.

Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® and Bifidobacterium, Bb-12® and Lactobacillus acidophilus La-5
Dosage CFU/day:

Rø et al. Reduced Th22 cell proportion and prevention of atopic dermatitis in infants following maternal probiotic supplementation. Clin Exp Allergy. 2017 Aug;47(8):1014-1021

Abstract: BACKGROUND: In the randomized, controlled study Probiotics in the Prevention of Allergy among Children in Trondheim (ProPACT), maternal probiotic supplementation reduced the incidence of atopic dermatitis (AD) in the offspring. In the current study, we hypothesized that the effect was mediated by a shift in the T helper (Th) cells in the children.
OBJECTIVE: To examine whether Th cell proportions were affected by maternal probiotic supplementation and thus could mediate the preventive effect of probiotics on AD.
METHODS: A total of 415 pregnant women were randomized to ingest a combination of Lactobacillus rhamnosus GG (LGG), Bifidobacterium animalis subsp. lactis Bb-12 (Bb-12) and Lactobacillus acidophilus La-5 (La-5) or placebo, and their offspring were assessed for AD during the first 2 years of life. Peripheral blood collected at 3 months of age was analysed for regulatory T cells (n=140) and Th subsets (n=77) including Th1, Th2, Th9, Th17 and Th22.
RESULTS: The proportion of Th22 cells was reduced in children in the probiotic group compared to the placebo group (median 0.038% vs 0.064%, P=.009). The difference between the probiotic and placebo groups was also observed in the children who did not develop AD during the 2-year follow-up. The proportion of Th22 cells was increased in children who developed AD compared to the children who did not develop AD (0.090% vs 0.044%, P<.001). Mediation analysis indicated that the preventive effect of probiotics was partially mediated through the reduction in Th22 cells.
CONCLUSION: Perinatal maternal probiotic supplementation with a combination of LGG, Bb-12 and La-5 reduced the proportion of Th22 cells in 3-month-old children. This may partially explain the preventive effect of probiotics on AD.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® and B. animalis subsp. lactis, BB-12®
Dosage CFU/day: 10^9 CFU/day

Groele et al. "Effects of Lactobacillus Rhamnosus GG and Bifidobacterium Lactis Bb12 on Beta-Cell Function in Children with Newly Diagnosed Type 1 Diabetes: Protocol of a Randomised Controlled Trial." Bmj Open 7.10 (2017)

Abstract: Introduction Recent evidence has demonstrated that, among other factors, dysbiosis (imbalances in the composition and function of the gut microbiota) may be relevant in the development of type 1 diabetes (T1D). Thus, gut microbiota may be a target for improving outcomes in subjects with T1D. The aim of the study is to examine the effects of Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 on beta-cell function in children with newly diagnosed T1D. Methods and analysis A total of 96 children aged 8 to 17 years with newly diagnosed T1D, confirmed by clinical history and the presence of at least one positive autoantibody, will be enrolled in a double-blind, randomised, placebo-controlled trial in which they will receive L. rhamnosus GG and B. lactis Bb12 at a dose of 109 colony-forming units or an identically appearing placebo, orally, once daily, for 6 months. The follow-up will be for 12 months. The primary outcome measures will be the area under the curve of the C-peptide level during 2-hour responses to a mixed meal. Ethics and dissemination The Bioethics Committee approved the study protocol. The findings of this trial will be submitted to a peer-reviewed paediatric journal. Abstracts will be submitted to relevant national and international conferences.

Research field: Infant and Children's Nutrition and Skin Health
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® + JS + BB-99 + LC-705
Dosage CFU/day: LGG: 2 x 5 billion, LC705: 2x5 billion, BB99: 2 x 0.2 billion, JS: 2 x 2 billion

Peldan et al. "Perinatal probiotics decreased eczema up to 10 years of age, but at 5-10 years, allergic rhino-conjunctivitis was increased". *Clinical & Experimental Allergy*, *47*(7), 975–979, (2017).

Abstract: The article discusses a study on the association of perinatal use of Lactobacillus GG (LGG) with eczema and allergic rhino-conjunctivitis in children. The study involved a group of children and their parents who were asked about allergic diseases, infections, use of antibiotics and probiotics, pet contacts and environmental tobacco smoke. The results showed that perinatal probiotics reduced the risk of eczema but increased the risk of allergic rhino-conjunctivitis in children.

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Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day:

Scalabrin et al. Long-term safety assessment in children who received hydrolyzed protein formulas with Lactobacillus rhamnosus GG: a 5-year follow-up. Eur J Pediatr. 2017 Feb;176(2):217-224.

Abstract: Extensively hydrolyzed (EH) formula with Lactobacillus rhamnosus GG (LGG) was demonstrated to alleviate cow's milk allergy (CMA) symptoms and promote faster acquisition of tolerance to cow's milk protein. We previously demonstrated that partially hydrolyzed (PH) and EH formulas with LGG supported normal growth in healthy-term infants through 120 days of age. The objective of the current study was to evaluate growth, development, and specific adverse events through 5 years of age in participants from that cohort who continued receiving study formula. Infants who completed a double-blind, randomized growth and tolerance study were eligible to continue receiving the assigned study formula through 1 year of age (control: EH casein formula, EHF, or one of two investigational formulas: EH casein formula with LGG (EHF-LGG) or a PH formula with LGG (PHF-LGG)) and participate in follow-up through 5 years of age. Anthropometric measures, behavior development, and specific adverse events were recorded. No significant differences in achieved weight and height or behavioral development outcomes at 3 or 5 years of age were observed among study groups. Few statistically significant differences in the incidence of specific infection-related events through years 3 or 5 were observed among study groups, none of which were considered clinically relevant.CONCLUSION: Extensively and partially hydrolyzed formulas with LGG were associated with normal growth and development and long-term safety through 5 years of age. What is Known: • Infants with cow's milk allergy often experience allergic manifestations that can lead to poor nutrition status and poor growth. • Providing partially hydrolyzed (PH) and EH formulas with or without LGG in infants can support normal growth in healthy-term infants. What is New: • This study provides long-term safety data for the first 5 years of life on the use of extensively and partially hydrolyzed formulas with LGG when fed through 1 year of age. • Extensively and partially hydrolyzed formulas with LGG are associated with normal growth, development, and long-term safety through 5 years of age.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 2 x 10 billion

Schnadower et al. "Randomised controlled trial of Lactobacillus rhamnosus (LGG) versus placebo in children presenting to the emergency department with acute gastroenteritis: The PECARN probiotic study protocol." *BMJ Open*, *7*(9), 1, (2017).

Abstract: Introduction Acute gastroenteritis (AGE) is a common and burdensome condition that affects millions of children worldwide each year. Currently available strategies are limited to symptomatic management, treatment and prevention of dehydration and infection control; no disease-modifying interventions exist. Probiotics, defined as live microorganisms beneficial to the host, have shown promise in improving AGE outcomes, but existing studies have sufficient limitations such that the use of probiotics cannot currently be recommended with confidence. Here we present the methods of a large, rigorous, randomised, double-blind placebo-controlled study to assess the effectiveness and side effect profile of Lactobacillus rhamnosus GG (LGG) (ATCC 53103) in children with AGE. Methods and analysis The study is being conducted in 10 US paediatric emergency departments (EDs) within the federally funded Pediatric Emergency Care Applied Research Network, in accordance with current SPIRIT and CONSORT statement recommendations. We will randomise 970 children presenting to participating EDs with AGE to either 5 days of treatment with LGG (1010colony-forming unit twice a day) or placebo between July 2014 to December 2017. The main outcome is the occurrence of moderate-to-severe disease over time, as defined by the Modified Vesikari Scale. We also record adverse events and side effects related to the intervention. We will conduct intention-to-treat analyses and use an enrichment design to restore the statistical power in case the presence of a subpopulation with a substantially low treatment effect is identified. Ethics and dissemination Institutional review board approval has been obtained at all sites, and data and material use agreements have been established between the participating sites. The results of the trial will be published in peer-reviewed journals. A deidentified public data set will be made available after the completion of all study procedures. Trial registration number NCT01773967. [ABSTRACT FROM AUTHOR]

Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 3.6 * 10^7
Product formulation: Milk powder
Reference number: 1712

Fatheree, et al. Hypoallergenic formula with Lactobacillus rhamnosus GG for babies with colic: A pilot study of recruitment, retention, and fecal biomarkers. *World Journal of Gastrointestinal Pathophysiology*, *7*(1), 160. (2016)

Abstract: AIM: To investigate recruitment, retention, and estimates for effects of formula supplementation with Lactobacillus rhamnosus GG (LGG) on inflammatory biomarkers and fecal microbial community in infants with colic. METHODS: A prospective, double-blind, placebo-controlled trial was conducted in otherwise healthy infants with colic. We screened 74 infants and randomized and analyzed results in 20 infants [9 receiving LGG (LGG+) and 11 not receiving LGG (LGG-)]. LGG was incorporated in the formula (Nutramigen((R))) (minimum of 3 x 10(7) CFU/d) in the LGG+ group. Fecal microbiota and inflammatory biomarkers, including fecal calprotectin (FC), plasma cytokines, circulating regulatory T cells (Tregs), and crying + fussing time were analyzed to determine optimal time points and effect sizes for a larger trial. RESULTS: Recruitment in this population was slow, with about 66% of eligible infants willing to enroll; subject retention was better (75%). These rates were influenced by parents' reluctance to volunteer their infant for a clinical trial and by their tendency to change formulas. The maximal difference of crying + fussing time was observed at day 14, comparing the 2 groups, with a mean difference of -91 (95%CI: -76, 259) min (P = NS). FC showed no significant difference, but the optimal time to determine a potential effect was at day 90 [with a mean difference of 121 (95%CI: -48, 291) mug/g stool], observing a lower level of FC in the LGG+ group. The fecal microbial communities were chaotic, as determined by Shannon's diversity index and not apparently influenced by the probiotic. No significant change was observed in plasma inflammatory cytokines or Tregs, comparing LGG+ to LGG- groups. CONCLUSION: Designing future colic trials involving a probiotic-supplemented formula for infants in the United States will require consideration for difficult enrollment. Infants with colic have major variations in feal microbiota and calprotectin, both of which improve with time, with optimal time points for measurement at days 14 and 90 after treatment.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 4 x 10^8

Korpela et al. "Lactobacillus rhamnosus GG Intake Modifies Preschool Children's Intestinal Microbiota, Alleviates Penicillin-Associated Changes, and Reduces Antibiotic Use." *PLoS ONE*, *11*(4), 1–16, (2016).

Abstract: © 2016 Korpela et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.Antibiotic use is considered among the most severe causes of disturbance to children's developing intestinal microbiota, and frequently causes adverse gastrointestinal effects ranging from mild and transient diarrhoea to life- Threatening infections. Probiotics are commonly advocated to help in preventing antibiotic- Associated gastrointestinal symptoms. However, it is currently unknown whether probiotics alleviate the antibiotic- Associated changes in children's microbiota. Furthermore, it is not known how long- Term probiotic consumption influences the developing microbiota of children. We analysed the influence of long- Term Lactobacillus rhamnosus GG intake on preschool children's antibiotic use, and antibiotic- Associated gastrointestinal complaints in a double blind, randomized placebo-controlled trial with 231 children aged 2-7. In addition, we analysed the effect of L. rhanmosus GG on the intestinal microbiota in a subset of 88 children. The results show that long- Term L. rhamnosus GG supplementation has an influence on the composition of the intestinal microbiota in children, causing an increase in the abundance of Prevotella, Lactococcus, and Ruminococcus, and a decrease in Escherichia. The treatment appeared to prevent some of the changes in the microbiota associated with penicillin use, but not those associated with macrolide use. The treatment, however, did reduce the frequency of gastrointestinal complaints after a macrolide course. Finally, the treatment appeared to prevent certain bacterial infections for up to 3 years after the trial, as indicated by reduced antibiotic use.

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Research field: Infant and Children´s Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 2 x 3 billion
Reference number: 1726

Bruzzese, et al. Randomised clinical trial: a Lactobacillus GG and micronutrient-containing mixture is effective in reducing nosocomial infections in children, vs. placebo. Aliment.Pharmacol.Ther. 2016;44(6):568-575

Abstract: BACKGROUND: Nosocomial infections are a major public health issue and preventative strategies using probiotics and micronutrients are being evaluated. AIM: To investigate the efficacy of a mixture of Lactobacillus GG and micronutrients in preventing nosocomial infections in children. METHODS: A randomised, double-blind, placebo-controlled trial was conducted in hospitalised children. Children (6 months to 5 years of age) received Lactobacillus GG (6 x 10(9) CFU/day) together with vitamins B and C and zinc or placebo, for 15 days, starting on the first day of hospitalisation. The incidence of gastrointestinal and respiratory nosocomial infections after discharge was determined by follow-up telephone call at 7 days. After 3 months, another telephone call estimated the incidence of further infections during follow-up. RESULTS: Ninety children completed the follow-up. Of 19/90 children with a nosocomial infection (20%), 4/45 children (9%) were in the treatment group and 15/45 (33%) in the placebo group (P = 0.016). Specifically, 2/45 (4%) children in the treatment group vs. 11/45 (24%) children in the placebo group (P = 0.007) presented with diarrhoea. The duration of hospitalisation was significantly shorter in the treatment group (3.9 days +/- 1.7 vs. 4.9 +/- 1.2; P = 0.003). At the follow-up, a total of 11/45 (24.4%) children in the treatment group had at least one episode of infection compared to 22/45 (48.9%) in the placebo group (P = 0.016). CONCLUSION: A mixture containing Lactobacillus GG and micronutrients may reduce the incidence of nosocomial infections, supporting the hypothesis that this may represent a valid strategy to prevent nosocomial infections.

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Research field: Women's Health and infant and children's nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® AND L. rhamnosus, LGG®
Dosage CFU/day: 7 billion in total
Product formulation: Capsule
Reference number: 1735

Okesene-Gafa, et al. A randomised controlled demonstration trial of multifaceted nutritional intervention and or probiotics: the healthy mums and babies (HUMBA) trial. BMC Pregnancy Childbirth, 16(1):373 (2016).

Abstract: BACKGROUND: Maternal obesity is associated with adverse pregnancy outcomes and has lifelong negative implications for offspring health. The Institute of Medicine recommends limited gestational weight gain (GWG) in obese women for optimal maternal and infant outcomes. However, there is a gap regarding an effective and sustainable intervention strategy to achieve this goal. The aim of the healthy mums and babies (HUMBA) demonstration trial is to assess whether a multifaceted nutritional intervention and/or an oral probiotic treatment in obese pregnant women can reduce excessive GWG and optimise pregnancy outcomes. METHODS AND DESIGN: The study is a two by two factorial randomised controlled demonstration trial conducted in Counties Manukau health region, New Zealand, a multi-ethnic region with a high prevalence of obesity. A total of 220 non-diabetic obese women with a singleton pregnancy will be recruited between 120 and 176 weeks. At recruitment, women are randomised to receive either a culturally tailored multifaceted dietary intervention or routine dietary advice, and either an oral probiotic or placebo capsule. Randomisation is undertaken via a web-based protocol, randomize.net, with a 1:1 ratio using stratification by body mass index (BMI) category (BMI of 30-34.9 or BMI >/=35 kg/m2). The dietary intervention includes 4 customised nutrition education visits by a trained community health worker combined with motivational text messaging. Probiotic capsules consist of Lactobacillus rhamnosus GG and Bifidobacterium lactis BB12 at a dose of 7 x 109 colony-forming units one per day until birth. Probiotic and placebo capsules are identically pre-packed and labelled by a third party, and are prescribed in a double blinded fashion. Research assessments are conducted at enrolment, 28 weeks, 36 weeks, at birth and at 5 months post-delivery. The primary outcomes for the study are proportion of women with excessive GWG and infant birthweight. DISCUSSION: The HUMBA demonstration trial will assess the efficacy of a culturally tailored multifaceted dietary intervention and probiotic treatment in limiting excessive GWG and optimising birthweight in a multiethnic sample of obese pregnant women. If successful, either one or both of the interventions may be incorporated into future studies powered to investigate important pregnancy outcomes. TRIAL REGISTRATION: Australian New Zealand Clinical Trials Registry registration number: ACTRN12615000400561 , Universal Trial Number: U1111-1155-0409. Date registered: 29th April 2015.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® and L. acidophilus, LA-5® and L. rhamnosus, LGG®
Dosage CFU/day: 5.2 billion LGG®, 5.9 billion BB-12® and 8.3 billion LA-5®
Product formulation: Fermented milk
Reference number: 1570

Fox, et al. Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double-blind, randomised, placebo-controlled study. BMJ Open 2015;5:1-6

Abstract: OBJECTIVE: To estimate the efficacy of a probiotic yogurt compared to a pasteurised yogurt for the prevention of antibiotic-associated diarrhoea in children. DESIGN AND SETTING: This was a multisite, randomised, double-blind, placebo-controlled clinical trial conducted between September 2009 and 2012. The study was conducted through general practices and pharmacies in Launceston, Tasmania, Australia. PARTICIPANTS AND INTERVENTIONS: Children (aged 1-12 years) prescribed antibiotics, were randomised to receive 200 g/day of either yogurt (probiotic) containing Lactobacillus rhamnosus GG (LGG), Bifidobacterium lactis (Bb-12) and Lactobacillus acidophilus (La-5) or a pasteurised yogurt (placebo) for the same duration as their antibiotic treatment. OUTCOMES: Stool frequency and consistency were recorded for the duration of treatment plus 1 week. Primary outcome was stool frequency and consistency, classified at different levels of diarrhoea severity. Due to the small number of cases of diarrhoea, comparisons between groups were made using Fisher's exact analysis. RESULTS: 72 children commenced and 70 children (36 placebo and 34 probiotic) completed the trial. There were no incidents of severe diarrhoea (stool consistency >/=6, >/=3 stools/day for >/=2 consecutive days) in the probiotic group and six in the placebo group (Fisher's exact p=0.025). There was also only one episode of minor diarrhoea (stool consistency >/=5, >/=2 stools/day for >/=2 days in the probiotic group compared to 21 in the placebo group (Fisher's exact p<0.001). The probiotic group reported fewer adverse events (1 had abdominal pain, 1 vomited and 1 had headache) than the placebo group (6 had abdominal pain, 4 had loss of appetite and 1 had nausea). CONCLUSIONS: A yogurt combination of LGG, La-5 and Bb-12 is an effective method for reducing the incidence of antibiotic-associated diarrhoea in children. TRIAL REGISTRATION NUMBER: Australian New Zealand Clinical Trials Registry ACTRN12609000281291.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: -
Product formulation: -
Reference number: 1695

Ovcinnikova, et al. Cost-effectiveness of using an extensively hydrolyzed casein formula plus the probiotic Lactobacillus rhamnosus GG compared to an extensively hydrolyzed formula alone or an amino acid formula as first-line dietary management for cow's milk allergy in the US. Clinicoecon Outcomes Res. 2015;7:145-152

Abstract: OBJECTIVES: The aim was to estimate the cost-effectiveness of using an extensively hydrolyzed casein formula (eHCF) plus the probiotic Lactobacillus rhamnosus GG (eHCF + LGG; Nutramigen LGG) compared to an eHCF alone (Nutramigen) and an amino acid formula (AAF; Neocate) as first-line dietary management for cow's milk allergy (CMA) in the US. METHODS: Using a cohort study design, the analysis was based on the case records of 136 eHCF-fed, 59 eHCF + LGG-fed, and 217 matched AAF-fed infants extracted from the Truven Health MarketScan((R)) Commercial Claims Database (a nationally representative database of the commercially insured population of the US). Clinical outcomes and health care resource use (with corresponding costs at 2012 prices), following first-line dietary management with each formula, were estimated over 12 months from the start of feeding. Differences in infants' outcomes and resource use between groups were adjusted for any differences in baseline covariates. RESULTS: Infants were <6 months of age at presentation. Fifty-six percent of eHCF + LGG-fed infants were estimated to have been successfully managed by 9 months compared to 38% of eHCF-fed infants and 35% of AAF-fed infants ($P<0.05$ and $P=0.003$ respectively). Infants in the AAF group used significantly more health care resources and prescribed drugs than infants in the other two groups. The estimated cost of managing a CMA infant over the first 12 months following the start of feeding was $3,577, $3,781, and $6,255 for an eHCF + LGG-fed, eHCF-fed, and AAF-fed infant, respectively. Parents' costs accounted for up to 10% of the total costs and the remainder was incurred by insurers. The analyses were robust to plausible changes in all variables. CONCLUSION: Using real world evidence, initial dietary management with eHCF + LGG appears to afford a more cost-effective use of health care resources than initial dietary management with eHCF or AAF since it releases health care resources for alternative use within the system and reduces costs without impacting on the time needed to manage the allergy.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. acidophilus LA-5 and L. rhamnosus LGG
Dosage CFU/day: 1 billion LA-5 + 10 billion BB-12 and LGG each
Product formulation: Fermented milk
Reference number: 1601

Dotterud, et al. Does Maternal Perinatal Probiotic Supplementation Alter the Intestinal Microbiota of Mother and Child? J.Pediatr.Gastroenterol.Nutr. 2015;61(2):200-207

Abstract: OBJECTIVES: Maternal probiotic supplementation has been shown to prevent the development of atopic dermatitis in the offspring. We aimed to investigate whether probiotics in pregnant and breast-feeding mothers altered the colonization pattern and the diversity of the mothers' and children's intestinal microbiota. METHODS: In a randomized, double-blind trial, women received probiotic milk or placebo from 36 weeks of gestation up to 3 months postnatally while breast-feeding. The probiotic milk contained Lactobacillus rhamnosus GG, L acidophilus La-5, and Bifidobacterium animalis subsp. lactis Bb-12. Stool samples were collected from the mothers at 30 to 36 weeks of gestation and 3 months after birth, and from the child at age 10 days, 3 months, 1 year, and 2 years, and bacteria were analyzed by quantitative polymerase chain reaction. Additionally, stool samples from 3-month-old and 2-year-old children were characterized using 16S ribosomal RNA gene deep sequencing to estimate the bacterial classes and genera, and the alpha- and beta-diversity. RESULTS: Three months after birth, both the prevalence and the relative abundance of the administered probiotic bacteria were significantly increased among the mothers in the probiotic group compared with among those in the placebo group. Only the Lactobacillus rhamnosus GG bacteria colonized the children at 10 days and at 3 months of age. There were no significant differences in the abundance of the administered probiotic bacteria between the groups at 1 and 2 years of age. For the bacterial classes and genera, and alpha- and beta-diversity, there were no significant differences between the groups. CONCLUSIONS: Different probiotic bacteria seem to have different ability to transfer from the mother to the child. We found no evidence that the probiotics altered the microbial composition or alpha- and beta-diversity of the children.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: -
Product formulation: Milk powder
Reference number: 1692

Berni Canani, et al. Differences in DNA methylation profile of Th1 and Th2 cytokine genes are associated with tolerance acquisition in children with IgE-mediated cow's milk allergy. Clin.Epigenetics 2015;7(1):38-015-0070-8. eCollection 2015

Abstract: BACKGROUND: Epigenetic changes in DNA methylation could regulate the expression of several allergy-related genes. We investigated whether tolerance acquisition in children with immunoglobulin E (IgE)-mediated cow's milk allergy (CMA) is characterized by a specific DNA methylation profile of Th2 (IL-4, IL-5) and Th1 (IL-10, IFN-gamma)-associated cytokine genes. RESULTS: DNA methylation of CpGs in the promoting regions of genes from peripheral blood mononuclear cells and serum level of IL-4, IL-5, IL-10 and INF-gamma were assessed in children with active IgE-mediated CMA (group 1), in children who acquired tolerance to cow's milk proteins (group 2) and in healthy children (group 3). Forty children (24 boys, aged 3 to 18 months) were enrolled: 10 in group 1, 20 in group 2, and 10 in the control group. The DNA methylation profiles clearly separated active CMA patients from healthy controls. We observed an opposite pattern comparing subjects with active IgE-mediated CMA with healthy controls and group 2 children who outgrew CMA. The IL-4 and IL-5 DNA methylation was significantly lower, and IL-10 and INF-gamma DNA methylation was higher in active IgE-mediated CMA patients. Gene promoter DNA methylation rates of all cytokines and respective serum levels were strongly correlated. Formula selection significantly influenced cytokine DNA methylation profiles in group 2. CONCLUSIONS: Tolerance acquisition in children with IgE-mediated CMA is characterized by a distinct Th1 and Th2 cytokine gene DNA methylation pattern. These results suggest that DNA methylation may be a target for CMA prevention and treatment.

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Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 4.5 billion CFU/day
Product formulation: Milk powder
Reference number: 1599

Pärtty, et al. Probiotic Lactobacillus rhamnosus GG therapy and microbiological programming in infantile colic: a randomized, controlled trial. *Pediatric Research*, *78*(4), 470–475, (2015).

Abstract: BACKGROUND: Probiotic Lactobacillus reuteri and reduced allergen load may lessen the daily crying of colic infants, but the role of Lactobacillus rhamnosus GG (LGG) has remained obscure. METHODS: Infants with colic (n = 30) were enrolled during the first 6 wk of life. All families received behavioral support and allergen avoidance diet: breastfeeding mothers followed cow's milk elimination diet and formula-fed infants received extensively hydrolyzed casein formula. The randomized, double-blind intervention employed of LGG 4.5 x 109 cfu/d or placebo for a 4-wk study period. Daily crying was recorded by diaries and parental interviews. Fecal calprotectin and gut microbiota composition by quantitative PCR were evaluated before and after the intervention. RESULTS: Daily crying time was comparable between the probiotic (173 min) and the placebo group (174 min; P = 0.99) at the end of the intervention according to the parental diary. However, parents reported a decrease of 68% (95% confidence interval (CI): 58-78) in daily crying in the probiotic and 49% (95% CI: 32-66) in the placebo group (P = 0.05). CONCLUSION: LGG in infants treated in tandem with behavioral support and a cow's milk elimination diet did not provide additional treatment effect for diary-verified colic crying although parental report of crying suggested the probiotic intervention effective.Pediatric Research (2015); doi:10.1038/pr.2015.127.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. acidophilus LA-5 and L. rhamnosus LGG
Dosage CFU/day: 1 billion LA-5 + 10 billion BB-12 and LGG each
Product formulation: Fermented milk
Reference number: 1597

Simpson, et al. Perinatal probiotic supplementation in the prevention of allergy related disease: 6 year follow up of a randomised controlled trial. *BMC Dermatology*, *15*(1), 1–9, (2015)

Abstract: BACKGROUND: Perinatal probiotics supplementation has been shown to be effective in the primary prevention of atopic dermatitis (AD) in early childhood, although the long term effects of probiotics on AD and other allergic diseases is less certain. We have previously reported a significant reduction in the cumulative incidence of AD at 2 years after maternal probiotic supplementation. In this study we present the effects of perinatal probiotics given to women from a general population on allergy related diseases in their offspring at 6 years. METHODS: Four hundred and fifteen pregnant women were randomised to receive probiotic or placebo milk in a double-blinded trial from 36 week gestation until 3 months postpartum. Probiotic milk contained Lactobacillus rhamnosos GG, L. acidophilus La-5 and Bifidobacterium animalis subsp. lactis Bb-12. At 6 years, children were re-assessed for AD, atopic sensitisation, asthma and allergic rhinoconjunctivitis (ARC). RESULTS: At 6 years, 81 and 82 children were assessed for AD in the probiotic and placebo groups, respectively. In a multiple imputation analysis, there was as trend towards a lower cumulative incidence of AD in the probiotic group compared to the placebo group (OR 0.64, 95 % CI 0.39-1.07, p = 0.086; NNT = 10). This finding was statistically significantly in the complete case analysis (OR 0.48, 95 % CI 0.25-0.92, p = 0.027, NNT = 6). The prevalence of asthma and atopic sensitisation, and the cumulative incidence of ARC were not significantly affected by the probiotic regime at 6 years of age. CONCLUSIONS: Maternal probiotic ingestion alone may be sufficient for long term reduction in the cumulative incidence of AD, but not other allergy related diseases. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT00159523.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: -
Product formulation: -
Reference number: 1693

Guest, et al. Relative cost-effectiveness of using an extensively hydrolyzed casein formula containing the probiotic Lactobacillus rhamnosus GG in managing infants with cow's milk allergy in Spain. Clinicoecon Outcomes Res. 2015;7:583-591

Abstract: OBJECTIVE: To estimate the cost-effectiveness of using an extensively hydrolyzed casein formula containing the probiotic Lactobacillus rhamnosus GG (eHCF + LGG; Nutramigen LGG) as a first-line management for cow's milk allergy compared with eHCF alone, and amino acid formulae in Spain, from the perspective of the Spanish National Health Service (SNS). METHODS: Decision modeling was used to estimate the probability of immunoglobulin E (IgE)-mediated and non-IgE-mediated allergic infants developing tolerance to cow's milk by 18 months. The models also estimated the SNS cost (at 2012/2013 prices) of managing infants over 18 months after starting a formula as well as the relative cost-effectiveness of each of the formulae. RESULTS: The probability of developing tolerance to cow's milk by 18 months was higher among infants with either IgE-mediated or non-IgE-mediated allergy who were fed eHCF + LGG compared with those fed one of the other formulae. The total health care cost of initially feeding infants with eHCF + LGG was less than that of feeding infants with one of the other formulae. Hence, eHCF + LGG affords the greatest value for money to the SNS for managing both IgE-mediated and non-IgE-mediated cow's milk allergy. CONCLUSION: Using eHCF + LGG instead of eHCF alone or amino acid formulae for first-line management of newly-diagnosed infants with cow's milk allergy affords a cost-effective use of publicly funded resources because it improves outcome for less cost. A randomized controlled study showing faster tolerance development in children receiving a probiotic-containing formula is required before this conclusion can be confirmed.

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Research field: Infant and children´s nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 0.045-0.085 Billion CFU/g
Product formulation: Milk powder
Reference number: 1710

Berni Canani, et al. Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. *The ISME Journal*, *10*(3), 742–750, (2015).

Abstract: Dietary intervention with extensively hydrolyzed casein formula supplemented with Lactobacillus rhamnosus GG (EHCF+LGG) accelerates tolerance acquisition in infants with cow's milk allergy (CMA). We examined whether this effect is attributable, at least in part, to an influence on the gut microbiota. Fecal samples from healthy controls (n=20) and from CMA infants (n=19) before and after treatment with EHCF with (n=12) and without (n=7) supplementation with LGG were compared by 16S rRNA-based operational taxonomic unit clustering and oligotyping. Differential feature selection and generalized linear model fitting revealed that the CMA infants have a diverse gut microbial community structure dominated by Lachnospiraceae (20.5+/-9.7%) and Ruminococcaceae (16.2+/-9.1%). Blautia, Roseburia and Coprococcus were significantly enriched following treatment with EHCF and LGG, but only one genus, Oscillospira, was significantly different between infants that became tolerant and those that remained allergic. However, most tolerant infants showed a significant increase in fecal butyrate levels, and those taxa that were significantly enriched in these samples, Blautia and Roseburia, exhibited specific strain-level demarcations between tolerant and allergic infants. Our data suggest that EHCF+LGG promotes tolerance in infants with CMA, in part, by influencing the strain-level bacterial community structure of the infant gut.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 10 billion CFU/day
Product formulation: capsule
Reference number: 1689

Pärtty, et al. A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. *Pediatr Res*, *77*(6), 823–828, (2015).

Abstract: BACKGROUND: Recent experimental evidence suggests that gut microbiota may alter function within the nervous system providing new insight on the mechanism of neuropsychiatric disorders. METHODS: Seventy-five infants who were randomized to receive Lactobacillus rhamnosus GG (ATCC 53103) or placebo during the first 6 mo of life were followed-up for 13 y. Gut microbiota was assessed at the age of 3 wk, 3, 6, 12, 18, 24 mo, and 13 y using fluorescein in situ hybridization (FISH) and qPCR, and indirectly by determining the blood group secretor type at the age of 13 y. The diagnoses of attention deficit hyperactivity disorder (ADHD) and Asperger syndrome (AS) by a child neurologist or psychiatrist were based on ICD-10 diagnostic criteria. RESULTS: At the age of 13 y, ADHD or AS was diagnosed in 6/35 (17.1%) children in the placebo and none in the probiotic group (P = 0.008). The mean (SD) numbers of Bifidobacterium species bacteria in feces during the first 6 mo of life was lower in affected children 8.26 (1.24) log cells/g than in healthy children 9.12 (0.64) log cells/g; P = 0.03. CONCLUSION: Probiotic supplementation early in life may reduce the risk of neuropsychiatric disorder development later in childhood possible by mechanisms not limited to gut microbiota composition.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 8-9 x 10^9
Reference number: 1686

Swanljung, et al. Lactobacillus rhamnosus GG in adenoid tissue: Double-blind, placebo-controlled, randomized clinical trial. Acta Otolaryngol. 2015;135(8):824-830

Abstract: CONCLUSION: Lactobacillus rhamnosus GG (L.GG) was present in all adenoids of children receiving the L. GG product. However, since L.GG was also found from the placebo group, one cannot confirm its effect on the occurrence of rhinovirus (RV) or enterovirus (EV). OBJECTIVES: The present study was conducted to determine whether a 3-week oral consumption of L.GG would lead to presence of the probiotic in adenoid tissue. Furthermore, nasopharyngeal RV and EV findings and symptom data were investigated. METHOD: The tissue samples were collected from 40 children aged 1-5 years about to undergo adenotomy due to recurrent acute/secretory otitis media, chronic rhinitis, or recurrent sinusitis after a 3-week daily consumption of L.GG (n = 20) or placebo (n = 20). Strain-specific real-time PCR was used to detect RV, EV, and L.GG in adenoid tissue. RESULTS: L.GG was recovered in the adenoid sample in 100% of children in the L.GG group and in 76% in the placebo group (p = 0.07). Both RV and EV were found in 31% of children in the L.GG group and in 18% of children in the placebo group (p = 0.67). The majority of the positive samples were positive for both RV and EV. Study diaries showed no differences in symptoms between the groups.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 10 Billion/day
Product formulation: Capsule
Reference number: 1646

Aggarwal, et al. Lactobacillus GG for treatment of acute childhood diarrhoea: an open labelled, randomized controlled trial. Indian J.Med.Res. 2014;139(3):379-385

Abstract: BACKGROUND & OBJECTIVES: Randomized controlled trials in developed countries have reported benefits of Lactobacillus GG (LGG) in the treatment of acute watery diarrhoea, but there is paucity of such data from India. The study was aimed to evaluate the efficacy and safety of Lactobacillus GG in the treatment of acute diarrhoea in children from a semi-urban city in north India. METHODS: In this open labelled, randomized controlled trial 2000 children with acute watery diarrhoea, aged between 6 months to 5 years visiting outpatient department and emergency room of a teaching hospital in north India were enrolled. The children were randomized into receiving either Lactobacillus GG in dose of 10 billion cfu/day for five days or no probiotic medication in addition to standard WHO management of diarrhoea. Primary outcomes were duration of diarrhoea and time to change in consistency of stools. RESULTS: Median (inter quartile range) duration of diarrhoea was significantly shorter in children in LGG group [60 (54-72) h vs. 78 (72-90) h; P<0.001]. Also, there was faster improvement in stool consistency in children receiving Lactobacillus GG than control group [36 (30-36) h vs. 42 (36-48) h; P<0.001]. There was significant reduction in average number of stools per day in LGG group (P<0.001) compared to the control group. These benefits were seen irrespective of rotavirus positivity in stool tests. INTERPRETATION & CONCLUSIONS: Our results showed that the use of Lactobacillus GG in children with acute diarrhoea resulted in shorter duration and faster improvement in stool consistency as compared to the control group.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 1 Billion/day day 1-30, 2 Billion/day day 31-60
Product formulation: Other
Reference number: 1647

Luoto, et al. Prebiotic and probiotic supplementation prevents rhinovirus infections in preterm infants: a randomized, placebo-controlled trial. J.Allergy Clin.Immunol. 2014;133(2):405-413

Abstract: BACKGROUND: Simple and safe strategies for the prevention of viral respiratory tract infections (RTIs) are needed. OBJECTIVE: We hypothesized that early prebiotic or probiotic supplementation would reduce the risk of virus-associated RTIs during the first year of life in a cohort of preterm infants. METHODS: In this randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov no. NCT00167700), 94 preterm infants (gestational age, >/=32 + 0 and 1500 g) treated at Turku University Hospital, Turku, Finland, were allocated to receive oral prebiotics (galacto-oligosaccharide and polydextrose mixture, 1:1), a probiotic (Lactobacillus rhamnosus GG, ATCC 53103), or placebo (microcrystalline cellulose) between days 3 and 60 of life. The primary outcome was the incidence of clinically defined virus-associated RTI episodes confirmed from nasal swabs by using nucleic acid testing. Secondary outcomes were the severity and duration of RTIs. RESULTS: A significantly lower incidence of RTIs was detected in infants receiving prebiotics (rate ratio [RR], 0.24; 95% CI, 0.12-0.49; P < .001) or probiotics (RR, 0.50; 95% CI, 0.28-0.90; P = .022) compared with those receiving placebo. Also, the incidence of rhinovirus-induced episodes, which comprised 80% of all RTI episodes, was found to be significantly lower in the prebiotic (RR, 0.31; 95% CI, 0.14-0.66; P = .003) and probiotic (RR, 0.49; 95% CI, 0.24-1.00; P = .051) groups compared with the placebo group. No differences emerged among the study groups in rhinovirus RNA load during infections, duration of rhinovirus RNA shedding, duration or severity of rhinovirus infections, or occurrence of rhinovirus RNA in asymptomatic infants. CONCLUSIONS: Gut microbiota modification with specific prebiotics and probiotics might offer a novel and cost-effective means to reduce the risk of rhinovirus infections.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 10 Billion CFU/day
Product formulation: Capsule
Reference number: 1644

Sindhu, et al. Immune response and intestinal permeability in children with acute gastroenteritis treated with Lactobacillus rhamnosus GG: a randomized, double-blind, placebo-controlled trial. Clin.Infect.Dis. 2014;58(8):1107-1115

Abstract: BACKGROUND: Probiotics have a possible role in the treatment of pediatric acute gastroenteritis. We report the effect of the probiotic Lactobacillus rhamnosus GG (LGG) on intestinal function, immune response, and clinical outcomes in Indian children with cryptosporidial or rotavirus diarrhea. METHODS: Children with gastroenteritis aged 6 months to 5 years, testing positive for either rotavirus or Cryptosporidium species in stool (coinfections were excluded), were randomized to LGG (ATCC 53103) or placebo, once daily for 4 weeks. Baseline demographic and clinical details were obtained. Sera were tested for immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies to Cryptosporidium and rotavirus, and the lactulose to mannitol ratio for intestinal permeability was determined at baseline and at the end of follow-up. RESULTS: Of the 124 children enrolled, 82 and 42 had rotavirus and cryptosporidial diarrhea, respectively. Median diarrheal duration was 4 days; one-third of the children had severe diarrhea. Baseline and clinical parameters were comparable between children receiving LGG and placebo. At the end of follow-up, fewer children with rotavirus diarrhea on LGG had repeated diarrheal episodes (25% vs 46%; P = .048) and impaired intestinal function (48% vs 72%; P = .027). Significant increase in IgG levels postintervention (456 vs 2215 EU; P = .003) was observed in children with rotavirus diarrhea receiving LGG. Among children with cryptosporidial diarrhea, those receiving LGG showed significant improvement in intestinal permeability. CONCLUSIONS: LGG has a positive immunomodulatory effect and may be useful in decreasing repeated episodes of rotavirus diarrhea. Improvement in intestinal function in children with rotavirus and cryptosporidial gastroenteritis emphasizes the role of probiotics in treating intestinal impairment after infection. CLINICAL TRIALS REGISTRATION: CTRI/2010/091/000339.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 16-18 Billion CFU/day
Product formulation: Capsule
Reference number: 1641

Tapiovaara, et al. Lactobacillus rhamnosus GG in the middle ear after randomized, double-blind, placebo-controlled oral administration. Int.J.Pediatr.Otorhinolaryngol. 2014;78(10):1637-1641

Abstract: OBJECTIVE: Probiotics may have potency in reducing upper respiratory infections, in particular in children. We studied findings from middle ear effusion (MEE) samples after randomized, placebo-controlled 3-week oral administration of probiotic Lactobacillus rhamnosus GG (L. GG) METHODS: 40 children referred to tympanostomy were randomized to receive either L. GG or placebo (1:1) for 3 weeks before surgery. MEE samples were collected from 13 children (in total, 25 samples, 19 from the L. GG group and 6 from the placebo group) and analyzed for L. GG and pathogenic bacterial and viral findings. RESULTS: L. GG was present in 5 of the 25 MEE samples (4 from the L. GG group). Haemophilus infuenzae was the most prominent pathogen in 12 samples (10 from the L. GG group). Rhinovirus was present in 12 samples (10 from the L. GG group) and enterovirus in 1 sample (L. GG group). CONCLUSIONS: L. GG was present in the middle ear of children suffering from otitis media with effusion, but did not reduce the presence of pathogenic bacteria or viruses.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG and B. Infantis
Dosage CFU/day: 0.5 billion of each strain
Product formulation: NA
Reference number: 1416

Havranek, et al. "Probiotics supplementation increases intestinal blood flow velocity in extremely low birth weight preterm infants." *Journal of Perinatology*, *33*(1), 40–44, (2013).

Abstract: Objective:To determine whether probiotics supplementation affects intestinal blood flow velocity in extremely low birth weight neonates.Study Design:In this randomized, double-blind, placebo-controlled study, probiotics were added to the first enteral feeding and continued until discharge or 34 weeks postmenstrual age. Pulsed Doppler was used to measure preprandial and postprandial (at 30 and 60 min) time-averaged mean velocity (TAMV), peak systolic velocity (PSV) and end diastolic velocity (EDV) during the second week of life after >/=7 days of probiotics supplementation.Result:A total of 31 infants were studied, 15 were randomized to the probiotic and 16 to the placebo groups. There was a significant postprandial increase in TAMV for the probiotic vs the placebo group (P=0.035), with PSV and EDV showing a trend. Demographic and clinical variables were similar between the groups.Conclusion:Probiotics administration significantly increases postprandial intestinal blood flow in extremely low birth weight preterm neonates when compared with the placebo group.Journal of Perinatology advance online publication, 22 March 2012; doi:10.1038/jp.2012.37.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 0.1 Billion/day
Product formulation: Milk powder
Reference number: 1650

Kumpu, et al. The use of the probiotic Lactobacillus rhamnosus GG and viral findings in the nasopharynx of children attending day care. J.Med.Virol. 2013;85(9):1632-1638

Abstract: Limited data are available on the effects of probiotics on the nasopharyngeal presence of respiratory viruses in children attending day care. In this substudy of a randomized, double-blinded, placebo-controlled 28-week intervention study, nasopharyngeal swab samples were collected, on visits to a physician due to symptoms of infection, from children receiving control milk (N = 97) and children receiving the same milk supplemented with probiotic Lactobacillus rhamnosus GG (N = 97). The presence of 14 respiratory viruses was assessed by PCR methods, and viral findings were compared with symptom prevalences in the intervention groups. Rhinovirus was identified in 28.6% of 315 swab samples, followed by respiratory syncytial virus (12.4%), parainfluenza virus 1 (12.1%), enterovirus (8.9%), influenza A(H1N1)pdm09 (7.9%), human bocavirus 1 (3.8%), parainfluenza virus 2 (3.2%), adenovirus (2.9%), and influenza A(H3N2) (0.6%). The children in the probiotic group had less days with respiratory symptoms per month than the children in the control group (6.48 [95% CI 6.28-6.68] vs. 7.19 [95% CI 6.98-7.41], P < 0.001). Probiotic intervention did not reduce significantly the occurrence of the examined respiratory viruses, or have an effect on the number of respiratory symptoms observed at the time of a viral finding. Rhinovirus, respiratory syncytial virus, and parainfluenza virus 1 were the most common respiratory viruses in symptomatic children. Children receiving Lactobacillus rhamnosus GG had fewer days with respiratory symptoms than children in the control group, although probiotic intervention was not effective in reducing the amount of viral findings or the respiratory symptoms associated with viral findings.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion first month, 2 billion second month
Product formulation: NA
Reference number: 1504

Pärtty, et al. Effects of early prebiotic and probiotic supplementation on development of gut microbiota and fussing and crying in preterm infants: a randomized, double-blind, placebo-controlled trial. J.Pediatr. 2013;163(5):1272-1277.e2

Abstract: OBJECTIVE: To evaluate the impact of early prebiotic and probiotic intervention on preterm infants' well-being, crying, growth, and microbiological programming. STUDY DESIGN: Ninety-four preterm infants (gestational age 32-36 weeks and birth weight >1500 g) randomized to receive prebiotics (mixture of galacto-oligosaccharide and polydextrose 1:1), probiotics (Lactobacillus rhamnosus GG), or placebo during the first 2 months of life were followed up for 1 year. Infants were categorized based on the extent of crying and irritability during the first 2 months of life, and their gut microbiota was investigated by fluorescence in situ hybridization (n = 66) and quantitative polymerase chain reaction (n = 63). RESULTS: A total of 27 of 94 infants (29%) infants were classified as excessive criers, significantly less frequently in the prebiotic and the probiotic groups than in the placebo group (19% vs 19% vs 47%, respectively; P = .02). The placebo group had a higher percentage of Clostridium histolyticum group bacteria in their stools than did the probiotic group (13.9% vs 8.9%, respectively; P = .05). There were no adverse events related to either supplementation. CONCLUSIONS: Early prebiotic and probiotic supplementation may alleviate symptoms associated with crying and fussing in preterm infants. This original finding may offer new therapeutic and preventive measures for this common disturbance in early life.

Research field: Infant & Children's Nutrition
Study type: Human
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: NA
Product formulation: Milk powder
Reference number: 1607

Berni Canani, et al. Formula selection for management of children with cow's milk allergy influences the rate of acquisition of tolerance: a prospective multicenter study. J.Pediatr. 2013;163(3):771-777

Abstract: OBJECTIVES: To prospectively evaluate the effect of different dietary management strategies on the rate of acquisition of tolerance in children with cow's milk allergy (CMA). STUDY DESIGN: Otherwise healthy children (aged 1-12 months) diagnosed with CMA were prospectively evaluated. The study population was divided into 5 groups based upon the formula used for management: (1) extensively hydrolyzed casein formula ([EHCF], n = 55); (2) EHCF + Lactobacillus rhamnosus GG [LGG], n = 71); (3) hydrolyzed rice formula (RHF, n = 46); (4) soy formula (n = 55); and (5) amino acid based formula (n = 33). A food challenge was performed after 12 months to assess acquisition of tolerance. RESULTS: Two hundred sixty children were evaluated (167 male, 64.2%; age 5.92 months, 95% CI 5.48-6.37; body weight 6.66 kg, 95% CI 6.41-6.91; IgE-mediated CMA 111, 42.7%). The rate of children acquiring oral tolerance after 12 months was significantly higher (P < .05) in the groups receiving EHCF (43.6%) or EHCF + LGG (78.9%) compared with the other groups: RHF (32.6%), soy formula (23.6%), and amino acid based formula (18.2%). Binary regression analysis coefficient (B) revealed that the rate of patients acquiring tolerance at the end of the study was influenced by 2 factors: (1) IgE-mediated mechanism (B -2.05, OR 0.12, 95% CI 0.06-0.26; P < .001); and (2) formula choice, such that those receiving either EHCF (B 1.48, OR 4.41, 95% CI 1.44-13.48; P = .009) or EHCF + LGG (B 3.35, OR 28.62, 95% CI 8.72-93.93; P < .001). CONCLUSIONS: EHCF accelerates tolerance acquisition in children with CMA if compared with other dietetic choices. This effect is augmented by LGG.

Research field: Pregnant women and Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG®
Dosage CFU/day: 1 x 10^{10}

Nylund et al. "Microarray analysis reveals marked intestinal microbiota aberrancy in infants having eczema compared to healthy children in at-risk for atopic disease. " *BMC Microbiology*, *13*, 12, (2013).

Abstract: BACKGROUND: Deviations in composition and diversity of intestinal microbiota in infancy have been associated with both the development and recurrence of atopic eczema. Thus, we decided to use a deep and global microarray-based method to characterize the diversity and temporal changes of the intestinal microbiota in infancy and to define specific bacterial signatures associated with eczema. Faecal microbiota at 6 and 18 months of age were analysed from 34 infants (15 with eczema and 19 healthy controls) selected from a prospective follow-up study based on the availability of faecal samples. The infants were originally randomized to receive either Lactobacillus rhamnosus GG or placebo.\n\nRESULTS: Children with eczema harboured a more diverse total microbiota than control subjects as assessed by the Simpson's reciprocal diversity index of the microarray profiles. Composition of the microbiota did not differ between study groups at age of 6 months, but was significantly different at age of 18 months as assessed by MCPP (p=0.01). At this age healthy children harboured 3 -fold greater amount of members of the Bacteroidetes (p=0.01). Microbiota of children suffering from eczema had increased abundance of the Clostridium clusters IV and XIVa, which are typically abundant in adults. Probiotic Lactobacillus rhamnosus GG supplementation in early infancy was observed to have minor long-term effects on the microbiota composition.\n\nCONCLUSION: A diverse and adult-type microbiota in early childhood is associated with eczema and it may contribute to the perpetuation of eczema.

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Research field: Infant & Children's Nutrition and Oral Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: Fermented milk
Reference number: 1435

Glavina, et al. Effect of LGG yoghurt on Streptococcus mutans and Lactobacillus spp. salivary counts in children Coll.Antropol. 2012;36(1):129-132

Abstract: The aim of this study was to establish effect of 14 day consumption of commercially available yoghurt containing Lactobacillus rhamnosus ATCC53103 - LGG (Bioaktiv LGG, Dukat, Croatia) on Streptococcus mutans and Lactobacillus spp. salivary counts in children. Twenty five patients, 6-10 yr old participated in the study. At the inclusion in the study caries risk for every patient was evaluated. The saliva samples were tested with chair side kits for saliva buffer capacity (CRT buffer, Vivadent, Schaan, Liechtenstein), S. Mutans and Lactobacillus counts (CRT bacteria test, Vivadent, Schaan, Liechtenstein). Seven, 14 and 30d after yoghurt consumption saliva samples were tested again with CRT buffer and CRT bacteria tests. Obtained data were analyzed using chi2 and Kruskal-Wallis tests. Results showed significant increase in saliva buffer capacity 30d after yoghurt consumption. S. Mutans salivary counts were significantly decreased after 30d. Significant differences in Lactobacillus counts were not observed. It could be concluded that daily consumption of yoghurt containing LGG have an inhibitory effect on oral pathogenic bacteria and may be beneficial in caries prevention.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 1319

Hoppu, et al. Probiotics and dietary counselling targeting maternal dietary fat intake modifies breast milk fatty acids and cytokines. Eur.J.Nutr. 2012;51(2):211-219

Abstract: PURPOSE: Breast milk fatty acids possess immunomodulatory properties, and new intervention strategies beyond supplementation of maternal diet with single oils are called for. The objective of the present study was to evaluate the effect of dietary intervention during pregnancy and breastfeeding on breast milk fatty acid and cytokine composition. METHODS: Pregnant women were randomised into three study groups: dietary intervention with probiotics (diet/probiotic) or with placebo (diet/placebo) and a control group (control/placebo). Dietary intervention included dietary counselling and provision of rapeseed oil-based food products. The probiotics used were Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12 in combination. Dietary intake was evaluated by food records at every trimester of pregnancy and 1 month postpartum. Breast milk samples were collected after birth (colostrum) and 1 month after delivery for fatty acid and cytokine analysis (n = 125). RESULTS:Dietary intervention improved the quality of fat in the diet. In breast milk, the proportion of α-linolenic acid and total n-3 fatty acids was higher in both dietary intervention groups compared with control group ($p < 0.05$). In the diet/probiotic group, the γ-linolenic acid content was higher compared with the diet/placebo group ($p < 0.05$). The concentrations of TNF-α, IL-10, IL-4 and IL-2 were higher in both dietary intervention groups compared with controls, and furthermore, long-chain n-3 fatty acids were associated with several cytokines in colostrum samples. CONCLUSION: The present intervention demonstrated the possibility of modifying breast milk immunomodulatory factors by dietary means.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsules
Reference number: 1443

Ou, et al. Prenatal and postnatal probiotics reduces maternal but not childhood allergic diseases: a randomized, double-blind, placebo-controlled trial Clin.Exp.Allergy 2012;42(9):1386-1396

Abstract: BACKGROUND: The prevalence of atopic diseases has increased rapidly in recent decades globally. The administration of probiotics to reduce gastrointestinal inflammation has been popular, but its role in the prevention or treatment of allergic disease remains controversial. This study evaluated the effectiveness of prenatal and postnatal probiotics in the prevention of early childhood and maternal allergic diseases. METHODS: In a prospective, double-blind, placebo-controlled clinical trial, pregnant women with atopic diseases determined by history, total immunoglobulin (Ig)E > 100 kU/L, and/or positive specific IgE were assigned to receive either probiotics (Lactobacillus GG; ATCC 53103; 1 x 10(10) colony-forming units daily) or placebo from the second trimester of pregnancy. Both of clinical evaluation performed by questionnaires concerning any allergic symptoms and plasma total IgE, and allergen-specific IgE were obtained in high-risk parents and children at 0, 6, 18, and 36 months of age. The primary and secondary outcomes were the point and cumulative prevalence of sensitization and developing of allergic diseases, and improvement of maternal allergic symptom score and plasma immune parameters before and after intervention, respectively. RESULTS: In total, 191 pregnant women (LGG group, n = 95; control group, n = 96) were enrolled. No significant effects of prenatal and postnatal probiotics supplementation on sensitization, development of allergic diseases, and maternal IgE levels between placebo and LGG groups. Symptoms of maternal allergic scores improved significantly in the LGG group (P = 0.002). Maternal allergic diseases improvement was more prominent in pregnant women with IgE > 100 kU/L (P = 0.01) and significantly associated with higher interleukin-12p70 levels (P = 0.013). CONCLUSIONS: LGG administration beginning at the second trimester of pregnancy reduced the severity of maternal allergic disease through increment of Th1 response, but not the incidence of childhood allergic sensitization or allergic diseases (ClinicalTrials.govnumber, IDNCT00325273).

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG and B. infantis
Dosage CFU/day: 0,5 billion
Product formulation: Milk powder
Reference number: 1312

Al-Hosni, et al. Probiotics-supplemented feeding in extremely low-birth-weight infants. J.Perinatol. 2012:253-259

Abstract: Objective:The objective of this trial was to test whether probiotic-supplemented feeding to extremely low-birth-weight (ELBW) infants will improve growth as determined by decreasing the percentage of infants with weight below the 10th percentile at 34 weeks postmenstrual age (PMA). Other important outcome measures, such as improving feeding tolerance determined by tolerating larger volume of feeding per day and reducing antimicrobial treatment days during the first 28 days from the initiation of feeding supplementation were also evaluated.Study Design:We conducted a multicenter randomized controlled double-blinded clinical study. The probiotics-supplementation (PS) group received Lactobacillus rhamnosus GG and Bifidobacterium infantis added to the first enteral feeding and continued once daily with feedings thereafter until discharge or until 34 weeks (PMA). The control (C) group received unsupplemented feedings. Infant weight and feeding volumes were recorded daily during the first 28 days of study period. Weights were also recorded at 34 weeks PMA.Result:A total of 101 infants were enrolled (PS 50 versus C 51). There was no difference between the two groups in the percentage of infants with weight below the 10th percentile at 34 weeks PMA (PS group 58% versus C group 60%, (P value 0.83)) or in the average volume of feeding during 28 days after study entry (PS group 59 ml kg(-1) versus C group 71 ml kg(-1), (P value 0.11)). Calculated growth velocity was higher in the PS group compared with the C group (14.9 versus 12.6 g per day, (P value 0.05)). Incidences of necrotizing enterocolitis (NEC), as well as mortality were similar between the two groups. Conclusion: Although probiotic-supplemented feedings improve growth velocity in ELBW infants, there was no improvement in the percentage of infants with growth delay at 34 weeks PMA. There were no probiotic-related adverse events reported.Journal of Perinatology advance online publication, 5 May 2011; doi:10.1038/jp.2011.51.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsules
Reference number: 1420

Pärtty, et al. Compositional development of Bifidobacterium and Lactobacillus microbiota is linked with crying and fussing in early infancy. PLoS One 2012;7(3):e32495-e32495

Abstract: Objectives: Methods: Results: Conclusions: Our aim was to establish whether there is an interconnection between the compositional development of the gut microbiota and the amount of fussing and crying in early infancy.Behavioral patterns of 89 infants during the 7(th) and 12(th) week of life were recorded in parental diaries. Total distress was defined as the sum of daily amounts of crying and fussing. Infants' gut microbiota profiles were investigated by several molecular assays during the first six months of life.The median (range) duration of total distress among the infants was 106 (0-478) minutes a day during the 7(th) and 58 (0-448) minutes a day during the 12(th) week. The proportion of Bifidobacterium counts to total bacterial counts was inversely associated with the amount of crying and fussing during the first 3 months of life (p = 0.03), although the number of Bifidobacterium breve was positively associated with total distress (p = 0.02). The frequency of Lactobacillus spp. at the age of 3 weeks was inversely associated with total infant distress during the 7(th) week of life (p = 0.02).Bifidobacterium and Lactobacillus appear to protect against crying and fussing. Identification of specific strains with optimal protective properties would benefit at-risk infants.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 2 billion
Product formulation: Sachet with powder
Reference number: 1433

Rautava, et al. Probiotics Modulate Host-Microbe Interaction in the Placenta and Fetal Gut: A Randomized, Double-Blind, Placebo-Controlled Trial Neonatology 2012;102(3):178-184

Abstract: Background: Early host-microbe interaction provides important maturational stimuli for the developing immune system. The role of prenatal microbial contact remains elusive. Objectives: Our aim was to investigate whether microbes in placenta or amniotic fluid affect fetal innate immune gene expression during late pregnancy and whether innate immune gene expression profiles in the placenta and the fetal gut may be modulated by dietary supplementation with specific probiotics. Methods: Altogether 43 pregnant women were randomized to receive (1) Bifidobacterium lactis, (2) B. lactis in combination with Lactobacillus rhamnosus GG (LGG) or (3) placebo for 14 days before elective cesarian section at full term in a double-blind clinical trial. Bacteria in amniotic fluid and placenta were detected by quantitative (q)PCR. The expression of Toll-like receptor (TLR)-related genes in the placenta and meconium samples was assessed by qPCR. Gene expression patterns in meconium were interpreted to reflect immune physiology in the fetal gut. Results: The study was completed by 29 mother-infant pairs. Bacterial DNA was detected in all placenta samples. Microbial DNA in amniotic fluid and placenta was associated with changes in TLR-related gene expression in the fetal intestine. Maternal probiotic supplementation significantly modulated the expression of TLR-related genes both in the placenta and in the fetal gut. Conclusions: Microbial contact in utero is associated with changes in fetal intestinal innate immune gene expression profile. Fetal and placental immune physiology may be modulated by maternal dietary intervention using specific probiotics.

Research field: Infant and Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 6 billion
Product formulation: Milk powder
Reference number: 1414

Chrzanowska-Liszewska, et al. The effect of Lactobacillus rhamnosus GG supplemented enteral feeding on the microbiotic flora of preterm infants-double blinded randomized control trial Early Hum.Dev. 2012;88(1):57-60

Abstract: BACKGROUND AND AIM: Intestinal flora of preterms, dominantly presents with decreased amounts of physiological microbiota. This double blinded randomized control trial compared the stool of bottle fed preterms, randomized to receive lactobacillus rhamnosus GG (LGG) 6x109or placebo with formula feeding. STUDY DESIGN: 46 enterally fed preterms were randomized to receive probiotics or placebo within 0-3days after birth. All personnel were blinded to treatment assignment. Faecal sampling was preformed at day 7, 21, 42. Presence of LGG colonization, somatic growth and length of hospital stay were recorded. RESULTS: 60 patients were initially identified and enrolled but after exclusion criteria were applied, 21 babies were analyzed in the probiotic group and 26 in the placebo group. The number of lactobacillus were significantly higher (p=0.014) on day 7, and 21 (p=0.024) in the study group, and so was the number of enterobacteriaceae on all study days (p=0.004, p=0.000, p=0.000), and Enterococcus sp on day 21 (p=0.000). The amount of samples positive for staphylococci was significantly higher in the study group, on days 7 and 42 (p=0.001 and 0.011). We did not show a significant difference in weight gain upon discharge between the groups p=0.567, 95% CI (-168; 305) or mean of hospital stay p=0.421 95% CI (-13.43;5.71). CONCLUSIONS: A preterm infant formula with an addition of probiotics leads to a rapid growth of LGG in the gut of bottle fed infants, but does not decrease the amount of pathogenic organisms, nor increase weight gain during enteral feeding, or decrease length of hospital stay.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: NA
Reference number: 1454

Nixon, et al. The Effect of Lactobacillus GG on Acute Diarrheal Illness in the Pediatric Emergency Department Pediatr.Emerg.Care 2012;28(10):1048-1051

Abstract: OBJECTIVE: The purpose of this study was to evaluate the effectiveness of the probiotic Lactobacillus GG (LGG) in reducing the duration of acute infectious diarrhea in the pediatric emergency department. METHODS: We conducted a double-blind, randomized controlled trial of children 6 months to 6 years presenting to the pediatric emergency department with a complaint of diarrhea. Patients were randomized to receive either placebo or LGG powder twice daily for 5 days. With each dose, parents recorded the stool history in a home diary and were followed up daily by a blinded researcher. Groups were compared in terms of time to normal stool and number of diarrheal stools. RESULTS: Of 155 patients enrolled, 129 completed the study: 63 in the LGG group and 66 in the placebo group. There was no significant difference in the median (interquartile range) time to normal stool (LGG: 60 hours [37-111] vs placebo: 74 hours [43-120]; P = 0.37) or the number of diarrheal stools (LGG: 5.0 [1-10] vs placebo: 6.5 [2-14]; P = 0.19). Among children who presented with more than 2 days of diarrhea, the LGG group returned to normal stool earlier (LGG: 51 hours [32-78] vs placebo: 74 hours [45-120]; P = 0.02), had fewer episodes of diarrheal stools (LGG: 3.5 [1.0-7.5] vs placebo: 7 [3.0-16.3]; P = 0.02), and were 2.2 times more likely to return to normal stool (95% confidence interval, 1.3-3.9; P = 0.01) compared with children in the placebo group. CONCLUSIONS: Lactobacillus GG may reduce the duration of acute diarrheal illness among children presenting with more than 2 days of symptoms.

Research field: Infant & Children's Nutrition and Immune Health,
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: Approx 0.1 billion
Product formulation: Fresh milk
Reference number: 1429

Kumpu, et al. "Milk containing probiotic Lactobacillus rhamnosus GG and respiratory illness in children: a randomized, double-blind, placebo-controlled trial." *European Journal of Clinical Nutrition*, *66*(9), 1020–1023, (2012)

Abstract: Background/Objectives: To determine whether long-term daily consumption of milk containing probiotic Lactobacillus rhamnosus GG (GG) decreases respiratory illness in children.Subjects/Methods:A randomized, double-blind, placebo-controlled trial was conducted with 523 children aged 2-6 years attending day care centers in Finland. Subjects received either normal milk or the same milk with GG on three daily meals for 28 weeks. Daily recording of childrens' symptoms was done by parents. Primary outcome data from 501 subjects were available for analysis, and data from 128 subjects were analyzed as completed cases in terms of recovery of GG in fecal samples. Results: Number of days with at least one respiratory symptom in all subjects was 5.03/month (95% confidence interval (CI): 4.92-5.15) in the GG group and 5.17/month (95% CI: 5.05-5.29) in the placebo group incidence rate ratio (IRR) 0.97; 95% CI: 0.94-1.00; P=0.098). In the completed cases, the figures were 4.71 days/month (95% CI: 4.52-4.90) in the GG group and 5.67 days/month (95% CI: 5.40-5.94) in the placebo group (IRR 0.83; 95% CI: 0.78-0.88; P<0.001). Conclusions: Consumption of GG reduced the occurence of respiratory illness in children attending day care centers in the completed cases subgroup, but not in the total population. Thus, future clinical trials are warranted to clarify the association between fecal recovery of a probiotic and the symptom prevalence.European Journal of Clinical Nutrition advance online publication, 13 June 2012; doi:10.1038/ejcn.2012.62.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: Capsule
Reference number: 1373

Lehtoranta, et al. Human bocavirus in the nasopharynx of otitis-prone children. Int.J.Pediatr.Otorhinolaryngol. 2012;76:206-211

Abstract: OBJECTIVES: Human bocavirus (HBoV) is frequently identified in children with respiratory tract infections, and its role in acute otitis media (AOM) has been suggested. The disease associations for the closely related bocaviruses HBoV2-4 remain unknown. Increasing evidence shows that probiotics may reduce the risk of AOM of viral origin. Objectives of the study was to examine the prevalence and persistence of bocaviruses in consecutive nasopharyngeal samples (NPS) of otitis-prone children, and whether an association exists between HBoV and the child's characteristics, respiratory symptoms, and AOM pathogens, and whether probiotics reduce the occurrence of HBoV. METHODS: In a double-blind, placebo-controlled, randomized, 6-month intervention study, 269 otitis-prone children (aged 9 months to 5.6 years), consumed daily either one capsule of probiotics (Lactobacillus rhamnosus GG, L. rhamnosus Lc705, Bifidobacterium breve 99 and Propionibacterium freudenreichii JS) or placebo. After a clinical examination and NPS collected at three-time points, the presence and persistence of HBoV1-4 DNA in NPS was determined by RT-qPCR at the baseline, after 3, and 6 months. RESULTS: A high load (>10,000copies/ml) of HBoV DNA was detected in 26 (17.1%) of 152 children, and 16 (10.5%) showed a prolonged presence of HBoV for at least 3 months. None had DNA of HBoV2-4. Higher number of siblings associated with increased HBoV prevalence (p=0.029). Prevalence or persistence of HBoV was not significantly associated with other characteristics, respiratory symptoms, or AOM pathogens. Probiotic intervention significantly reduced the number of HBoV DNA-positive samples (probiotic vs. placebo: 6.4% vs. 19.0%, OR=0.25, CI 95%=0.07-0.94, p=0.039). CONCLUSIONS: HBoV, but not HBoV2-4, DNA occurs often in the nasopharynx of otitis-prone children, and may persist for 3-6 months. Probiotic treatment possibly reduced the presence of HBoV.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 0.1 billion cfu/g
Product formulation: Milk powder
Reference number: 1401

Muraro, et al. Extensively hydrolysed casein formula supplemented with Lactobacillus rhamnosus GG maintains hypoallergenic status: randomised double-blind, placebo-controlled crossover trial BMJ Open 2012;2(2):e000637-.

Abstract: OBJECTIVE: To evaluate the hypoallergenicity of an extensively hydrolysed (EH) casein formula supplemented with Lactobacillus rhamnosus GG (LGG). DESIGN: A prospective, randomised, double-blind, placebo-controlled crossover trial. SETTING: Two study sites in Italy and The Netherlands. STUDY PARTICIPANTS: Children with documented cow's milk allergy were eligible for inclusion in this trial. INTERVENTIONS: After a 7-day period of strict avoidance of cow's milk protein and other suspected food allergens, participants were tested with an EH casein formula with demonstrated hypoallergenicity (control, EHF) and a formula of the same composition with LGG added at 10(8) colony-forming units per gram powder (EHF-LGG) in randomised order in a double-blind placebo-controlled food challenge (DBPCFC). After absence of adverse reactions in the DBPCFC, an open challenge was performed with EHF-LGG, followed by a 7-day home feeding period with the same formula. MAIN OUTCOME MEASURE: Clinical assessment of any adverse reactions to ingestion of study formulae during the DBPCFC. RESULTS: For all participants with confirmed cow's milk allergy (n=31), the DBPCFC and open challenge were classified as negative. CONCLUSION: The EH casein formula supplemented with LGG is hypoallergenic and can be recommended for infants and children allergic to cow's milk who require an alternative to formulae containing intact cow's milk protein. TRIAL REGISTRATION NUMBER: http://ClinicalTrials.gov Identifier: NCT01181297.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1.4 x 10^7 cfu/ 100ml

Canani et al. "Effect of Lactobacillus GG on tolerance acquisition in infants with cow's milk allergy: A randomized trial." *Journal of Allergy and Clinical Immunology*, *129*(2), (2012).

Abstract: Background: Lactobacillus GG (LGG)modulates immune function and has beenproposed for the prevention and treatmentof paediatric allergic diseases. To investigatewhether the addition of LGG to anextensively casein hydrolyzed formula(EHCF) could accelerate tolerance acquisitionin infants affected by cow's milkallergy (CMA).Method: Infants (1-12 months) affected byIgE- or non-IgE-mediated CMA, confirmedby oral food challenge, were randomlyallocated to one of the followingdietary interventions: (i) EHCF (Nutramigen; Mead Johnson, Italy); (ii) EHCFcontaining LGG (at least 1x106 CFU/gof formula powder) (Nutramigen LGG;Mead Johnson). The trial was registeredin the Australian New Zealand ClinicalTrials Registry (ID number: ACTRN12610000566033).Oral food challengeswere performed to explore tolerance acquisitionat 6 and 12 months. Primary outcomewas clinical tolerance to cow's milkat 12 months.Result: Fifty-five infants were enrolled (37male, 67.3%; age 3.5, 95%CI 2.7-4.4 months; body weight 5.7, 95%CI 5.2-6.3 kg; IgE-mediated CMA 21, 38.2%). Atdiagnosis, symptoms of CMA were gastrointestinal(65.5%), cutaneous (43.6%), andrespiratory (18.2%). After 6 months of dietaryintervention, tolerance was acquired in6/28 infants in group 1 (21.4%), and in 16/27 in group 2 (59.3%, P = 0.004). After12 months of dietary intervention, tolerancewas acquired in 9/28 infants in group1 (32.1%), and in 22/27 in group 2 (81.5%,P < 0.0001). Regression analysis revealed that the rate of infants acquiring toleranceat the end of the study was positively influencedby the presence of gastrointestinalsymptoms (B+ 3.703, P = 0.05), and negativelyby male gender (B -2.616,P = 0.019) and by IgE-mediated mechanismof CMA (B -2.642, P = 0.003).Conclusion: Supplementation of LGG toan EHCF accelerate tolerance acquisitionin infants with CMA.

Research field: Maternal Health and Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus, LGG® and B. animalis subsp. lactis, BB-12®
Dosage CFU/day: 10^{10} of each
Product formulation: Capsule
Reference number: 1655

Luoto, et al. Impact of maternal probiotic-supplemented dietary counseling during pregnancy on colostrum adiponectin concentration: a prospective, randomized, placebo-controlled study. Early Hum.Dev. 2012;88(6):339-344

Abstract: BACKGROUND: The breast milk bioactive substances such as adiponectin, have a presumably long-term impact upon the health and well-being of a child. AIM: To determine the impact of probiotic-supplemented dietary counseling during pregnancy on colostrum adiponectin concentration. STUDY DESIGN AND SUBJECTS: Altogether 256 pregnant women were randomized into three study groups: dietary intervention with probiotics (diet/probiotics) or with placebo (diet/placebo) and a control group (control/placebo). The intervention group received dietary counseling provided by a nutritionist, the main focus being the amount and the type of dietary fat. The probiotics used were Lactobacillus rhamnosus GG and Bifidobacterium lactis in combination. Dietary intake was evaluated by food records at every trimester of pregnancy. Breast milk samples were collected after birth (colostrum) for adiponectin concentration analysis (n=181). RESULTS: The dietary intervention increased the colostrum adiponectin concentration (ng/mL, geometric mean [95% CI]), the difference being significant when comparing to the control group; 12.7 [10.6-29.7] vs. 10.2 [9.9-13.2], P=0.024. Maternal weight gain during pregnancy (kg) correlated inversely with colostrum adiponectin concentration; beta (SE)=-1.7 (0.1), P=0.020, and gestational diabetes mellitus was associated with the likelihood of adiponectin concentration falling into the lowest quartile; OR 2.36, 95% CI 1.1-3.2, P=0.028. CONCLUSIONS: In showing that the colostrum adiponectin concentration is markedly dependent on maternal diet and nutritional status during pregnancy, and considering that colostrum adiponectin has potential effects on metabolism, nutrition, and immune function in the neonates, the results of this study underscore the importance of the metabolic homeostasis of the mother for the child's initial nutritional environment.

Research field: Maternal Health and Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 0756

Aaltonen, et al. Impact of maternal diet during pregnancy and breastfeeding on infant metabolic programming: a prospective randomized controlled study. Eur.J.Clin.Nutr. 2011;65:10-19.

Abstract: Objectives:To evaluate the impact of maternal diet and intensive dietary counselling during pregnancy and breastfeeding on the infant's metabolic status.Subjects/Methods:At the first trimester of pregnancy, 256 women were randomized into a control/placebo group and two dietary counselling groups (diet/probiotics and diet/placebo). The counselling, with double-blind randomization to probiotics (Lactobacillus rhamnosus GG and Bifidobacterium lactis BB-12) or placebo, targeted excessive saturated fat and low fibre consumption. Maternal diet was evaluated repeatedly during pregnancy and postpartum by means of 3 days' food diaries. Metabolic markers, serum 32-33 split and intact proinsulin, leptin/adiponectin ratio, skinfold thickness and waist circumference were measured of 194 healthy infants at the age of 6 months, and the high levels were taken to mirror adverse metabolic status.Results:The proportion of infants with a high 32-33 split proinsulin was significantly lower in dietary counselling with probiotics (n=6/62, 9.7%) or placebo (n=7/69, 10.1%) compared with the control/placebo group (n=17/63, 27.0%). The high split proinsulin was associated with larger skinfold thickness, waist circumference and higher leptin/adiponectin ratio in the infants (P<0.05). With respect to maternal diet during pregnancy, the highest and lowest tertiles of fat intake increased the infant's risk of high split proinsulin, whereas those of butter associated correspondingly with the infant's waist circumference. Further, breastfed infants showed a reduced risk of high split proinsulin and leptin/adiponectin ratio compared with formula-fed infants.Conclusions:Modification of maternal diet during pregnancy and breastfeeding may benefit infant metabolic health. High split proinsulin reflects adverse metabolic status in infancy, which can be improved by early dietary counselling.

Research field: Maternal Health
Study type: Human study
Probiotic strain: B. animalis subsp. lactis, BB-12® , L. acidophilus, LA-5®, L. rhamnosus, LGG®
Dosage CFU/day: -
Product formulation: Fermented milk
Reference number: 1728

Myhre, et al. Intake of probiotic food and risk of spontaneous preterm delivery Am.J.Clin.Nutr. 2011;93(8):151-157

Abstract: Background: Preterm delivery represents a substantial problem in perinatal medicine worldwide. Current knowledge on potential in- fluences of probiotics in food on pregnancy complications caused by microbes is limited. Objective: We hypothesized that intake of food with probiotics might reduce pregnancy complications caused by pathogenic micro- organisms and, through this, reduce the risk of spontaneous preterm delivery. Design: This study was performed in the Norwegian Mother and Child Cohort on the basis of answers to a food-frequency question- naire.We studied intake of milk-based products containing probiotic lactobacilli and spontaneous preterm delivery by using a prospective cohort study design (n = 950 cases and 17,938 controls) for the preg- nancy outcome of spontaneous preterm delivery (,37 gestational weeks). Analyses were adjusted for the covariates of parity, maternal educational level, and physical activity. Results: Pregnancies that resulted in spontaneous preterm delivery were associated with any intake of milk-based probiotic products in an adjusted model [odds ratio (OR): 0.857; 95% CI: 0.741, 0.992]. By categorizing intake into none, low, and high intakes of the milk- based probiotic products, a significant association was observed for high intake (OR: 0.820; 95% CI: 0.681, 0.986). Conclusion: Women who reported habitual intake of probiotic dairy products had a reduced risk of spontaneous preterm delivery.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: NA
Reference number: 1372

Rose, et al. Follow-up of probiotic Lactobacillus GG effects on allergic sensitization and asthma in infants at risk. Clin.Exp.Allergy 2011;41(12):1819-1821

Abstract: NA

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 0960

Ilmonen, et al. Impact of dietary counselling and probiotic intervention on maternal anthropometric measurements during and after pregnancy: A randomized placebo-controlled trial. Clin.Nutr. 2011;30(2):156-164

Abstract: BACKGROUND & AIMS: To establish whether probiotic supplemented dietary counselling influences maternal anthropometric measurements during and after pregnancy.METHODS: At the first trimester of pregnancy 256 women were randomly assigned to receive nutrition counselling to modify dietary intake according to current recommendations or as controls; dietary intervention groups were further randomized to receive probiotics Lactobacillus rhamnosus GG (ATCC 53103) and Bifidobacterium lactis (diet/probiotics) or placebo (diet/placebo) capsules in a double-blind manner, whilst the controls received placebo (control/placebo). The intervention lasted until the end of exclusive breastfeeding for up to six months.RESULTS: The risk of central adiposity defined as waist circumference 80 cm or more was lowered in women in the diet/probiotics group compared with the control/placebo group (OR 0.30, 95%CI 0.11-0.85, p = 0.023 adjusted for baseline BMI), whilst the diet/placebo group did not differ from the controls (OR 1.00, 95% CI 0.38-2.68, p = 0.994) at 6 months postpartum. The number needed to treat (NNT) with diet/probiotics to prevent one woman from developing a waist circumference of 80 cm or more was 4. Healthy eating pattern at 12 months postpartum (p = 0.001) and BMI prior to pregnancy (p < 0.001) were strong determinants of BMI at 12 months postpartum when adjusted for dietary intervention and exercise.CONCLUSION: The impact of probiotics-supplemented dietary counselling on central adiposity, may offer a novel means for the prevention and management of obesity. This trial was registered at clinicaltrials.gov as NCT 00167700, section 3.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 3.4 billion
Product formulation: Milk powder
Reference number: 1100

Nermes, et al. Interaction of orally administered Lactobacillus rhamnosus GG with skin and gut microbiota and humoral immunity in infants with atopic dermatitis. . *Clinical and Experimental Allergy*, *41*(3), 370–377, (2011)

Abstract: Background The intestinal mucosa functions as a defence barrier against gut intraluminar antigens. The maturational events in the gut parallel its step-wise colonization. Atopic dermatitis (AD) is associated with aberrant barrier functions of the skin epithelium and, in a subgroup of patients, of the gut mucosa. Objective To investigate the interaction of Lactobacillus rhamnosus GG (LGG) with skin and gut microbiota and humoral immunity in infants with AD. Methods Thirty-nine infants with AD were randomized for a 3-month period in a double-blind design to receive extensively hydrolysed casein formula supplemented with (n=19) or without (n=20) LGG (ATCC 53103) 5.0 x 10(7) CFU/g to achieve a daily intake of 3.4 x 10(9) CFU. Sampling (blood and fecal samples, cotton swab from the skin) was carried out at entry, 1 and 3 months thereafter. Ig-secreting cells were determined by enzyme-linked immunospot and the proportions of CD19(+) CD27(+) B cells among peripheral blood leucocytes by flow cytometry. The major groups of gut and skin bacteria were characterized using PCR. Results The proportions of IgA- and IgM-secreting cells decreased significantly in the treated group; the baseline-adjusted ratios for treated vs. untreated at 1 month were 0.59 (95%CI 0.36-0.99, P=0.044) for IgA- and 0.53 (95%CI 0.29-0.96, P=0.036) for IgM-secreting cells. The proportions of CD19(+) CD27(+) B cells increased in the probiotic-treated infants but not in the untreated. There were no significant differences in bifidobacterial species composition of the gut between the study groups. On the skin, the bacterial counts of Bifidobacterium genus vs. Clostridium coccoides in the treated and untreated infants were similar. Conclusion and Clinical Relevance Specific probiotics may enhance gut barrier function and aid in the development of immune responses. Thus, specific probiotics may afford protection against offending macromolecules in the gut and provide control for future infections by accelerated immunological maturation (ClinicalTrials.gov ID NCT01148667).

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion cfu/ 100 ml

McFarland et al. " Lactobacillus GG prevented nosocomial gastrointestinal and respiratory tract infections. " *Archives of Disease in Childhood - Education and Practice*, *96*(6), 238–238. (2010)

Abstract: NA

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: NA
Reference number: 1385

Cox, et al. Lactobacillus casei abundance is associated with profound shifts in the infant gut microbiome. PLoS One 2010:e8745

Abstract: Colonization of the infant gut by microorganisms over the first year of life is crucial for development of a balanced immune response. Early alterations in the gastrointestinal microbiota of neonates has been linked with subsequent development of asthma and atopy in older children. Here we describe high-resolution culture-independent analysis of stool samples from 6-month old infants fed daily supplements of Lactobacillus casei subsp. Rhamnosus (LGG) or placebo in a double-blind, randomized Trial of Infant Probiotic Supplementation (TIPS). Bacterial community composition was examined using a high-density microarray, the 16S rRNA PhyloChip, and the microbial assemblages of infants with either high or low LGG abundance were compared. Communities with high abundance of LGG exhibited promotion of phylogenetically clustered taxa including a number of other known probiotic species, and were significantly more even in their distribution of community members. Ecologically, these aspects are characteristic of communities that are more resistant to perturbation and outgrowth of pathogens. PhyloChip analysis also permitted identification of taxa negatively correlated with LGG abundance that have previously been associated with atopy, as well as those positively correlated that may prove useful alternative targets for investigation as alternative probiotic species. From these findings we hypothesize that a key mechanism for the protective effect of LGG supplementation on subsequent development of allergic disease is through promotion of a stable, even, and functionally redundant infant gastrointestinal community.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: Fermented milk
Reference number: 0755

Hojsak, et al. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. Pediatrics 2010;125:e1171

Abstract: OBJECTIVE: The incidence of nosocomial infections, predominantly gastrointestinal and respiratory, in children in developed countries is high, ranging from 5% to 44%. There is no effective strategy for preventing these infections. The objective of our study was to investigate the role of Lactobacillus GG (LGG) in preventing nosocomial gastrointestinal and respiratory tract infections at a pediatric hospital. METHODS: We conducted a randomized, double-blind, placebo-controlled trial of 742 hospitalized children. They were randomly allocated to receive for their hospitalization LGG at a dose of 10(9) colony-forming units in 100 mL of a fermented milk product (LGG group, n = 376) or placebo that was the same postpasteurized fermented milk product without LGG (placebo group, n = 366). RESULTS: In the LGG group, compared with the placebo group, we found a significantly reduced risk for gastrointestinal infections (relative risk [RR]: 0.40 [95% confidence interval (CI): 0.25-0.70]; number needed to treat: 15 [95% CI: 9-34)], respiratory tract infections (RR: 0.38 [95% CI: 0.18-0.85]; number needed to treat: 30 [95% CI: 16-159]), vomiting episodes (RR: 0.5 [95% CI: 0.3-0.9]), diarrheal episodes (RR: 0.24 [95% CI: 0.10-0.50]), episodes of gastrointestinal infections that lasted >2 days (RR: 0.40 [95% CI: 0.25-0.70]), and episodes of respiratory tract infections that lasted >3 days (RR: 0.4 [95% CI: 0.2-0.9]). Groups did not differ in hospitalization duration (P = .1). CONCLUSIONS: LGG administration can be recommended as a valid measure for decreasing the risk for nosocomial gastrointestinal and respiratory tract infections in pediatric facilities.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: Fermented milk
Reference number: 0754

Hojsak, 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

Abstract: BACKGROUND & AIMS: The aim of our study was to investigate the role of Lactobacillus GG (LGG) in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers.METHODS: We conducted a randomized, double-blind, placebo-controlled trial in 281 children who attend day care centers. They were randomly allocated to receive LGG at a dose of 10(9) colony-forming units in 100ml of a fermented milk product (LGG group, n=139) or placebo that was the same post-pasteurized fermented milk product without LGG (placebo group, n=142) during the 3-month intervention period.RESULTS: Compared to the placebo group, children in the LGG group had a significantly reduced risk of upper respiratory tract infections (RR 0.66, 95% CI 0.52 to 0.82, NNT 5, 95% CI 4 to 10), a reduced risk of respiratory tract infections lasting longer than 3 days (RR 0.57, 95% CI 0.41 to 0.78, NNT 5, 95% CI 4 to 11), and a significantly lower number of days with respiratory symptoms ($p<0.001$). There was no risk reduction in regard to lower respiratory tract infections (RR 0.82, 95% CI 0.24 to 2.76). Compared with the placebo group, children in the LGG group had no significant reduction in the risk of gastrointestinal infections (RR 0.63, 95% CI 0.38 to 1.06), vomiting episodes (RR 0.60, 95% CI 0.29 to 1.24), and diarrheal episodes (RR 0.63, 95% CI 0.35 to 1.11) as well as no reduction in the number of days with gastrointestinal symptoms ($p=0.063$).CONCLUSION: LGG administration can be recommended as a valid measure for decreasing the risk of upper respiratory tract infections in children attending day care centers.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 0,0146 billion
Product formulation: Milk powder
Reference number: 0779

Baldassarre, et al. Lactobacillus GG improves recovery in infants with blood in the stools and presumptive allergic colitis compared with extensively hydrolyzed formula alone. J.Pediatr. 2010;156:397-401

Abstract: OBJECTIVES: To determine the benefits of Lactobacillus rhamnosus GG (LGG) in an extensively hydrolyzed casein formula (EHCF) in improving hematochezia and fecal calprotectin over EHCF alone. STUDY DESIGN: Fecal calprotectin was compared in 30 infants with hematochezia and 4 weeks after milk elimination with that of a healthy group. We also compared fecal calprotectin and hematochezia on 26 formula-fed infants randomly assigned to EHCF with LGG (Nutramigen LGG) (EHCF + LGG) or without (Nutramigen) (EHCF - LGG) and on 4 breastfed infants whose mothers eliminated dairy. RESULTS: Fecal calprotectin in those with hematochezia was significantly higher than in comparisons (mean +/- SD 325.89 +/- 152.31 vs 131.97 +/- 37.98 microg/g stool, t = 6.79, P < .0001). At 4 weeks, fecal calprotectin decreased to 50% of baseline but was still significantly higher than in comparisons (157.5 +/- 149.13 vs 93.72 +/- 36.65 microg/g, P = .03). Fecal calprotectin mean decrease was significantly larger among EHCF + LGG compared with EHCF - LGG (-214.5 +/- 107.93 vs -112.7 +/- 105.27 microg/g, t = 2.43, P = .02). At 4 weeks, none of the EHCF + LGG had blood in stools, and 5/14 on EHCF - LGG did (P = .002). CONCLUSION: Fecal calprotectin is elevated in infants with hematochezia and possible allergic colitis. EHCF + LGG resulted in significant improvement of hematochezia and fecal calprotectin compared with the EHCF alone.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 1042

Luoto, et al. The impact of perinatal probiotic intervention on the development of overweight and obesity: follow-up study from birth to 10 years. Int.J.Obes. 2010;34:.

Abstract: Background:The achievements in combating the increasing trend of overweight and obesity have thus far been inadequate. The recently discovered instrumental role of the gut microbiota in host metabolism may offer a novel target in the prevention and management of obesity.Objective:To evaluate the impact of perinatal probiotic intervention on childhood growth patterns and the development of overweight during a 10-year follow-up.Patients and methods:Altogether 159 women were randomized and double-blinded to receive probiotics (1 x 10(10) colony-forming units of Lactobacillus rhamnosus GG, ATCC 53103) or placebo 4 weeks before expected delivery; the intervention extending for 6 months postnatally. Anthropometric measurements of the children were taken at the ages of 3, 6, 12 and 24 months and at 4, 7 and 10 years in 113 (72%) children.Results:The excessive weight gain was detected to be two-parted; the initial phase of excessive weight gain initiating during fetal period and continuing until 24-48 months of age and a second phase of excessive weight gain starting after the age of 24-48 months. The perinatal probiotic intervention appeared to moderate the initial phase of excessive weight gain, especially among children who later became overweight, but not the second phase of excessive weight gain, the impact being most pronounced at the age of 4 years (P=0.063, analysis of variance for repeated measures). The effect of intervention was also shown as a tendency to reduce the birth-weight-adjusted mean body mass index at the age of 4 years (P=0.080, analysis of covariance).Conclusions:Early gut microbiota modulation with probiotics may modify the growth pattern of the child by restraining excessive weight gain during the first years of life. This novel observation calls for further epidemiological and clinical trials, with precise data on early growth patterns and on confounding factors influencing weight development.International Journal of Obesity advance online publication, 16 March 2010; doi:10.1038/ijo.2010.50.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: Fermented milk
Reference number: 1155

Salmi, et al. Cow's milk allergy is associated with changes in urinary organic acid concentrations. Pediatr. Allergy Immunol. 2010;21:e401

Abstract: Cow's milk allergy (CMA) is the most common form of food allergy affecting 2.5% of children, but the diagnosis is often difficult. Both intestinal microbiota and barrier function seem to be disturbed in patients with food allergies, and administration of probiotics has been shown to normalize intestinal microbiota and alleviate symptoms. We hypothesized that the differences in intestinal metabolic activity and permeability could lead to detectable changes in the end-products of metabolism in patients with CMA. This could offer new diagnostic possibilities. The urinary concentrations of 37 organic acids were studied by a mass spectrometry-based method in 35 infants aged under 1 yr with atopic eczema, 16 of them having CMA diagnosed with a double-blind placebo-controlled food challenge test. The control group consisted of the remaining 19 infants with only atopic eczema. In a second study, Lactobacillus rhamnosus GG (LGG) or placebo was administered to the infants with CMA for 4 wk and the urinary organic acids were analysed again. CMA patients and patients with only atopic eczema had statistically significant differences in urinary concentrations of hydroxybutyrate ($p<0.001$); adipate and isocitrate ($p<0.01$ for both); homovanillate, suberate, tartarate, 3-indoleacetate and 5-hydroxyindoleacetate ($p<0.05$ for all). These concentrations did not change significantly following LGG administration to the CMA patients, but a trend towards the control group was seen. Thus, CMA is associated with changes in some urinary organic acid levels. These differences between atopic infants with and without CMA could be investigated as a novel approach for CMA diagnosis.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 6 billion

Luoto et al. "Incidence of necrotizing enterocolitis in very-low-birth-weight infants related to the use of Lactobacillus GG". *Acta Paediatrica, International Journal of Paediatrics*, *99*(8), 1135–1138, (2010).

Abstract: BACKGROUND: One of the five level III neonatal intensive care units (NICU) in Finland has used prophylactic Lactobacillus GG (LGG) for very-low-birth-weight (VLBW) infants since 1997.\n\nAIM: To examine retrospectively the incidence of necrotizing enterocolitis (NEC) in all five university hospital NICUs in Finland in relation to the use of LGG during the years each unit has belonged to the Vermont Oxford Network (VON).\n\nMETHODS: The incidence of NEC was analysed from the national database and from the VON databases separately in all five level III NICUs and additionally in three groups according to the probiotic practice in the hospitals: prophylactic LGG group, probiotics 'on demand' group and no probiotics group.\n\nRESULTS: The incidence of NEC was 4.6% vs. 3.3% vs. 1.8% in the prophylactic LGG group, the no probiotics group and the probiotics 'on demand' group [corrected] respectively; p = 0.0090, chi-square. LGG had no influence on the clinical course of NEC.\n\nCONCLUSIONS: The results of this retrospective report failed to show that LGG prophylaxis protects VLBW infants from the occurrence of NEC, in contrast to previously published results. Our results call for more research regarding effective ways to administer probiotics, including data on appropriate bacteria, strain, dose and timing of administration to achieve clinically robust effects.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: ≥ 5 billion
Product formulation: Capsule
Reference number: 1143

Ritchie, et al. Efficacy of Lactobacillus GG in aboriginal children with acute diarrhoeal disease: a randomised clinical trial. J.Pediatr.Gastroenterol.Nutr. 2010;50:619-624

Abstract: OBJECTIVE: The effectiveness of probiotic therapy for acute rotavirus infectious diarrhoea in an indigenous setting with bacterial/parasitic diarrhoea is unclear. In the present study, we assessed the efficacy of probiotics in Australian Aboriginalchildren in the Northern Territory admitted to hospital with diarrhoealdisease. PATIENTS AND METHODS: A randomised double-blind placebo-controlled study was conducted in Aboriginalchildren (ages 4 months-2 years), admitted to hospital with acutediarrhoealdisease (>3 loose stools per day). Children received either oral LactobacillusGG (5 x 10(9) colony-forming units 3 times per day for 3 days; n = 33) or placebo (n = 31). Small intestinal functional capacity was assessed by the noninvasive 13C-sucrose breath test on days 1 and 4. RESULTS: Both groups showed mean improvement in the sucrose breath test after 4 days; however, there was no difference (mean, 95% confidence interval) between probiotic (2.9 [cumulative percentage of dose recovered at 90 minutes]; 1.7-4.2) and placebo (3.7; 2.3-5.2) groups. Probiotics did not change the duration of diarrhoea, total diarrhoea stools, or diarrhoea score compared with placebo. There was a significant (P < 0.05) difference in diarrhoea frequency on day 2 between probiotics (3.3 [loose stools]; 2.5-4.3) and placebo (4.7; 3.8-5.7) groups. CONCLUSIONS: LactobacillusGG did not appear to enhance short-term recovery following acutediarrhoeal illness in this setting.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. acidophilus LA-5 and L. rhamnosus LGG
Dosage CFU/day: 1 billion LA-5 + 10 billion BB-12 and LGG each
Product formulation: Fermented milk
Reference number: 0855

Dotterud, et al. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. Br.J.Dermatol. 2010;163:616-623

Abstract: Summary Background Previous reports have suggested that certain probiotics given to mothers and children at risk of atopy halves the incidence of atopic dermatitis (AD) at 2 years of age. Objectives To examine if probiotics given to pregnant women in a nonselected population could prevent atopic sensitization or allergic diseases during the child's first 2 years. Methods In a randomized, double-blind trial of children from a nonselected maternal population (ClinicalTrials.gov identifier: NCT00159523), women received probiotic milk or placebo from 36 weeks of gestation to 3 months postnatally during breastfeeding. The probiotic milk contained Lactobacillus rhamnosus GG, L. acidophilus La-5 and Bifidobacterium animalis subsp. lactis Bb-12. Children with an itchy rash for more than 4 weeks were assessed for AD. At 2 years of age, all children were assessed for atopic sensitization, AD, asthma and allergic rhinoconjunctivitis. The intention-to-treat (ITT) analysis was enabled by multiple imputations. Results Four hundred and fifteen pregnant women were computer randomized. At 2 years, 138 and 140 children in the probiotic and the placebo groups, respectively, were assessed. In the ITT analysis, the odds ratio (OR) for the cumulative incidence of AD was 0.51 in the probiotic group compared with the placebo [95% confidence interval (CI) 0.30-0.87; P = 0.013]. There were no significant effects on asthma (OR 0.68, 95% CI 0.26-1.80; P = 0.437) or atopic sensitization (OR 1.52, 95% CI 0.74-3.14; P = 0.254). Conclusions Probiotics given to nonselected mothers reduced the cumulative incidence of AD, but had no effect on atopic sensitization.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 1145

Rose, et al. Efficacy of probiotic Lactobacillus GG on allergic sensitization and asthma in infants at risk. Clin.Exp.Allergy 2010;40:.

Abstract: Summary Background Probiotics are perceived to exert beneficial effects in the prevention and treatment of allergic diseases. Objective There are conflicting data from studies as to an impact on allergic sensitization and asthma. Methods Our prospective double-blind study randomly assigned 131 children (6-24 months old) with at least two wheezing episodes and a first-degree family history of atopic disease to 6 months of Lactobacillus rhamnosus (LGG, 10(10) colony forming units) or placebo. Atopic dermatitis and asthma-related events (e.g. need of inhalation, symptom-free days) were documented throughout the intervention and 6-month follow-up. We determined IgE, a representative panel of specific IgE, eosinophils, eosinophilic cationic protein, and TGF-beta before, at the end of intervention, and after 6 months of follow-up. Results There were no significant differences as to atopic dermatitis or asthma-related events. In a subgroup with antecedent allergic sensitizations, asthmatic complaints were even slightly worse. We found fewer sensitizations towards aeroallergens after 6 months of LGG (P=0.027) and after 6 months of follow-up (P=0.03). Supplementation was well-tolerated and no severe adverse events occurred. Conclusions In young children with recurrent wheeze and an atopic family history, oral LGG had no clinical effect on atopic dermatitis or asthma-related events, and only mild effects on allergic sensitization. This effect persisted 6 months after the cessation of the supplementation.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 1043

Luoto, et al. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br.J.Nutr. 2010;103(12):1792-1799

Abstract: The perinatal nutritional environment impacts upon the health and well-being of mother and child also in the long term. The aim of the present study was to determine the safety and efficacy of perinatal probiotic-supplemented dietary counselling by evaluating pregnancy outcome and fetal and infant growth during the 24 months' follow-up. Altogether, 256 women were randomised at their first trimester of pregnancy into a control and a dietary intervention group. The intervention group received intensive dietary counselling provided by a nutritionist and were further randomised, double-blind to receive probiotics (Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb12; diet/probiotics) or placebo (diet/placebo). Firstly, probiotic intervention reduced the frequency of gestational diabetes mellitus (GDM); 13 % (diet/probiotics) v. 36 % (diet/placebo) and 34 % (control); P = 0.003. Secondly, the safety of this approach was attested by normal duration of pregnancies with no adverse events in mothers or children. No significant differences in prenatal or postnatal growth rates among the study groups were detected. Thirdly, distinctive effects of the two interventions were detected; probiotic intervention reduced the risk of GDM and dietary intervention diminished the risk of larger birth size in affected cases; P = 0.035 for birth weight and P = 0.028 for birth length. The results of the present study show that probiotic-supplemented perinatal dietary counselling could be a safe and cost-effective tool in addressing the metabolic epidemic. In view of the fact that birth size is a risk marker for later obesity, the present results are of significance for public health in demonstrating that this risk is modifiable.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10^9

Underwood et al. "A Randomized Placebo-controlled Comparison of Two Prebiotic/ Probiotic Combinations in Preterm Infants: Impact on Weight Gain, Intestinal Microbiota, and Fecal Short Chain Fatty Acids". *Journal of Pediatrics, The*, *48*(2), 216–225; (2009)

Abstract: Objective—To compare the effect of two prebiotic/probiotic products on weight gain, stool microbiota, and stool short chain fatty acid content of premature infants. Methods—This randomized, blinded, placebo-controlled trial included 90 premature infants treated with either a dietary supplement containing two lactobacillus species plus fructo-oligosaccharides (CUL, Culturelle®, ConAgra, Omaha, Nebraska, USA), a supplement containing several species of lactobacilli and bifidobacteria plus fructo-oligosaccharides (PBP, ProBioPlus DDS®, UAS Laboratories, Eden Prairie, Minnesota, USA), or placebo (a dilute preparation of Pregestamil formula) twice daily for 28 days or until discharge if earlier. The primary outcome was weight gain. Secondary outcomes were stool bacterial analysis by culture and 16S rDNA qPCR and stool short chain fatty acid content by high performance liquid chromatography. Results—Both prebiotic/probiotic combinations contained more bacterial species than noted on the label. No significant effect on growth of either prebiotic/probiotic supplement was observed. By cultures, 64% of infants receiving PBP became colonized with bifidobacteria, compared to 18% of infants receiving CUL and 27% of infants receiving placebo (Chi Squared p=0.064). No differences were noted between groups in colonization rates for lactobacilli, Gram-negative enteric bacteria or staphylococci. By 16S rDNA PCR analysis, the bifidobacteria content in the stools of the infants receiving PBP was higher than in the infants receiving CUL or placebo (Kruskal-Wallis p=0.011). No significant differences in stool short chain fatty acid content were detected between groups. No adverse reactions were noted. Conclusions—Infants receiving PBP were more likely to become colonized with bifidobacteria. No significant differences in weight gain or stool short chain fatty acid content were detected.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG and BB536
Dosage CFU/day: 0.4 billion
Product formulation: Capsule
Reference number: 1384

Rouge, et al. Oral supplementation with probiotics in very-low-birth-weight preterm infants: a randomized, double-blind, placebo-controlled trial. Am.J.Clin.Nutr. 2009;89:1828-1835

Abstract: BACKGROUND: Although recent reports suggest that supplementation with probiotics may enhance intestinal function in premature infants, the mechanisms are unclear, and questions remain regarding the safety and efficacy of probiotics in extremely low-birth-weight infants. OBJECTIVE: The objective was to evaluate the efficacy of probiotics on the digestive tolerance to enteral feeding in preterm infants born with a very low or extremely low birth weight. DESIGN: In a bicentric, double-blind, randomized controlled clinical trial that was stratified for center and birth weight, 45 infants received enteral probiotics (Bifidobacterium longum BB536 and Lactobacillus rhamnosus GG; BB536-LGG) and 49 received placebo. The primary endpoint was the percentage of infants receiving >50% of their nutritional needs via enteral feeding on the 14th day of life. A triangular test was used to perform sequential analysis. RESULTS: The trial was discontinued after the fourth sequential analysis concluded a lack of effect. The primary endpoint was not significantly different between the probiotic (57.8%) and placebo (57.1%) groups (P = 0.95). However, in infants who weighed >1000 g, probiotic supplementation was associated with a shortening in the time to reach full enteral feeding (P = 0.04). Other than colonization by the probiotic strains, no alteration in the composition of intestinal microbiota or changes in the fecal excretion of calprotectin was observed. No colonization by probiotic strains was detected in infants who weighed 1000 g. This trial was registered at clinicaltrials.gov as NCT 00290576.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and L. rhamnosus LC705 and B. breve Bb99
Dosage CFU/day: 5 billion and 5 billion and 0,2 billion and 2 billion
Product formulation: Capsule
Reference number: 1004

Kuitunen, et al. Pro- and prebiotic supplementation induces a transient reduction in hemoglobin concentration in infants. J.Pediatr.Gastroenterol.Nutr. 2009;49:626-630

Abstract: OBJECTIVES:: Regarding safety, we investigated the effect of prenatal probiotic and 6 months of pro- and prebiotic supplementation of infants on their hematologic values at 6 months and 2 years and factors affecting these values. PATIENTS AND METHODS:: In a prospective randomized controlled probiotic intervention trial in infants at high risk for allergy, we obtained blood samples consecutively from 98 infants at 6 months and from 658 children at 2 years to measure hematologic values. We collected fecal samples at 3 and 6 months to measure immunologic development by calprotectin, alpha-1-antitrypsin, tumor necrosis factor-alpha, and immunoglobulin A. RESULTS:: At 6 months, infants in the probiotic group had significantly lower hemoglobin (Hb) values than did the placebo group, mean (SD): 119.8 g/L (6.3) versus 123.3 g/L (8.4), P = 0.025. Adjustment for factors that might affect Hb values (breast-feeding duration, solid-food introduction, and sex), revealed no need for adjustment. A significant negative correlation emerged between Hb values at 6 months and fecal calprotectin at age 3 months r = -0.301, P = 0.009, which was affected neither by breast-feeding, sex, nor study group. At 2 years, hematologic values in both groups became similar. CONCLUSIONS:: Probiotics cause a gut mucosal inflammation with decreased Hb values during intervention, corrected after halting the supplementation.

Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG
Dosage CFU/day: 10 billion of each
Product formulation: Milk powder
Reference number: 0494

Rautava, et al. Specific probiotics in reducing the risk of acute infections in infancy--a randomised, double-blind, placebo-controlled study. Br.J.Nutr. 2009;101(11):1722-1726

Abstract: A randomised, double-blind, placebo-controlled study was conducted to determine whether probiotics might be effective in reducing the risk of infections in infancy. Infants requiring formula before the age of 2 months were recruited from community well-baby clinics. Infant formula supplemented with the probiotics Lactobacillus rhamnosus GG and Bifidobacterium lactis Bb-12 or placebo was administered daily until the age of 12 months. Incidence of early infections (before the age of 7 months) and incidence of recurrent (three or more) infections during the first year of life were recorded as the main outcome measures of the study. During the first 7 months of life, seven out of thirty-two (22 %) infants receiving probiotics and twenty out of forty (50 %) infants receiving placebo experienced acute otitis media (risk ratio (RR) 0.44 (95 % CI 0.21, 0.90); P = 0.014) and antibiotics were prescribed for ten out of thirty-two (31 %) infants receiving probiotics and twenty-four out of forty (60 %) infants receiving placebo (RR 0.52 (95 % CI 0.29, 0.92); P = 0.015). During the first year of life, nine out of thirty-two (28 %) infants receiving probiotics and twenty-two out of forty (55 %) infants receiving placebo encountered recurrent respiratory infections (RR 0.51 (95 % CI 0.27, 0.95); P = 0.022). These data suggest that probiotics may offer a safe means of reducing the risk of early acute otitis media and antibiotic use and the risk of recurrent respiratory infections during the first year of life. Further clinical trials are warranted.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and L. rhamnosus LC705 and B. breve Bb99
Dosage CFU/day: 5 billion and 5 billion and 0,2 billion and 2 billion
Product formulation: Capsule
Reference number: 1003

Kuitunen, et al. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. . *Journal of Allergy and Clinical Immunology*, *123*(2), 335–341 (2009)

Abstract: BACKGROUND: Less microbial exposure in early childhood is associated with more allergic disease later. Allergic children have a different fecal microflora, with less lactobacilli and bifidobacteria. Beneficial effects regarding the development of allergy have been suggested to come through probiotic supplementation. OBJECTIVE: We sought to study the effect of probiotic and prebiotic supplementation in preventing allergies. METHODS: In a double-blinded, placebo-controlled study we randomized 1223 mothers with infants at high risk for allergy to receive a probiotic mixture (2 lactobacilli, bifidobacteria, and propionibacteria) or placebo during the last month of pregnancy and their infants to receive it from birth until age 6 months. Infants also received a prebiotic galacto-oligosaccharide or placebo. At 5 years, we evaluated the cumulative incidence of allergic diseases (eczema, food allergy, allergic rhinitis, and asthma) and IgE sensitization. RESULTS: Of the 1018 intent-to-treat infants, 891 (88%) attended the 5-year visit. Frequencies of allergic and IgE-associated allergic disease and sensitization in the probiotic and placebo groups were similar: 52.6% versus 54.9% and 29.5% versus 26.6%, respectively, and 41.3% in both. No significant difference appeared in frequencies of eczema (39.3% vs 43.3%), atopic eczema (24.0% vs 25.1%), allergic rhinitis (20.7% vs 19.1%), or asthma (13.0% vs 14.1%) between groups. However, less IgE-associated allergic disease occurred in cesarean-delivered children receiving probiotics (24.3% vs 40.5%; odds ratio, 0.47; 95% CI, 0.23% to 0.96%; P = .035). CONCLUSIONS: No allergy-preventive effect that extended to age 5 years was achieved with perinatal supplementation of probiotic bacteria to high-risk mothers and children. It conferred protection only to cesarean-delivered children.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: NA
Product formulation: Milk powder
Reference number: 1171

Scalabrin, et al. Growth and tolerance of healthy term infants receiving hydrolyzed infant formulas supplemented with Lactobacillus rhamnosus GG: randomized, double-blind, controlled trial. Clin.Pediatr. 2009;48:734-744

Abstract: Healthy, term infants received extensively hydrolyzed casein formula (EHF; control), the same formula supplemented with Lactobacillus rhamnosus GG (EHF-LGG), or partially hydrolyzed whey:casein (60:40) formula supplemented with LGG (PHF-LGG), in this double-blind, randomized, controlled, parallel, prospective study. Anthropometric measures and 24-hour dietary and tolerance recalls were obtained at 30, 60, 90, 120, and 150 days of age. Blood collected in a subset of infants was analyzed for fatty acid profiles in plasma and red blood cells and for markers of allergic sensitization. Adverse events were recorded throughout the study. Growth rates were not statistically different between EHF and PHF-LGG and between EHF and EHF-LGG from day 14 to day 30, 120, or 150. No relevant differences in formula tolerance, adverse events, or allergic and immune markers were demonstrated between groups. The extensively and partially hydrolyzed formulas supplemented with LGG support normal growth in healthy, term infants and are well tolerated and safe.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 0690

Aaltonen, et al. Evidence of infant blood pressure programming by maternal nutrition during pregnancy: a prospective randomized controlled intervention study. J.Pediatr. 2008;152:79-84

Abstract: OBJECTIVES: To evaluate the impact of maternal nutrition during pregnancy on infant blood pressure. STUDY DESIGN: Pregnant women (n = 256) were randomized into 3 groups: modified dietary intake according to current recommendations and probiotics (diet/probiotics), placebo (diet/placebo), and a control/placebo group. In the infants born to these women, blood pressure was recorded at age 6 months using an automated oscillometric DINAMAP R. RESULTS: Despite significant differences in maternal dietary intakes between the study groups, the intervention focusing on maternal fat intake showed no direct impact on infants' blood pressure. Instead, a complex U-shaped interrelationship was uncovered; the highest and lowest quartiles of intakes of specific nutrients, carbohydrate (P = .006 for systolic pressure and P = .015 for diastolic pressure), and monounsaturated fatty acids (P = .029 for diastolic pressure) compared with the middle quartiles resulted in higher blood pressure at age 6 months. The pattern between maternal carbohydrate intake during pregnancy and infants' blood pressure remained significant even after adjustment for breastfeeding and body length. A reverse U-shaped trend again was observed between maternal intake of fruits and infants' systolic blood pressure (P = .077). CONCLUSION: With a view toward programming blood pressure to adulthood, our results suggest an opportunity for dietary counseling to promote child health.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Capsules
Reference number: 0693

Sentongo, et al. Intestinal permeability and effects of Lactobacillus rhamnosus therapy in children with short bowel syndrome. J.Pediatr.Gastroenterol.Nutr. 2008;46:41-47

Abstract: BACKGROUND: The present study was conducted to investigate the effects of Lactobacillus rhamnosus (also known as LGG) on intestinal permeability (IP) in children with short bowel syndrome (SBS). PATIENTS AND METHODS: In a double-blind, placebo-controlled crossover clinical trial, baseline IP (ie, lactulose-to-mannitol ratio) was measured in subjects with SBS and healthy control subjects. Subjects with SBS received LGG or placebo for 4 weeks, followed by a 3-week washout before therapy was crossed over for another 4 weeks. IP, quantitative fecal cultures for Lactobacillus species (in colony-forming units [cfu] per gram of stool) and hydrogen breath test (HBT) were performed during LGG and placebo phases of therapy. RESULTS: Twenty-one children (SBS, n = 9; control, n = 12) with a median age of 4.5 years (range 1.6-16.4 years) enrolled. Baseline IP measurements were similar in patients with SBS and control subjects: 0.08 +/- 0.06 (mean +/- SD) versus 0.07 +/- 0.05 (P = 1.0). IP was correlated with age in control subjects (r = -0.83, P = 0.001) but not among patients with SBS (r = -0.55, P = 0.16). Fecal colonization with Lactobacillus species did not differ during LGG versus placebo therapy (median 1.4 x 10(9) cfu/g [range 4.0 x 10(5) to 4.0 x 10(9) cfu/g] vs 6.0 x 10(9) cfu/g [1.0 x 10(3) to 1.0 x 10(10) cfu/g], respectively; P = 0.83). LGG therapy had no consistent effects on IP (P = 0.58) or its relationship with age (r = -0.40, P = 0.29), and was associated with conversion to positive HBT results in 1 subject. CONCLUSIONS: In this sample of children with SBS, the IP was within normal limits but did not correlate with age. LGG therapy had no consistent effects on IP. These findings do not support empiric LGG therapy to enhance IP in children with SBS.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 50 billion
Product formulation: Capsules
Reference number: 0703

Marschan, et al. Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. Clin.Exp.Allergy 2008;38:611-618

Abstract: BACKGROUND: Probiotics are widely studied both in the treatment and prevention of allergic diseases, but their mode of action is poorly known. OBJECTIVE: Our aim was to examine the effect of probiotic bacteria on in vivo cytokine, antibody, and inflammatory responses in allergy-prone infants. METHODS: In a randomized double-blind study, probiotic bacteria or placebo were given for 1 month before delivery to mothers and for 6 months to infants with a family history of allergy. Plasma samples were analysed for C-reactive protein (CRP), total IgA and IgE, food-specific IgA, IgG, and IgE, IL-2, IL-4, IL-6, IL-10, TNF-alpha, and IFN-gamma. We analysed the associations of immunological and inflammatory parameters at age 6 months with probiotic treatment and allergic phenotype at 2 years. RESULTS: Infants receiving probiotic bacteria had higher plasma levels of CRP (P=0.008), total IgA (P=0.016), total IgE (P=0.047), and IL-10 (P=0.002) than infants in the placebo group. Increased plasma CRP level at age 6 months was associated with a decreased risk of eczema [odds ratio (OR) 0.41 [95% confidence interval (CI) 0.17-0.99], P=0.046], and with a decreased risk of allergic disease [OR 0.38 (95% CI 0.16-0.87), P=0.023] at age 2 years, when adjusted with probiotic use. CONCLUSION: The association of CRP with a decreased risk of eczema at 2 years of age in allergy-prone children supports the view that chronic, low-grade inflammation protects from eczema. Probiotic-induced low-grade inflammation was characterized by elevation of IgE, IgA, and IL-10, the changes typically observed in helminth infection-associated induction of regulatory mechanisms. The findings emphasize the role of chronic microbial exposure as an immune modulator protecting from allergy.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 65 billion
Product formulation: Juice
Reference number: 1131

Piirainen, et al. In school-aged children a combination of galacto-oligosaccharides and Lactobacillus GG increases bifidobacteria more than Lactobacillus GG on its own. Ann.Nutr.Metab. 2008;52:204-208

Abstract: The aim of this study was to compare a combination of Lactobacillus GG (LGG) and galacto-oligosaccharides (GOS) with LGG on its own, and their effects on the intestinal microbiota in school-aged children. The randomized, double-blinded, crossover study comprised 30 healthy children. There were two 3-week study periods with a 4-week wash-out period in between. The children ingested daily 65 ml of milk-based fruit juice containing either LGG alone (6.5 × 109 CFU) or LGG plus 2 g of GOS. Symptom diaries were filled during the study periods. Fecal samples were collected at the beginning and end of both study periods. At the end of both study periods, the amount of bifidobacteria was significantly greater after the ingestion of LGG + GOS compared with LGG alone (geometric mean 9.33 × 109 vs. 4.28 × 109 CFU/g, $p < 0.001$). No significant differences were seen in the amount of lactobacilli or LGG, nor did gastrointestinal symptoms, defecation frequency, consistency of stools or ease of defecation differ between the two study periods. Ingestion of LGG combined with 2 g of GOS increased the bifidobacteria more than LGG on its own and thus GOS clearly has a prebiotic effect in children.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. breve BB99
Dosage CFU/day: mothers 16 - 18 billion, infants 8 - 9 billion
Product formulation: Capsules
Reference number: 0728

Kukkonen, et al. Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. *Pediatrics*, *122*(1), 8–12, (2008).

Abstract: OBJECTIVE: Live probiotic bacteria and dietary prebiotic oligosaccharides (together termed synbiotics) increasingly are being used in infancy, but evidence of long-term safety is lacking. In a randomized, placebo-controlled, double-blind trial, we studied the safety and long-term effects of feeding synbiotics to newborn infants. METHODS: Between November 2000 and March 2003, pregnant mothers carrying infants at high risk for allergy were randomly assigned to receive a mixture of 4 probiotic species (Lactobacillus rhamnosus GG and LC705, Bifidobacterium breve Bb99, and Propionibacterium freudenreichii ssp shermanii) or a placebo for 4 weeks before delivery. Their infants received the same probiotics with 0.8 g of galactooligosaccharides, or a placebo, daily for 6 months after birth. Safety data were obtained from clinical examinations and interviews at follow-up visits at ages 3, 6, and 24 months and from questionnaires at ages 3, 6, 12, and 24 months. Growth data were collected at each time point. RESULTS: Of the 1018 eligible infants, 925 completed the 2-year follow-up assessment. Infants in both groups grew normally. We observed no difference in neonatal morbidity, feeding-related behaviors (such as infantile colic), or serious adverse events between the study groups. During the 6-month intervention, antibiotics were prescribed less often in the synbiotic group than in the placebo group (23% vs 28%). Throughout the follow-up period, respiratory infections occurred less frequently in the synbiotic group (geometric mean: 3.7 vs 4.2 infections). CONCLUSION: Feeding synbiotics to newborn infants was safe and seemed to increase resistance to respiratory infections during the first 2 years of life.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Unknown
Reference number: 0958

Huurre, et al. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: a double-blind placebo-controlled study. Clin.Exp.Allergy 2008;38:1342-1348

Abstract: BACKGROUND: The effects of breastfeeding and probiotics on infant sensitization still remain discrepant. OBJECTIVE: To explore probable explanatory factors in infant sensitization and the protective effect of probiotics. METHODS: Altogether 171 mother-infant pairs from an ongoing placebo-controlled double-blind study with nutrition modulation by dietary counselling and probiotic supplementation were studied. Skin prick testing was done in infants at 6 and 12 months and in mothers at third trimester of pregnancy. The breast milk concentrations of cytokines TGF-beta2, soluble CD14, IFN-gamma, TNF-alpha, IL-10, IL-6, IL-4 and IL-2 were measured. RESULTS: The risk of sensitization increased in infants with allergic mothers breastfeeding over 6 months [odds ratio (OR=4.83, P=0.005)], or exclusively breastfeeding over 2.5 months (OR=3.4, P=0.018). Probiotic supplementation had a protective effect against sensitization in infants with a high hereditary risk due to maternal sensitization (OR=0.3, P=0.023). The concentration of TGF-beta2 tended to be higher in the colostrum of the mothers in the probiotic group as compared with those on placebo (probiotic/placebo ratio=1.50, P=0.073). A similar result was obtained in the subgroup of allergic mothers (probiotic/placebo ratio=1.56, P=0.094). CONCLUSION: Infants of atopic mothers, specifically when breastfed exclusively over 2.5 months or totally over 6 months, had a higher risk of sensitization at the age of 12 months. This risk could be reduced by the use of probiotics during pregnancy and lactation, partly by resulting in a beneficial composition of the breast milk.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12 and L. acidophilus LA-5
Dosage CFU/day: 15 billion BB-12, 15 billion LGG, 1.5 billion LA-5
Product formulation: Fermented milk
Reference number: 1354

Kloster Smerud, et al. Effect of a probiotic milk product on gastrointestinal and respiratory infections in children attending day-care. Microb.Ecol.Health Dis. 2008;20:80-85

Abstract: Gastrointestinal and respiratory infections are common among children attending day-care, particularly among younger children. The aim of the present randomized, double-blind and placebo-controlled study was to investigate whether Biola, a commercial milk product with a combination of three different probiotic strains (Lactobacillus rhamnosus GG (LGG), L. acidophilus LA-5, and Bifidobacterium Bb-12) given daily to 240 children younger than 3 years, during 7 winter months of their first year in a day-care centre, could prevent such infections. Information about symptoms of respiratory and gastrointestinal infections was collected by use of a diary completed by the parents and the number of days with respiratory and gastrointestinal symptoms and absences from day-care because of illness were studied. There was no significant difference between the two groups when analysing the total number of days with gastrointestinal and/or respiratory symptoms (26.5 days for the Biola group versus 26.9 days for the placebo group, p=0.52). However, the results indicate that Biola may reduce the number of days with gastrointestinal symptoms only (1.7 days for the Biola group versus 3.0 days for placebo, p=0.02). No significant difference between treatments was seen with respect to respiratory symptoms alone.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Capsules
Reference number: 0704

Marschan, et al. Increased activation of GATA-3, IL-2 and IL-5 of cord blood mononuclear cells in infants with IgE sensitization. Pediatr.Allergy Immunol. 2008;19:132-139

Abstract: Risk of allergic diseases has been linked to abnormal patterns of fetal immune development, suggesting that priming of the immune system may occur in utero. The aim of the study was to investigate whether the pattern of immune response in cord blood mononuclear cells (CBMC) shows association with allergic diseases and IgE sensitization at 2 yr of age, and to study the effect of maternal probiotic supplementation on CBMC immune responses. CBMC were isolated from 98 neonates in a randomized double-blinded intervention study. CBMC were stimulated with beta-lactoglobulin, and phytohemaglutinin (PHA). Secretion of interferon-gamma (IFN-gamma), interleukin-5 (IL-5), and IL-13 was measured by an ELISA; IL-2, IL-4, and IL-10 by a cytokine bead assay. T-cell polarization-associated IL-4 receptor and IL-12R expressions, and the respective transcription factors GATA-3 and T-bet were analyzed with RT-PCR. The above responses were compared with the development of allergic diseases and IgE sensitization at 2 yr of age, and with the maternal probiotic or placebo supplementation. PHA-stimulated GATA-3 expression and IL-2 secretion in CBMC were higher in IgE-sensitized children at an age of 2 yr than in the non-sensitized, non-allergic children ($p = 0.03$ and 0.026). PHA-induced expression of GATA-3 correlated with IL-5 ($p = 0.003$, $r = 0.300$) and IL-13 ($p = 0.007$, $r = 0.278$) secretion of CBMC, and IL-5 secretion of beta-lactoglobulin-stimulated CBMC was higher in IgE-sensitized children at 2 yr of age than in the non-sensitized, non-allergic children ($p = 0.013$). Probiotic bacteria had no effect on CBMC immune responses. In CBMC-enhanced induction of GATA-3, which activates several Th2 cytokines genes, was a risk factor for IgE sensitization. The immune deviation towards Th2-type immunity developed already in utero and seemed to modulate the pattern of immune response favoring an IgE response to environmental antigens.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 12.2 billion
Product formulation: Capsules
Reference number: 0715

Mentula, et al. Microbial composition and fecal fermentation end products from colicky infants - a probiotic supplementation pilot. Microb.Ecol.Health Dis. 2008;20(1):37-47

Abstract: Objectives: The etiology of infantile colic has remained unknown. The present study aimed to identifo possible differences in the fecal microbial composition and metabolic end products becween colicþ and non-colicþ infants and to examine whethei an orally administered probiotic supplementation has any effect on the microbiota and relief in colicþ symptoms. Subjeus and methods: The study population consisted of nine colicky and nine non-colicþ infants. Five colicky infants received probiotic supplementatiot (Lactobacilhts rhantnosus GG, Lactobacillus rhomnosw LC705, BiJidobacteriunt breue Bbig9, and Propionibacteriuin freudenreichü ssp. shennanü JS) and four colicþ infants received placebo for 2 weeks. Fecal microbiota of all infants was studied by culture, cellular fatty acid (CFA) analysis, and gas and short chain fatty acid (SCFA) production in 48 h fermentation. Microbial parameters and crying profiles were compåred between the cases and controls at baseline and between the probiotic and placebo supplementation after 2 weeks. Resubs: Although SCFA and gas production and bacterial total counts were similar, the prevalence of indole-producing coliforms was significantly higher in colicky infants compared with conuols (89% vs 33%), whìle many aerobic genera present in controls were not detected in colicþ infants. CFA composition reflected the differences, since >2o/o of the CFAs were present exclusively in the colicþ group. After probiotic supplementation, the total counts of anaerobic bacteria, especially lactobacilli and bifidobacteria, increased significantly. Fermentation parameters were not extensively affected; however, acetic and lactic acid production tended to increase and hydrogen production tended to decrease. No significant difference was observed in crying patterns between the probiotic and placebo group. Conclusion: Ttrc composition of the intestinal microbiota differs between colicþ and non- colicþ infants. Although no apparent relief in colicþ symptoms was achieved, the probiotic supplementarion seems to increase the bacterial diversity and srengthen the succession towards a balanced commensal gut microbiota.

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Research field: Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Capsule
Reference number: 1130

Piirainen, et al. Effect of Lactobacillus rhamnosus GG on rBet v1 and rMal d1 specific IgA in the saliva of patients with birch pollen allergy. Ann.Allergy Asthma Immunol. 2008;100:338-342

Abstract: BACKGROUND: Lactobacillus rhamnosus GG (LGG) has demonstrated promising results in the treatment and prevention of atopic eczema. OBJECTIVE: To study the effects of LGG on the oral immune response in adolescents and adults with birch pollen allergy combined with oral allergy syndrome. METHODS: Patients received either LGG (n = 19) or a placebo (n = 19) for 5.5 months (from February 8 to August 6, 1999), starting 2.5 months before the birch pollen season. An oral apple challenge test was performed before, during, and after the pollen season. Saliva samples were collected before and after the challenges, and serum samples were collected before the challenges. Total IgA, IgG, and IgM and rBet v1 and rMal dl specific IgA, IgG, IgG1, and IgG4 levels were measured from saliva with an enzyme-linked immunosorbent assay (ELISA). Serum rBet v1 specific IgE ELISA and birch radioallergosorbent testing were performed. RESULTS: After 5.5 months, rBet v1 and rMal dl specific IgA levels had increased from baseline in the LGG compared with the placebo group (delta rBet v1 IgA, 0.319 vs. -0.136 relative units; P = .02; delta rMal d1 IgA, 0.097 vs -0.117, P = .02). rBet v1 specific IgE serum levels did not differ between the groups. In the LGG group, rBet v1 specific IgE levels correlated positively with stimulated total IgA (P = .04) and IgG (P = .003) in saliva. In the placebo group, rBet vl specific IgE levels correlated negatively with stimulated rBet v1 and rMal d1 IgA levels (P = .009 for both) and IgG (P = .02 and P = .03, respectively). CONCLUSION: LGG showed immunostimulating effects on oral mucosa seen as increased allergen specific IgA levels in saliva.

Research field: Infant & Children's Nutrition and Maternal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12
Dosage CFU/day: 2 billion
Product formulation: Capsule
Reference number: 0689

Kaplas, et al. Dietary counseling and probiotic supplementation during pregnancy modify placental phospholipid fatty acids. Lipids 2007;42:865-870

Abstract: It has previously been shown that maternal nutrition affects the fetal environment, with consequences for the infant's health. From early pregnancy onwards participants here received a combination of dietary counseling and probiotics (Lactobacillus GG and Bifidobacterium lactis Bb12; n = 10), dietary counseling with placebo (n = 12), or placebo alone (n = 8). The major differences in placental fatty acids were attributable to a higher concentration of n-3 polyunsaturated fatty acids in both intervention arms than in controls. Further, dietary counseling with probiotics resulted in higher concentrations of linoleic (18:2n-6) and dihomo-gamma-linolenic acids (20:3n-6) compared with dietary counseling with placebo or controls.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 1 billion
Product formulation: Capsule
Reference number: 0914

Grüber, et al. Randomized, placebo-controlled trial of Lactobacillus rhamnosus GG as treatment of atopic dermatitis in infancy. Allergy 2007;62(11):1270-1276

Abstract: BACKGROUND: Some studies have suggested that supplementation of food with lactobacilli may prevent or improve atopic dermatitis in children. This study was designed to investigate the therapeutic effect of Lactobacillus rhamnosus GG (LGG) as a food supplement in infants suffering from atopic dermatitis. METHODS: Infants aged 3-12 months suffering from mild-to-moderate atopic dermatitis (severity scoring of atopic dermatitis or SCORAD index of 15-40) without current antiinflammatory treatment were randomized to receive LGG (5 x 10(9) colony forming units b.i.d.) or placebo as a food supplement for 12 weeks. Severity scoring of atopic dermatitis index and use of hydrocortisone 1% ointment as rescue medication (2 points per application) were recorded at 4, 8, and 12 weeks of treatment and combined as symptom load (SL). RESULTS: Fifty-four infants (LGG group, mean +/- SD SCORAD index 24.6 +/- 8.8) and 48 infants (placebo group, SCORAD index 23.6 +/- 7.8) were randomized and completed the treatment period (intention-to-treat analysis). Symptom load generally improved over time at 4 weeks (LGG vs placebo, 23.8 +/- 12.4 vs 20.6 +/- 9.9), 8 weeks (22.5 +/- 14.6 vs 17.9 +/- 13.1), and 12 weeks (19.6 +/- 15.4 vs 15.1 +/- 12.1), without statistically significant group differences. When stratified for age, eczema severity or use of rescue medication, no statistically significant group differences, in improvement, were found. No significant group differences were found for the use of rescue medication (0.8 +/- 45.0 g vs 3.5 +/- 29.8 g), increase in mean logarithmic total serum IgE (0.17 +/- 0.30 kU/l vs 0.26 +/- 0.45 kU/l), and newly developed allergic sensitization against hen's egg or cow's milk (18.8%vs 10.0%). CONCLUSION: This placebo-controlled trial showed no therapeutic effect of LGG against mild-to-moderate atopic dermatitis in infancy.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 6 billion
Product formulation: NA
Reference number: 0635

Bruzzese, et al. Effect of Lactobacillus GG supplementation on pulmonary exacerbations in patients with cystic fibrosis: a pilot study. Clin.Nutr. 2007;26:322-328

Abstract: BACKGROUND & AIMS: Probiotics reduce intestinal inflammation in children with cystic fibrosis (CF). We want to determine the effects of Lactobacillus GG (LGG) on pulmonary exacerbations in CF. METHODS: A prospective, randomized, placebo-controlled, cross-over study was performed. Nineteen children received LGG for 6 months and then shifted to oral rehydration solution (ORS) for 6 months. In parallel nineteen received ORS and then shifted to LGG. Main outcome parameters were: incidence of pulmonary exacerbations and of hospital admissions, forced expiratory volume (FEV1), and modifications of body weight. RESULTS: Patients treated with LGG showed a reduction of pulmonary exacerbations (Median 1 vs. 2 , range 4 vs. 4, median difference 1, CI 95% 0.5-1.5; p=0.0035) and of hospital admissions (Median 0 vs. 1, range 3 vs. 2, median difference 1, CI 95% 1.0-1.5; p=0.001) compared to patients treated with ORS. LGG resulted in a greater increase in FEV1 (3.6% +/- 5.2 vs. 0.9% +/- 5; p=0.02) and body weight (1.5 kg +/- 1.8 vs. 0.7 kg +/- 1.8; p=0.02). CONCLUSIONS: LGG reduces pulmonary exacerbations and hospital admissions in patients with CF. These suggest that probiotics may delay respiratory impairment and that a relationship exists between intestinal and pulmonary inflammation.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12
Dosage CFU/day: 1 billion
Product formulation: Capsule
Reference number: 0702

Gronlund, et al. Maternal breast-milk and intestinal bifidobacteria guide the compositional development of the Bifidobacterium microbiota in infants at risk of allergic disease. Clin.Exp.Allergy 2007;37(3):1764-1772

Abstract: BACKGROUND: The sources and the impact of maternal bacteria on the initial inoculum of the intestinal microflora of newborn infants remain elusive. OBJECTIVE: To assess the association between maternal breast-milk and fecal bifidobacteria and infants' fecal bifidobacteria. METHODS: Sixty-one mother-infant pairs were included, special emphasis being placed on the maternal allergic status. Bifidobacteria were analysed by a direct PCR method in fecal samples from mothers at 30-35 weeks of gestation and from infants at 1 month of age and from breast-milk samples 1 month post-partum. RESULTS: Fecal Bifidobacterium adolescentis and Bifidobacterium bifidum colonization frequencies and counts among mother-infant pairs correlated significantly (P=0.005 and 0.02 for frequencies, respectively, and P=0.002 and 0.01 for counts, respectively). Only infants of allergic, atopic mothers were colonized with B. adolescentis. Each of the breast-milk samples contained bifidobacteria [median 1.4 x 10(3) bacterial cells/mL; interquartile range (IQR) 48.7-3.8 x 10(3)]. Bifidobacterium longum was the most frequently detected species in breast-milk. Allergic mothers had significantly lower amounts of bifidobacteria in breast-milk compared with non-allergic mothers [median 1.3 x 10(3) bacterial cells/mL (IQR 22.4-3.0 x 10(3)) vs. 5.6 x 10(3) bacterial cells/mL (1.8 x 10(3)-1.8 x 10(4)), respectively, (P=0.004)], and their infants had concurrently lower counts of bifidobacteria in feces [3.9 x 10(8) bacterial cells/g (IQR 6.5 x 10(6)-1.5 x 10(9)) in infants of allergic mothers, vs. 2.5 x 10(9) bacterial cells/g (6.5 x 10(8)-3.2 x 10(10)) in infants of non-allergic mothers, P=0.013]. CONCLUSIONS: Breast-milk contains significant numbers of bifidobacteria and the maternal allergic status further deranges the counts of bifidobacteria in breast-milk. Maternal fecal and breast-milk bifidobacterial counts impacted on the infants' fecal Bifidobacterium levels. Breast-milk bacteria should thus be considered an important source of bacteria in the establishment of infantile intestinal microbiota.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 8-9 billion
Product formulation: Capsule
Reference number: 0630

Hatakka, et al. Treatment of acute otitis media with probiotics in otitis-prone children-a double-blind, placebo-controlled randomised study. Clin.Nutr. 2007;26:314-321

Abstract: BACKGROUND & AIMS: To examine whether probiotics would reduce the occurrence or duration of acute otitis media (AOM), or the nasopharyngeal carriage of otitis pathogens in otitis-prone children. METHODS: During this double-blind, placebo-controlled, randomised, 24-week intervention, 309 otitis-prone children (10 months-6 years) consumed either one probiotic capsule (Lactobacillus rhamnosus GG and LC705, Bifidobacterium breve 99 and Propionibacterium freudenreichii JS) (n=155) or placebo (n=154) daily. Clinical examinations were carried out and nasopharyngeal samples taken three times. Parents recorded the symptoms of upper respiratory infection (URI) in a diary. RESULTS: Probiotic treatment did not reduce the occurrence (probiotic vs. placebo: 72% vs. 65%, OR=1.48, 95% CI 0.87-2.52, p=n.s.) or the recurrence (three) of AOM episodes (18% vs. 17%, OR=1.04, 95% CI 0.55-1.96, p=n.s.). The median duration of AOM episodes was 5.6 (IQR 3.5-9.4) vs. 6.0 (IQR 4.0-10.5) days, respectively (p= n.s.). There was a tendency showing a reduction in the occurrence of recurrent (4 to 6) respiratory infections in the probiotic group (OR for 4 URIs: 0.56, 95%CI 0.31-0.99, p=0.046; OR for 6 URIs: 0.59, 95% CI 0.34 to 1.03, p=n.s.). Probiotics did not affect the carriage of Streptococcus pneumoniae or Haemophilus influenzae, but increased the prevalence of Moraxella catarrhalis (OR=1.79, 95% CI 1.06-3.00, p=0.028). CONCLUSIONS: Probiotics did not prevent the occurrence of AOM or the nasopharyngeal carriage of otitis pathogens in otitis-prone children. A tendency showing a reduction in recurrent respiratory infections must be confirmed in further studies.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 0625

Kukkonen, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. J.Allergy Clin.Immunol. 2007;119:192-198

Abstract: Background: The increase in allergic diseases is attributed to a relative lack of microbial stimulation of the infantile gut immune system. Probiotics, live health-promoting microbes, might offer such stimulation. Objective: We studied the effect of a mixture of 4 probiotic bacterial strains along with prebiotic galacto-oligosaccharides in preventing allergic diseases. Methods: We randomized 1223 pregnant women carrying high-risk children to use a probiotic preparation or a placebo for 2 to 4 weeks before delivery. Their infants received the same probiotics plus galacto-oligosaccharides (n = 461) or a placebo (n = 464) for 6 months. At 2 years, we evaluated the cumulative incidence of allergic diseases (food allergy, eczema, asthma, and allergic rhinitis) and IgE sensitization (positive skin prick test response or serum antigen-specific IgE level >0.7 kU/L). Fecal bacteria were analyzed during treatment and at age 2 years. Results: Probiotic treatment compared with placebo showed no effect on the cumulative incidence of allergic diseases but tended to reduce IgE-associated (atopic) diseases (odds ratio [OR], 0.71; 95% CI, 0.50-1.00; P = .052). Probiotic treatment reduced eczema (OR, 0.74; 95% CI, 0.55-0.98; P = .035) and atopic eczema (OR, 0.66; 95% CI, 0.46-0.95; P = .025). Lactobacilli and bifidobacteria more frequently (P < .001) colonized the guts of supplemented infants. Conclusion: Probiotic treatment showed no effect on the incidence of all allergic diseases by age 2 years but significantly prevented eczema and especially atopic eczema. The results suggest an inverse association between atopic diseases and colonization of the gut by probiotics. Clinical implications: The prevention of atopic eczema in high-risk infants is possible by modulating the infant's gut microbiota with probiotics and prebiotics. © 2007 American Academy of Allergy, Asthma & Immunology.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 0953

Honeycutt, et al. Probiotic administration and the incidence of nosocomial infection in pediatric intensive care: a randomized placebo-controlled trial. *Pediatric Critical Care Medicine*, *8*(5), 452–458, (2007)

Abstract: OBJECTIVE: To evaluate the efficacy of probiotics in reducing the rates of nosocomial infection in pediatric intensive care.\n\nDESIGN: Randomized, double-blind, placebo-controlled trial.\n\nSETTING: A 16-bed pediatric intensive care unit in a university-affiliated children's hospital.\n\nPATIENTS: Sixty-one pediatric patients were enrolled from April 2004 until December 2004. Screening of all patients admitted occurred on a daily basis. Patients were excluded if they had the following: evidence/suspicion of intestinal perforation, evidence/suspicion of mechanical gastrointestinal obstruction, absolute neutrophil count <or =0.5 x 10(9) cells/L, judgment by the attending physician that unable to tolerate the enteral volume necessary for administration, use of a probiotic preparation at any time in the week before study entry, participation in another clinical trial, lack of parental presence, or lack of parental consent.\n\nINTERVENTIONS: Patients were randomized to receive either one capsule of Lactobacillus rhamnosus strain GG (Culturelle, ConAgra Foods, Omaha, NE) or placebo capsule of insulin once a day until discharge from the hospital.\n\nRESULTS: Sixty-one patients were randomized: 31 in the treatment group and 30 on the placebo group. Three patients in the control group developed four infections. Six patients in the treatment group developed 11 infections. The relative risk of developing infection in the treatment group was 1.94 (confidence interval [CI], 0.53 to 7.04; p = .31). The mean number of infections in the treatment and control groups was 1.83 and 1.33, respectively, with a difference of 0.5 (p = .52). No serious adverse effects in the study population were noted. However, due to recent safety concerns regarding the administration of L. rhamnosus strain GG and a lack of benefit in this interim analysis, the study was terminated by the study investigators.\n\nCONCLUSIONS: The results of this preliminary investigation were unexpected but important in view of the increased use of probiotic preparations in medically fragile pediatric patients. In this randomized, placebo-controlled trial, L. rhamnosus strain GG was not shown to be effective in reducing the incidence of nosocomial infections. In fact, a statistically nonsignificant trend toward an increase in infection was seen (four vs. 11). Further studies with a larger patient population are needed to establish both safety and efficacy of probiotics in pediatric critical care.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion

Kalliomäki et al Probiotics during the first 7 years of life: A cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *Journal of Allergy and Clinical Immunology*, *119*(4), 1018–1019; (2007).

Abstract: NA

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: NA
Product formulation: NA
Reference number: 0605

Gueimonde, et al. Effect of maternal consumption of lactobacillus GG on transfer and establishment of fecal bifidobacterial microbiota in neonates. J.Pediatr.Gastroenterol.Nutr. 2006;42:166-170

Abstract: BACKGROUND: Establishment of the gut microbiota at birth provides a substantial source of microbial stimuli for the maturation of the immune system. Deviations in this process precede the development of specific diseases providing the rationale for the use of probiotics to counteract them. OBJECTIVE: This study was designed to characterize both the mother-infant bifidobacteria transfer at birth and the development of bifidobacteria microbiota during the first weeks of life in infants whose mothers received Lactobacillus rhamnosus GG or placebo. METHODS: Species-specific PCR was used to assess the fecal bifidobacterial composition of mothers before and after delivery and in infants at 5 days and 3 weeks of age. RESULTS: Bifidobacterium longum was the species most commonly found in the mothers. Bifidobacterium catenulatum was the most prevalent group in infants at 5 days of age and B. longum the predominant species at 3 weeks. At 5 days of age, infants whose mothers received L. rhamnosus GG showed a significantly higher occurrence of B. breve and lower of B. adolescentis than those from the placebo group. In addition, L. rhamnosus GG consumption increased the bifidobacterial diversity in infants and reduced the Bifidobacterium microbiota similarity between mother and infant. CONCLUSIONS: These results indicate that specific changes in the transfer and initial establishment of bifidobacteria in neonates take place as consequence of the consumption of L. rhamnosus GG by the mothers.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Unknown
Reference number: 1142

Rinne, et al. Probiotic intervention in the first months of life: short-term effects on gastrointestinal symptoms and long-term effects on gut microbiota. J.Pediatr.Gastroenterol.Nutr. 2006;43:200-205

Abstract: OBJECTIVES: To determine whether probiotics administered for 6 months postnatally affect gastrointestinal symptoms, crying and the compositional development of the gut microbiota through infancy. METHODS: The study comprised of 132 newborns whose mothers were randomized to receive placebo or Lactobacillus rhamnosus GG (ATCC 53103) before delivery. The treatments of mothers/infants continued for 6 months postnatally. A specific symptom chart was used to monitor gastrointestinal symptoms and infant's crying during the 7th and the 12th weeks of life. Fluorescent in situ hybridization was used to establish the Bifidobacterium, Lactobacillus/Enterococcus, Bacteroides and Clostridium counts in fecal samples at 6, 12, 18 and 24 months of age. RESULTS: Numbers of different types of stools, vomits and crying time were comparable between the groups during the 7th and the 12th weeks of life. Dominant microbiota consisted of bifidobacteria throughout the study. At 6 months, there were less clostridia in faeces in the placebo compared with the probiotic group (P = 0.026), whereas after long-term follow-up at 2 years, there were less lactobacilli/enterococci and clostridia in faeces in the probiotic group than in the placebo group (P = 0.011 and P = 0.032, respectively), reflecting the impact of clostridia as a marker of microbiota succession in healthy infants. CONCLUSIONS: Probiotic administration in the first months of life was well tolerated and did not significantly interfere with long-term composition or quantity of gut microbiota.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 0922

Gueimonde, et al. Probiotic intervention in neonates--will permanent colonization ensue? J.Pediatr.Gastroenterol.Nutr. 2006;42:604-606

Abstract: The presence of Lactobacillus rhamnosus GG at 6 and 12 months in the feces of 128 infants receiving the strain or placebo for 6 months after birth was monitored. No permanent establishment of the strain was found, but transient colonization was observed at 6 months of age. The presence of the strain at the end of the administration period was correlated with a reduced prevalence of atopic eczema later in life.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and B. animalis subsp. lactis BB-12
Dosage CFU/day: 10 billion BB-12 and 10 billion LGG
Product formulation: Milk powder
Reference number: 0509

Rautava, et al. Specific probiotics in enhancing maturation of IgA responses in formula-fed infants. Pediatr.Res. 2006;60:221-224

Abstract: The first months of life represent a critical period for the maturation of the infant's immune system and, thus, a window of opportunity for measures to reduce the risk of disease. We hypothesized that specific probiotics might promote mucosal immunologic maturation in formula-fed infants. The numbers of cow's milk-specific and total IgA-secreting cells were measured at 3, 7, and 12 mo of age in a double-blind placebo-controlled study of 72 infants with early artificial feeding. The infants consumed infant formula supplemented with specific probiotics (Lactobacillus GG and Bifidobacterium lactis Bb-12) or placebo during the first year of life. Further analyses of the serum concentrations of the IgA-inducing cytokine TGF-beta2 and the soluble innate microbial receptor sCD14 were conducted. The numbers of cow's milk-specific IgA secreting cells were significantly higher in infants receiving probiotics compared with those receiving placebo ($p = 0.045$, ANOVA for repeated measures). At 12 mo of age, the serum concentrations of sCD14 were 1479 pg/mL [95% confidence interval (CI) 1373-1592] in infants receiving probiotics and 1291 pg/mL (95% CI 1152-1445) in infants receiving placebo ($p = 0.046$). Administration of the probiotics Lactobacillus GG and Bifidobacterium lactis Bb-12 at the time of introduction of cow's milk in the infant's diet results in cow's milk-specific IgA antibody responsiveness that may be the result of increased production of sCD14.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: NA
Product formulation: Milk powder
Reference number: 0607

Vendt, et al. Growth during the first 6 months of life in infants using formula enriched with Lactobacillus rhamnosus GG: double-blind, randomized trial. J.Hum.Nutr.Diet. 2006;19:51-58

Abstract: BACKGROUND: Probiotic bacteria have beneficial effects on the immune system and gastrointestinal tract, but the impacts of their long-term consumption on health and growth in early infancy are not well documented. The aim of this study was to evaluate the influence of Lactobacillus rhamnosus GG (LGG)-enriched formula on growth and faecal microflora during the first 6 months of life in normal healthy infants. MATERIALS AND METHODS: One hundred and twenty healthy infants (up to 2 months) received LGG-supplemented formula or regular formula in a double-blind, randomized manner until the age of 6 months. Weight, length and head circumference were measured monthly and transformed into standard deviation scores (SDS). Faecal samples were obtained from a random sample of infants (n=25) at entry and at the end of the study. RESULTS: One hundred and five infants (51 in the LGG group) completed the study. Children receiving LGG-supplemented formula grew better: their changes in their length and weight SDS (DeltaSDS) at the end of the study were significantly higher than those receiving regular formula (0.44+/- 0.37 versus 0.07+/- 0.06, P< 0.01 and 0.44+/- 0.19 versus 0.07+/- 0.06, P< 0.005, respectively). The LGG group had a significant, higher defecation frequency 9.1+/-2.06 versus 8.0+/- 2.8 (P<0.05). More frequent colonization with lactobacilli was found in the LGG group, 91% versus 76% (P<0.05) at the end of the study. CONCLUSIONS Infants fed with LGG-enriched formula grew better than those fed with regular formula. Further studies are necessary to clarify the mechanism of LGG in infant growth.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: NA
Product formulation: NA
Reference number: 0889

Galpin, et al. Effect of Lactobacillus GG on intestinal integrity in Malawian children at risk of tropical enteropathy. Am.J.Clin.Nutr. 2005;82:1040-1045

Abstract: BACKGROUND: Tropical enteropathy is an asymptomatic villous atrophy of the small bowel that is prevalent in the developing world and is associated with altered intestinal function and integrity. The histology of tropical enteropathy resembles that seen in small-bowel bacterial overgrowth. OBJECTIVE: This study tested the hypothesis that treatment of 3-5-y-old Malawian children with the probiotic Lactobacillus GG would improve their intestinal function and integrity. DESIGN: Clinically healthy children (n = 164) were enrolled in a placebo-controlled, randomized, double-blind trial. Intestinal function and integrity were measured by using the site-specific sugar-absorption test before and after 30 d of treatment with Lactobacillus GG or placebo. The primary outcomes were the ratios of urinary lactulose to mannitol (L:M) and of urinary sucrose to lactulose (S:L) excretion. RESULTS: Of the 161 children who completed the study, 119 (73%) had tropical enteropathy on enrollment (L:M > 0.10). Children receiving Lactobacillus GG did not differ significantly from the placebo group in the excretion (in % of dose administered) of mannitol (mean +/- SD: 8.9 +/- 4.4 and 8.9 +/- 3.9, respectively), lactulose (0.31 +/- 0.20 and 0.33 +/- 0.23, respectively), or sucrose (0.078 +/- 0.058 and 0.082 +/- 0.075, respectively). L:M and S:L also did not differ significantly between the Lactobacillus and placebo groups (0.19 +/- 0.13 and 0.20 +/- 0.12, respectively, for L:M; 0.58 +/- 0.46 and 0.65 +/- 0.57, respectively, for S:L). CONCLUSION: Administration of Lactobacillus GG for 30 d had no effect on the intestinal integrity of 3-5-y-old Malawian children.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: a: 5 billion LGG b: 5 billion LGG + 5 billion LC705 + 0.2 billion Bb99 + 2 billion JS
Product formulation: Other
Reference number: 0576

Viljanen, et al. Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. Allergy 2005;60:494-500

Abstract: BACKGROUND: Probiotic bacteria are suggested to reduce symptoms of the atopic eczema/dermatitis syndrome (AEDS) in food-allergic infants. We aimed to investigate whether probiotic bacteria have any beneficial effect on AEDS. METHODS: Follow-up of severity of AEDS by the Severity Scoring of Atopic Dermatitis (SCORAD) index in 230 infants with suspected cow's milk allergy (CMA) receiving, in a randomized double-blinded manner, concomitant with elimination diet and skin treatment, Lactobacillus GG (LGG), a mixture of four probiotic strains, or placebo for 4 weeks. Four weeks after the treatment, CMA was diagnosed with a double-blind placebo-controlled (DBPC) milk challenge in 120 infants. RESULTS: In the whole group, mean SCORAD (at baseline 32.5) decreased by 65%, but with no differences between treatment groups immediately or 4 weeks after the treatment. No treatment differences were observed in infants with CMA either. In IgE-sensitized infants, however, the LGG group showed a greater reduction in SCORAD than did the placebo group, -26.1 vs-19.8 (P=0.036), from baseline to 4 weeks after the treatment. Exclusion of infants who had received antibiotics during the study reinforced the findings in the IgE-sensitized subgroup. CONCLUSION: Treatment with LGG may alleviate AEDS symptoms in IgE-sensitized infants but not in non-IgE-sensitized infants.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: NA
Reference number: 0670

Bousvaros, et al. A randomized, double-blind trial of Lactobacillus GG versus placebo in addition to standard maintenance therapy for children with Crohn's disease. Inflamm.Bowel Dis. 2005;11:833-839

Abstract: Probiotics are widely used by patients with Crohn's disease (CD) in an attempt to improve their health, but few controlled studies have been done to evaluate the efficacy of these therapies. We conducted a randomized, placebo-controlled trial of the probiotic Lactobacillus rhamnosus strain GG (LGG) to see if the addition of LGG to standard therapy prolonged remission in children with CD. Concomitant medications allowed in the study included aminosalicylates, 6-mercaptopurine, azathioprine, and low-dose alternate day corticosteroids. Seventy-five children (age range, 5-21 yr) with CD in remission were randomized to either LGG (n=39) or placebo (n=36) and followed for up to 2 years. The median time to relapse was 9.8 months in the LGG group and 11.0 months in the placebo group (P=0.24); 31% (12/39) of patients in the LGG group developed a relapse compared with 6/36 (17%) of the placebo group (P=0.18). The LGG was well tolerated, with a side effect profile comparable with placebo. This study suggests that LGG does not prolong time to relapse in children with CD when given as an adjunct to standard therapy.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: Control:0 - low: 0.1 billion - medium: 1 billion- high: 10 billion
Product formulation: Milk powder
Reference number: 0583

Petschow, et al. Effects of feeding an infant formula containing Lactobacillus GG on the colonization of the intestine: a dose-response study in healthy infants. J.Clin.Gastroenterol. 2005;39:786-790

Abstract: OBJECTIVES: This study aimed to determine whether feeding Lactobacillus GG (LGG) at varying levels (10 to 10 cfu/day) would result in colonization, defined as > or =1,000 cfu of LGG per gram of stool in 3 of 5 samples collected during the feeding period. METHODS: Infants received unsupplemented formula during a 7-day baseline, 1 of 4 formulas containing 0 (control), 10 (low), 10 (medium), or 10 (high) cfu of LGG per day during a 2-week test, and unsupplemented formula during a 2-week follow-up. Baseline, test, and follow-up stool samples were evaluated for levels of viable LGG. RESULTS: During test, supplemented infants were colonized, compared with control ($P < 0.05$). Median stool counts of LGG (log10 cfu/g) in colonized infants were 5.24 (low), 6.05 (medium), and 5.97 (high). LGG persisted in the stools for 7 to 14 days after discontinuing LGG. No differences were observed among groups in stool consistency, flatulence, fussiness, or adverse events. CONCLUSION: A 2-week oral administration of 10 to 10 cfu/day LGG was well tolerated; all levels successfully colonized the intestinal tract of healthy, term infants.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Milk powder
Reference number: 0710

Laitinen, et al. Evaluation of diet and growth in children with and without atopic eczema: follow-up study from birth to 4 years. Br.J.Nutr. 2005;94:565-574

Abstract: Current research into dietary factors contributing to the development of allergic diseases is directed towards new active approaches instead of passive elimination diets. The present study aimed to investigate the explanatory role of the diet in a probiotic intervention study on the appearance of atopic eczema (AE) in childhood and the safety of perinatal supplementation with probiotics (Lactobacillus rhamnosus strain GG; ATCC 53 103). A prospective follow-up study from birth to 48 months of children (n 159) with a family history of allergic disease was carried out. Outcome measures included growth, dietary intake assessed with 4 d food diaries and their association with AE by logistic regression models. Increased intakes of retinol, Ca and Zn, with perinatal administration of probiotics, reduced the risk of AE, whilst an increase in intake of ascorbic acid increased the likelihood of AE. Perinatal administration of probiotics was safe, as it did not influence the height (mean difference 0.04 (95 % CI -0.33, 0.40) sd scores, P=0.852) or the weight-for-height (mean difference -3.35 (95 % CI -7.07, 0.37)%, P=0.077) of the children at 48 months with and without perinatal administration of probiotics. Up to 48 months, AE did not affect height (mean difference -0.05 (95 % CI -0.42, 0.33) sd scores, P=0.815), but mean weight-for-height in children with AE was -5.1 % (95 % CI -8.9, -1.2 %) lower compared with children without (P=0.010). The joint effects of nutrients and probiotics need to be considered in active prevention and management schemes for allergic diseases.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Capsule
Reference number: 0586

Bausserman, Michail. The use of Lactobacillus GG in irritable bowel syndrome in children: a double-blind randomized control trial. J.Pediatr. 2005;147:197-201

Abstract: OBJECTIVE: To determine whether oral administration of the probiotic Lactobacillus GG under randomized, double-blinded, placebo-controlled conditions would improve symptoms of irritable bowel syndrome (IBS) in children. STUDY DESIGN: Fifty children fulfilling the Rome II criteria for IBS were given Lactobacillus GG or placebo for 6 weeks. Response to therapy was recorded and collected on a weekly basis using the Gastrointestinal Symptom Rating Scale (GSRS). RESULTS: Lactobacillus GG was not superior to placebo in relieving abdominal pain (40.0% response rate in the placebo group vs 44.0% in the Lactobacillus GG group; P=.774). There was no difference in the other gastrointestinal symptoms, except for a lower incidence of perceived abdominal distention (P=.02 favoring Lactobacillus GG). CONCLUSIONS: Lactobacillus GG was not superior to placebo in the treatment of abdominal pain in children with IBS but may help relieve such symptoms as perceived abdominal distention.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion LGG, 10 billion LC507, 0.4 billion BB-99, 4 billion PJS
Product formulation: Capsule
Reference number: 0650

Viljanen, et al. Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants. Pediatr.Allergy Immunol. 2005;16:65-71

Abstract: Probiotic bacteria are proposed to alleviate intestinal inflammation in infants with atopic eczema/dermatitis syndrome (AEDS) and food allergy. In such infants we investigated effects of probiotic bacteria on faecal IgA, and on the intestinal inflammation markers tumour necrosis factor-alpha (TNF-alpha), alpha1-antitrypsin (AT), and eosinophil cationic protein (ECP). A total of 230 infants with AEDS and suspected cow's milk allergy (CMA) received in a randomized double-blinded manner, concomitant with elimination diet, Lactobacillus GG (LGG), a mixture of four probiotic strains (MIX), or placebo for 4 wk. Four weeks after treatment, CMA was diagnosed with a double-blind placebo-controlled milk challenge. Faecal samples of 102 infants, randomly chosen for analysis, were collected before treatment, after 4-wk treatment, and on the first day of milk challenge. After treatment, IgA levels tended to be higher in probiotic groups than in the placebo group (LGG vs. placebo, p=0.064; MIX vs. placebo, p=0.064), and AT decreased in the LGG group, but not in other treatment groups. After challenge in IgE-associated CMA infants, faecal IgA was higher for LGG than for placebo (p=0.014), and TNF-alpha was lower for LGG than for placebo, but non-significantly (p=0.111). In conclusion, 4-wk treatment with LGG may alleviate intestinal inflammation in infants with AEDS and CMA.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Milk powder
Reference number: 0668

Rinne, et al. Effect of probiotics and breastfeeding on the bifidobacterium and lactobacillus/enterococcus microbiota and humoral immune responses. J.Pediatr. 2005;147:186-191

Abstract: OBJECTIVE: To assess impact of probiotics and breastfeeding on gut microecology. STUDY DESIGN: Mothers were randomized to receive placebo or Lactobacillus rhamnosus GG before delivery, with treatment of the infants after delivery. We assessed gut microbiota, humoral immune responses, and measured soluble cluster of differentiation 14 (sCD14) in colostrum in 96 infants. RESULTS: Fecal Bifidobacterium and Lactobacillus/Enterococcus counts were higher in breastfed than formula-fed infants at 6 months; P <.0001 and P=.01, respectively. At 3 months, total number of immunoglobulin (Ig)G-secreting cells in breastfed infants supplemented with probiotics exceeded those in breastfed infants receiving placebo; P=.05, and their number correlated with concentration of sCD14 in colostrum. Total numbers of IgM-, IgA-, and IgG-secreting cells at 12 months were higher in infants breastfed exclusively for at least for 3 months and supplemented with probiotics as compared with breastfed infants receiving placebo; P=.005, P=.03 and P=.04, respectively. Again, sCD14 in colostrum correlated with numbers of IgM and IgA cells; P=.05 in both. CONCLUSIONS: We found an interaction between probiotics and breastfeeding on number of Ig-secreting cells, suggesting that probiotics during breastfeeding may positively influence gut immunity.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG® and LC705 and BB-99
Dosage CFU/day: 10 billion LGG, 10 billion Lc705, 0.4 billion BB-99, 4 billion PJS
Product formulation: Capsule
Reference number: 0659

Viljanen, et al. Induction of inflammation as a possible mechanism of probiotic effect in atopic eczema-dermatitis syndrome. J.Allergy Clin.Immunol. 2005;115:1254-1259

Abstract: BACKGROUND: The immunomodulating mechanisms of Lactobacillus GG (LGG) and other probiotics are poorly understood. OBJECTIVE: We studied in vivo the immunologic effects of probiotics in infants with atopic eczema-dermatitis syndrome (AEDS) and cow's milk allergy (CMA). METHODS: Two hundred thirty infants with AEDS and suspected CMA received, concomitant with elimination diet, either LGG, a mixture of 4 probiotic strains (MIX), or placebo for 4 weeks. All available paired pretreatment and posttreatment plasma samples (n = 132) were analyzed for concentrations of IL-2, IL-4, IL-6, IL-10, TNF-alpha, IFN-gamma, soluble intercellular adhesion molecule 1, soluble E-selectin, TGF-beta1, TGF-beta2, and C-reactive protein. RESULTS: In infants with IgE-associated AEDS, treatment with LGG induced higher C-reactive protein levels than in the placebo group (geometric mean, 0.83 microg/mL [95% CI, 0.56-0.81] vs 0.42 microg/mL [95% CI, 0.27-0.65]; P = .021). Concomitantly, IL-6 levels increased after treatment with LGG (P = .023) but not with MIX or placebo. Soluble E-selectin levels were higher after probiotic than after placebo treatment in infants with IgE-mediated CMA (LGG geometric mean, 86.7 ng/mL [95% CI, 75.2-100]; MIX geometric mean, 91.6 ng/mL [95% CI, 74.8-111.9]; and placebo geometric mean, 64.9 ng/mL [95% CI, 53-79.3]; analysis of covariance, P = .035; LGG vs placebo, P = .023; MIX vs placebo, P = .020). Use of MIX induced an increase in plasma IL-10 levels (P = .016). CONCLUSION: Probiotics induced systemically detectable low-grade inflammation, which might explain the clinical effects of probiotics in AEDS and CMA.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: NA
Product formulation: NA
Reference number: 1172

Schultz, et al. Administration of oral probiotic bacteria to pregnant women causes temporary infantile colonization. J.Pediatr.Gastroenterol.Nutr. 2004;38:293-297

Abstract: BACKGROUND: It is difficult to permanently change the composition of the complex intestinal microflora of the adult. Orally administered probiotic bacteria produce only temporary colonization of the intestine in patients with a fully developed gut microflora. The gastrointestinal tract of a healthy fetus is sterile. During the birth process and rapidly thereafter, microbes from the mother and the surrounding environment colonize the gastrointestinal tract until a dense, complex microflora develops. Probiotic bacteria have been shown to beneficially influence the intestinal and systemic immune system and mediate protection against nosocomial infections affecting the neonate. OBJECTIVES: The purpose of this study was to determine whether oral administration of the probiotic micro-organism Lactobacillus rhamnosus strain GG (L. GG) to the pregnant woman leads to colonization of the newborn infant. METHODS: The authors identified six women who were taking L. GG during late pregnancy. None of the children received L. GG after birth, and their mothers discontinued its consumption at the time of delivery. L. GG concentration in fecal samples was determined by colony morphology and molecular analysis. RESULTS: In all four children delivered vaginally and in one of two children delivered by cesarean section, L. GG was present in fecal samples at 1 and 6 months of age. Three children remained colonized for at least 12 months, and in two children L. GG was detected in fecal samples at 24 months of age. Three mothers were tested 1 month post partum and no L. GG was present in fecal samples. No L. GG was found in one of these women 24 months post partum. There was no L. GG detectable in stools of the siblings of two children at the 2-year and 3-years after birth of the index child. L. GG was not isolated from the stools of children whose mothers were not taking L. GG. CONCLUSIONS: Temporary colonization of an infant with L. GG may be possible by colonizing the pregnant mother before delivery. Colonization is stable for as long as 6 months, and in unexplained circumstances may persist for as long as 24 months.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: NA
Product formulation: Milk powder
Reference number: 0642

Salazar-Lindo, et al. Lactobacillus casei strain GG in the treatment of infants with acute watery diarrhea: a randomized, double-blind, placebo controlled clinical trial. *BMC Pediatrics*, *4*(1), 1–9, 2004.

Abstract: BACKGROUND: Adjuvant therapy to ORT with probiotic bacteria for infants with acute watery diarrhea has been under active investigation. Most studies have been done in the developed world showing benefit only for viral mild gastroenteritis. We evaluated the effect of a milk formula containing one billion (109) cfu/ml of Lactobacillus casei strain GG (LGG) upon duration and severity of diarrhea in infants in an environment with more severe acute diarrhea, where etiologic agents other than rotavirus are involved more frequently, and where mixed infections are more prevalent. METHODS: Male infants aged 3-36 months brought for treatment of acute watery diarrhea of less than 48 hours were eligible. After rehydration was completed with the WHO's oral rehydration solution, patients were randomly assigned to receive a milk formula either containing LGG or not. Stool volume was periodically measured using a devise suited to collect stools separate from urine. Duration of diarrhea was estimated based on stools physical characteristics. RESULTS: Eighty nine patients received the placebo milk formula and ninety received the LGG containing formula. Both groups were comparable in their baseline characteristics. Total stool output was significantly larger ($p = 0.047$) in the LGG group (247.8 ml/kg) than in the placebo group (195.0 ml/kg). No significant differences were found in duration of diarrhea (58.5 hours with LGG vs. 50.4 hours with placebo), rate of treatment failure (21.1% with LGG vs. 18.0% with placebo), and proportion of patients with unresolved diarrhea after 120 hours (12.2% with LGG vs. 12.5% with placebo). The rate of stools with reducing substances after 24 hours of treatment increased significantly in both groups (from 41.4% to 72.2% with LGG and from 45.9% to 68.0% with placebo). CONCLUSION: This study did not show a positive effect of LGG on the clinical course of acute watery diarrhea. Positive beneficial effects of LGG, as had been reported elsewhere, could have been masked in our study by worsening diarrhea due to transient lactose malabsorption. Further studies with low-lactose or non-lactose conveyors of LGG are desirable.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: a: 5 billion LGG b: 5 billion LGG + 5 billion LC705 + 0.2 billion Bb99 + 2 billion JS
Product formulation: Other
Reference number: 0578

Pohjavuori, et al. Lactobacillus GG effect in increasing IFN-gamma production in infants with cow's milk allergy. J.Allergy Clin.Immunol. 2004;114:131-136

Abstract: BACKGROUND: Probiotic bacteria are potentially beneficial to maturation of the infant's immune system. OBJECTIVE: To examine the role of probiotic bacteria in treatment of cow's milk allergy (CMA) and IgE-associated dermatitis, we investigated the immunologic effects of Lactobacillus rhamnosus GG (LGG) and a mixture of 4 bacterial species (MIX). METHODS: In a randomized, double-blind study design, concomitantly with elimination diet and skin treatment, LGG, MIX, or placebo was given for 4 weeks to infants with suspected CMA. After anti-CD3 (OKT3) and anti-CD28 stimulation of PBMCs, IFN-gamma, IL-4, IL-5, and IL-12 levels were measured in culture supernatants by ELISA. Intracellular IFN-gamma, IL-4, and IL-5 production on CD4 lymphocytes was analyzed with fluorescence-activated cell sorting. RESULTS: Secretion of IFN-gamma by PBMCs before the treatment was significantly lower in infants with CMA (P=.016) and in infants with IgE-associated CMA (P=.003) than in non-CMA infants. Among the infants who received LGG, the level of secreted IFN-gamma increased in those with CMA (P=.006) and in those with IgE-associated dermatitis (P=.017) when compared with the placebo group. Secretion of IL-4 increased significantly in infants with CMA in the MIX (P=.034) but not in the LGG group. CONCLUSION: Deficiency in IFN-gamma response appears to be related to CMA. LGG raises IFN-gamma production of PBMC in infants with CMA and in infants with IgE-associated dermatitis and may thus provide beneficial TH1 immunomodulatory signals. MIX, although containing LGG, appears to modulate the immune responses differently.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 2 billion
Product formulation: Capsule
Reference number: 0759

Agarwal, et al. Effects of oral Lactobacillus GG on enteric microflora in low-birth-weight neonates. J.Pediatr.Gastroenterol.Nutr. 2003;36:397-402

Abstract: BACKGROUND: Colonization patterns, especially by anaerobic flora, may play an important role in neonatal gut function. Probiotics could affect disease risk either directly through colonization or indirectly by promoting changes in gut microbial ecology. METHODS: To study the ability of Lactobacillus GG(LGG) to colonize the neonatal gut and modify its microbial ecology, a prospective, randomized study was performed in 71 preterm infants of less than 2000 g birth weight. Infants less than 1500 g (24 treated, 15 control) received 10(9) LGG orally twice daily for 21 days. Those infants weighing 1500 to 1999 g (23 treated, 9 control) were treated for 8 days. Stools were collected before treatment and on day 7 to 8 (and day 14 and 21, in the infants weighing less than 1500 g) for quantitative aerobic and anaerobic cultures. RESULTS: Colonization with LGG occurred in 5 of 24 (21%) infants who weighed less than 1500 g versus 11 of 23 (47%) in larger infants. Colonization was limited to infants who were not on antibiotics within 7 days of treatment with LGG. There was a paucity of bacterial species at baseline, although larger infants had more bacterial species (1.59 +/- 0.13 (SEM) vs 1.11 +/- 0.12; P < 0.03) and higher mean log colony forming units (CFU) (8.79 +/- 0.43 vs 7.22 +/- 0.63; P < 0.05) compared with infants weighing less than 1500 g LGG. Treatment in infants weighing less than 1500 g resulted in a significant increase in species number by day 7, with further increases by day 21. This increase was mainly the result of increased Gram (+) and anaerobic species. No difference in species number was noted in controls. Mean log CFU of Gram (-) bacteria did not change in treated infants weighing less than 1500 g. However, Gram (+) mean log CFU showed a significant increase on day 21 (6.1 +/- 0.9) compared with day 0 (3.5 +/- 0.9) (P < 0.05). No significant changes in species number or quantitative counts were noted after LGG treatment in the infants weighing 1500 to 1999 g LGG was well tolerated in all infants. CONCLUSION: The neonatal response to a probiotic preparation is dependent on gestational and post-natal age and prior antibiotic exposure. Although LGG is a relatively poor colonizer in infants, especially those infants weighing less than 1500 g at birth, it does appear to affect neonatal intestinal colonization patterns.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG
Dosage CFU/day: 1 billion
Product formulation: Milk powder
Reference number: 0580

Kirjavainen, et al. Probiotic bacteria in the management of atopic disease: underscoring the importance of viability. *Journal of Pediatric Gastroenterology and Nutrition*, *36*(2), 223–227; 2003.

Abstract: OBJECTIVES: The aim of this study was to assess the efficacy of oral supplementation of viable and heat-inactivated probiotic bacteria in the management of atopic disease and to observe their effects on the composition of the gut microbiota. METHODS: The study population included 35 infants with atopic eczema and allergy to cow's milk. At a mean age of 5.5 months, they were assigned in a randomized double-blind manner to receive either extensively hydrolyzed whey formula (placebo group) or the same formula supplemented with viable (viable LGG group) or heat-inactivated Lactobacillus GG (heat-inactivated LGG group), respectively. The changes in symptoms were assessed by the SCORAD method and the presence of some predominant bacterial genera in the feces detected with 16S rRNA-specific probes. RESULTS: The treatment with heat-inactivated LGG was associated with adverse gastrointestinal symptoms and diarrhea. Consequently, the recruitment of patients was stopped after the pilot phase. Within the study population, atopic eczema and subjective symptoms were significantly alleviated in all the groups; the SCORAD scores (interquartile range) decreased from 13 (range, 4-29) to 8 (range, 0-29) units in the placebo group, from 19 (range, 4-47) to 5 (range, 0-18) units in the viable LGG group, and from 15 (range, 0-29) to 7 (range, 0-26) units in the heat-inactivated LGG group. The decrease in the SCORAD scores within the viable LGG group tended to be greater than within the placebo group. The treatments did not appear to affect the bacterial numbers within the genera enumerated. CONCLUSIONS: Supplementation of infant formulas with viable but not heat-inactivated LGG is a potential approach for the management of atopic eczema and cow's milk allergy.

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Research field: Infant & Children's Nutrition, Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Other
Reference number: 0612

Costa-Ribeiro, et al. Limitations of probiotic therapy in acute, severe dehydrating diarrhea. J.Pediatr.Gastroenterol.Nutr. 2003;36:112-115

Abstract: BACKGROUND: Recent studies have shown that probiotics, most commonly, may be useful in treating acute gastroenteritis. However, beneficial effects appear to be limited to a modest decrease in the duration of diarrhea. No studies have evaluated this therapy in moderate to severe dehydrating diarrhea in a metabolic facility. METHODS: Male children less than 2 years of age were admitted to a metabolic unit of the Department of Pediatrics at the Federal University of Bahia, Brazil, with moderate dehydration and were randomized in a double-blind, placebo-controlled fashion. Oral rehydration solution (ORS) was administered per protocol and either placebo or was given in combination with the ORS. Output of urine, stool, and vomitus was recorded along with stool weight, nude body weight, and standard laboratory assessments for hydration. RESULTS: There was no significant reduction in diarrhea duration and stool output in the group. However, Kaplan-Meier survival analysis demonstrated that, even in moderate to severe diarrhea, resolution of the illness occurred so rapidly, that statistically significant benefits of probiotic therapy could not be demonstrated. CONCLUSION: Our data implies that colonization must occur before benefits of probiotics can be realized. Probiotics are, therefore, likely to be of limited benefit in treating diarrheal illnesses of short duration such as viral enteritis. The beneficial effects of probiotics may be limited to prophylactic usage in high-risk populations.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Capsule
Reference number: 0573

Kalliomaki, et al. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 2003;361:1869-1871

Abstract: Perinatal administration of the probiotic Lactobacillus rhamnosus strain GG (ATCC 53103), reduces incidence of atopic eczema in at-risk children during the first 2 years of life (infancy). We have therefore assessed persistence of the potential to prevent atopic eczema at 4 years. Atopic disease was diagnosed on the basis of a questionnaire and a clinical examination. 14 of 53 children receiving lactobacillus had developed atopic eczema, compared with 25 of 54 receiving placebo (relative risk 0.57, 95% CI 0.33-0.97). Skin prick test reactivity was the same in both groups: ten of 50 children previously given lactobacillus compared with nine of 50 given placebo tested positive. Our results suggest that the preventive effect of lactobacillus GG on atopic eczema extends beyond infancy.

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Research field: Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: ≥ 5 billion
Product formulation: Capsule
Reference number: 0945

Helin, et al. No effect of oral treatment with an intestinal bacterial strain, Lactobacillus rhamnosus (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. Allergy 2002;57:243-246

Abstract: BACKGROUND: Oral probiotic bacteriotherapy with Lactobacillus rhamnosus has given promising results in small children with food allergy. We studied the effects of similar therapy in teenagers and young adults, who were allergic to birch pollen and apple food and had intermittent symptoms of atopic allergy and/or mild asthma. METHODS: We conducted a double-blind, placebo-controlled study, in which respiratory and eye symptoms and use of medications in two groups were compared. Open oral challenge tests with a slice of apple were performed trice: before, during and after the birch-pollen season. There were 18 patients in each group. They used Lactobacillus rhamnosus for 5.5 months; 2.5 months before the pollen season, 1 month during the season (May), and 2 months after. RESULTS: The results were negative. The treatment did not alleviate the symptoms of the patients or reduce their use of medication during the birch-pollen season or the subsequent 2 months. The treatment did not significantly affect the symptoms caused by apple in the oral challenge tests. CONCLUSIONS: We found no indication of a beneficial treatment effect in our patients. As the number of patients was relatively small, conclusions should be drawn with caution.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Other
Reference number: 0587

Rautava, et al. Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant. J.Allergy Clin.Immunol. 2002;109:119-121

Abstract: The prevalence of atopic diseases is increasing throughout the Western world, and means of primary prevention are needed to reverse this trend. The role of breast-feeding, the best source of infant nutrition, in protection against atopic disease remains elusive. In this double-blinded, placebo-controlled study of 62 mother-infant pairs, it is shown that administering probiotics to the pregnant and lactating mother increased the immunoprotective potential of breast milk, as assessed by the amount of anti-inflammatory transforming growth factor beta2 (TGF-beta2) in the milk (2885 pg/mL [95% CI, 1624-4146] in mothers receiving probiotics vs 1340 pg/mL [95% CI, 978-1702] in mothers receiving placebo; P =.018). The risk of developing atopic eczema during the first 2 years of life in infants whose mothers received probiotics was significantly reduced in comparison with that in infants whose mothers received placebo (15% and 47%, respectively; relative risk, 0.32 [95% CI, 0.12-0.85]; P =.0098). Maternal atopy was a clear risk factor for atopic eczema in the infant. The infants most likely to benefit from maternal probiotic supplementation were those with an elevated cord blood IgE concentration. Administering probiotics during pregnancy and breast-feeding thus offers a safe and effective mode of promoting the immunoprotective potential of breast-feeding and provides protection against atopic eczema during the first 2 years of life.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 130 - 260 million
Product formulation: Fermented milk
Reference number: 0574

Hatakka, 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(7298):1327

Abstract: OBJECTIVE: To examine whether long term consumption of a probiotic milk could reduce gastrointestinal and respiratory infections in children in day care centres. DESIGN: Randomised, double blind, placebo controlled study over seven months. SETTING: 18 day care centres in Helsinki, Finland. PARTICIPANTS: 571 healthy children aged 1-6 years: 282 (mean (SD) age 4.6 (1.5) years) in the intervention group and 289 (mean (SD) age 4.4 (1.5) years) in the control group. Intervention: Milk with or without Lactobacillus GG. Average daily consumption of milk in both groups was 260 ml. MAIN OUTCOME MEASURES: Number of days with respiratory and gastrointestinal symptoms, absences from day care because of illness, respiratory tract infections diagnosed by a doctor, and course of antibiotics. RESULTS: Children in the Lactobacillus group had fewer days of absence from day care because of illness (4.9 (95% confidence interval 4.4 to 5.5) v 5.8 (5.3 to 6.4) days, 16% difference, P=0.03; age adjusted 5.1 (4.6 to 5.6) v 5.7 (5.2 to 6.3) days, 11% difference, P=0.09). There was also a relative reduction of 17% in the number of children suffering from respiratory infections with complications and lower respiratory tract infections (unadjusted absolute % reduction -8.6 (-17.2 to -0.1), P=0.05; age adjusted odds ratio 0.75 (0.52 to 1.09), P=0.13) and a 19% relative reduction in antibiotic treatments for respiratory infection (unadjusted absolute % reduction -9.6 (-18.2 to -1.0), P=0.03; adjusted odds ratio 0.72 (0.50 to 1.03), P=0.08) in the Lactobacillus group. CONCLUSIONS: Lactobacillus GG may reduce respiratory infections and their severity among children in day care. The effects of the probiotic Lactobacillus GG were modest but consistently in the same direction.

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Research field: Infant & Children's Nutrition and Oral Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 0.1-0.3 billion
Product formulation: Fermented milk
Reference number: 0575

Näse, et al. Effect of long-term consumption of a probiotic bacterium, Lactobacillus rhamnosus GG, in milk on dental caries and caries risk in children. Caries Res. 2001;35(6):412-420

Abstract: Lactobacillus rhamnosus GG, ATCC (LGG), has shown antagonism to many bacteria including mutans streptococci. This randomized, double-blind, placebo-controlled intervention study was designed to examine whether milk containing LGG has an effect on caries and the risk of caries in children when compared with normal milk. 594 children, 1-6 years old, from 18 municipal day-care centres were included. The children received the milk with meals from coded containers 5 days a week in the day-care centres for 7 months. The children's oral health was recorded at baseline and at the end, using WHO criteria. The caries risk was calculated based on clinical and microbiological data, comprising mutans streptococcus levels from dental plaque and saliva. The risk was classified as high if the child had a dmft/DMFT or initial caries score >0, and a mutans streptococcus count > or = 10(5) CFU/ml. The results showed less dental caries in the LGG group and lower mutans streptococcus counts at the end of the study. LGG was found to reduce the risk of caries significantly (OR = 0.56, p = 0.01; controlled for age and gender, OR = 0.51, p = 0.004). The effect was particularly clear in the 3- to 4-year-olds. Thus, milk containing the probiotic LGG bacteria may have beneficial effects on children's dental health.

Research field: Infant & Children's Nutrition and Immune Health

Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Capsule
Reference number: 0572

Kalliomaki, et al. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001;357(9262):1076-1079

Abstract: BACKGROUND: Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of Lactobacillus GG (which is safe at an early age and effective in treatment of allergic inflammation and food allergy). METHODS: In a double-blind, randomised placebo-controlled trial we gave Lactobacillus GG prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Chronic recurring atopic eczema, which is the main sign of atopic disease in the first years of life, was the primary endpoint. FINDINGS: Atopic eczema was diagnosed in 46 of 132 (35%) children aged 2 years. Asthma was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0.51 [95% CI 0.32-0.84]). The number needed to treat was 4.5 (95% CI 2.6-15.6). INTERPRETATIONS: Lactobacillus GG was effective in prevention of early atopic disease in children at high risk. Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics, for prevention of atopic disease.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Capsule
Reference number: 0924

Gupta, et al. Is lactobacillus GG helpful in children with Crohn's disease? Results of a preliminary, open-label study. J.Pediatr.Gastroenterol.Nutr. 2000;31:453-457

Abstract: BACKGROUND: Lactobacillus GG is a safe probiotic bacterium known to transiently colonize the human intestine. It has been found to be useful in treatment of several gastrointestinal conditions characterized by increased gut permeability. In the current study, the efficacy of Lactobacillus GG was investigated in children with Crohn's disease. METHODS: In this open-label pilot evaluation viewed as a necessary preliminary step for a possible subsequent randomized placebo-controlled trial, four children with mildly to moderately active Crohn's disease were given Lactobacillus GG (10(10) colony-forming units [CFU]) in enterocoated tablets twice a day for 6 months. Changes in intestinal permeability were measured by a double sugar permeability test. Clinical activity was determined by measuring the pediatric Crohn's disease activity index. RESULTS: There was a significant improvement in clinical activity 1 week after starting Lactobacillus GG, which was sustained throughout the study period. Median pediatric Crohn's disease activity index scores at 4 weeks were 73% lower than baseline. Intestinal permeability improved in an almost parallel fashion. CONCLUSIONS: Findings in this pilot study show that Lactobacillus GG may improve gut barrier function and clinical status in children with mildly to moderately active, stable Crohn's disease. Randomized, double-blind, placebo-controlled trials are warranted for a final assessment of the efficacy of Lactobacillus GG in Crohn's disease.

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Research field: Infant & Children's Nutrition
Study type: Human study
Probiotic strain: B. animalis subsp. lactis BB-12 and L. rhamnosus LGG®
Dosage CFU/day: Child-dependent
Product formulation: Milk powder
Reference number: 0388

Isolauri, et al. Probiotics in the management of atopic eczema. Clin.Exp.Allergy 2000;30(11):1604-1610

Abstract: BACKGROUND: Over the last two decades the incidence of allergic diseases has increased in industrialized countries, and consequently new approaches have to be explored. OBJECTIVE: The potential of probiotics to control allergic inflammation at an early age was assessed in a randomized double-blind placebo-controlled study. METHODS: A total of 27 infants, mean age 4.6 months, who manifested atopic eczema during exclusive breast-feeding and who have had no exposure to any infant or substitute formula were weaned to probiotic-supplemented, Bifidobacterium lactis Bb-12 or Lactobacillus strain GG (ATCC 53103), extensively hydrolysed whey formulas or to the same formula without probiotics. The extent and severity of atopic eczema, the growth and nutrition of infants, and concentrations of circulating cytokines/chemokines and soluble cell surface adhesion molecules in serum and methyl-histamine and eosinophilic protein X in urine were determined. RESULTS: The SCORAD score reflecting the extent and severity of atopic eczema was 16 (7-25) during breast-feeding, median (interquartile range). After 2 months, a significant improvement in skin condition occurred in patients given probiotic-supplemented formulas, as compared to the unsupplemented group; chi(2) = 12.27, P = 0.002. SCORAD decreased in the Bifidobacterium lactis Bb-12 group to 0 (0-3.8), and in the Lactobacillus GG group to 1 (0.1-8.7), vs unsupplemented 13.4 (4.5-18.2), median (interquartile range), in parallel with a reduction in the concentration of soluble CD4 in serum and eosinophilic protein X in urine. CONCLUSION: The results provide the first clinical demonstration of specific probiotic strains modifying the changes related to allergic inflammation. The data further indicate that probiotics may counteract inflammatory responses beyond the intestinal milieu. The combined effects of these probiotic strains will guide infants through the weaning period, when sensitization to newly encountered antigens is initiated. The probiotic approach may thus offer a new direction in the search for future foods for allergy treatment and prevention strategies.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Capsule
Reference number: 0577

Pessi, et al. Interleukin-10 generation in atopic children following oral Lactobacillus rhamnosus GG. Clin.Exp.Allergy 2000;30(12):1804-1808

Abstract: Oral Lactobacillus rhamnosus GG ingestion for 5 days to 4 weeks has been shown to alleviate clinical symptoms of gastrointestinal inflammation and atopic dermatitis. To determine whether oral Lactobacillus rhamnosus GG may act by generating immunosuppressive mediator in atopic children. Lactobacillus rhamnosus GG (ATCC 53103) at a daily dose of 2 x 1010 cfu was added for 4 weeks to the diets of nine children (mean age, 21 months) with atopic dermatitis. Blood and faecal samples were collected before supplementation and at early (2 weeks) and late stage (4 and 8 weeks from the beginning). The concentrations of interleukin-6 (IL-6), IL-10, IL-12, tumour necrosis factor-alpha (TNFalpha) and interferon-gamma (IFNgamma) in sera, as well as the production of IL-2, IL-4, IL-10 and IFNgamma in mitogen-induced peripheral blood mononuclear cells, were assessed. Secretory IgA and TNFalpha were also determined in faeces. The serum IL-10 concentration differed significantly between before, early and late samples ($P < 0.001$) due to the elevation of serum IL-10 in the later phase of oral Lactobacillus rhamnosus GG ingestion. The enhancement of IL-10 production in mitogen-induced cultures preceded the rise in serum IL-10. The enhanced IL-10 generation in vivo substantiates the anti-inflammatory properties of specific probiotic bacteria strains, and provides an additional reason for considering such treatments for patients with intestinal inflammation.

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Research field: Infant & Children's Nutrition, Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: NA
Product formulation: NA
Reference number: 1241

Vanderhoof, et al. In children receiving antibiotics, does coadministration of lactobacillus GG reduce the incidence of diarrhea? West.J.Med. 2000;173:397

Abstract: NA

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 37 billion
Product formulation: Capsule
Reference number: 0558

Oberhelman, et al. A placebo-controlled trial of Lactobacillus GG to prevent diarrhea in undernourished Peruvian children. J.Pediatr. 1999;134:15-20

Abstract: OBJECTIVE: Lactobacillus GG (L-GG), an acid- and bile-resistant strain that colonizes the intestinal mucosa, has been used to manage diarrhea in children. Our objective was to evaluate the prophylactic use of L-GG to prevent diarrhea in children at high risk from a developing country in a randomized, placebo-controlled trial. STUDY DESIGN: Two hundred four undernourished children 6 to 24 months old from an indigent peri-urban Peruvian town received either L-GG or placebo in flavored gelatin once daily, 6 days a week, for 15 months. Episodes of diarrhea were documented by daily home visits, and diagnostic studies were done in a subset of cases. Recovery of L-GG in stool from subjects and from family contacts was examined. RESULTS: Subjects in the L-GG group had significantly fewer episodes of diarrhea (5.21 episodes diarrhea/child/year ['ecy'] L-GG group, 6. 02 ecy placebo group; P =.028). The decreased incidence of diarrhea in the L-GG group was greatest in the 18- to 29-month age group (P =. 004) and was largely limited to nonbreastfed children (Breastfed: 6. 59 ecy L-GG, 6.32 ecy placebo, P =.7; Nonbreastfed: 4.69 ecy L-GG, 5. 86 ecy placebo, P =.005). The duration of diarrhea episodes and the causes of diarrhea were similar in both groups, except adenovirus was more common in the placebo group. CONCLUSION: L-GG supplementation may be useful as a prophylactic measure to control diarrhea in undernourished children at increased risk, especially nonbreastfed children in the toddler age group.; PIP: This article features a placebo-controlled trial of Lactobacillus GG (L-GG) for diarrhea prevention in undernourished children in Peru. The purpose of the study was to evaluate the use of L-GG as prophylactic treatment for diarrhea. The study population included 204 undernourished children aged 6-24 months, 99 of which were on L-GG and 105 on placebo. Subjects were followed by daily home visits to document diarrhea episodes and diagnostic studies were conducted. Results revealed that children receiving L-GG experienced fewer episodes of diarrhea, which were more pronounced among 18-29 month old children and largely limited to non-breast-fed children. Moreover, the duration of diarrhea episodes and its causes were similar in both groups, except that adenovirus was detected more frequently in the placebo group. In conclusion, L-GG supplementation would decrease diarrhea incidence in high-risk children.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 40 billion
Product formulation: Capsule
Reference number: 0550

Arvola, et al. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. Pediatrics 1999;104:e64

Abstract: OBJECTIVES: Antimicrobial treatment may disturb the colonization resistance of gastrointestinal microflora, which may induce clinical symptoms, most commonly diarrhea. The severity of antibiotic-associated diarrhea may range from a brief, self-limiting disease to devastating diarrhea with electrolyte disturbances, dehydration, crampy abdominal pain, pseudomembranous colitis, toxic megacolon, or even death. The incidence of diarrhea in children receiving a single antimicrobial treatment is unclear. In addition to more critical use of antimicrobials, adjunctive preventive measures to antibiotic-associated diarrhea are needed. The objective of this study was to evaluate the incidence of diarrhea after antimicrobial treatment in children with no history of antimicrobial use during the previous 3 months. Another aim of this study was to assess the preventive potential of Lactobacillus rhamnosus GG (Lactobacillus GG; American Type Culture Collection 53103), a probiotic strain with a documented safety record and a therapeutic effect in viral gastroenteritis on antibiotic-associated diarrhea. METHODS: Oral antimicrobial agents were prescribed for the treatment of acute respiratory infections at the clinics of the Health Care Center of the City of Tampere or Tampere University Hospital, Finland, to 167 patients who were invited to participate in the study. Of the patients, 48 were lost to follow-up; therefore, the final study population consisted of 119 children from 2 weeks to 12. 8 years of age (mean: 4.5 years). All study subjects met the inclusion criteria: they had not received any antimicrobial medication during the previous 3 months, they did not suffer from gastrointestinal disorders, and they did not need intravenous antimicrobial treatment. The patients were randomized to receive placebo or 2 x 10(10) colony-forming units of Lactobacillus GG in capsules given twice daily during the antimicrobial treatment. Lactobacillus GG and placebo capsules were indistinguishable in appearance and taste. The parents kept a daily symptom diary and recorded stool frequency and consistency at home for 3 months. Diarrhea was defined as at least three watery or loose stools per day for a minimum of 2 consecutive days. In the case of diarrhea, viral (adenovirus, rotavirus, calicivirus and astrovirus) and bacterial (Salmonella, Shigella, Yersinia, Campylobacter, Clostridium difficile, Staphylococcus aureus, and yeasts) analyses were studied in fecal samples. The metabolic activity of the gut microflora was assessed by analysis of fecal urease, beta-glucosidase, and beta-glucuronidase activities. The primary outcome measure was diarrhea during the first 2 weeks after the beginning of the antimicrobial treatment, because this period most likely reflects the effects of antimicrobial use. Secondary outcome measures were the activities of fecal urease, beta-glucuronidase, and beta-glucosidase. RESULTS: On the entire follow-up, 80% of any gastrointestinal symptoms were reported during the first 2 weeks after the beginning of the antimicrobial treatment. The incidence of diarrhea was 5% in the Lactobacillus GG group and 16% in the placebo group within 2 weeks of antimicrobial therapy (chi(2) = 3.82). The treatment effect (95% confidence interval) of Lactobacillus GG was -11% (-21%-0%). In diarrheal episodes, the viral and bacterial analyses were positive for Clostridium difficile in 2 cases and for Norwalk-like calicivirus in 3 cases. The age of the patients with diarrhea was between 3 months and 5 years in 75% of cases in both groups. The severity of diarrhea was comparable in the study groups, as evidenced by similar stool frequency (mean: 5 per day; range: 3-6) and the duration of diarrhea (mean: 4 days; range: 2-8). The activities of fecal urease and beta-glucuronidase, but not beta-glucosidase, changed significantly after the beginning of the antimicrobial treatment in the Lactobacillus GG group and in the placebo group alike. (ABSTRACT TRUNCATED)

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10-20 billion
Product formulation: Capsule
Reference number: 0551

Vanderhoof, et al. Lactobacillus GG in the prevention of antibiotic-associated diarrhea in children. J.Pediatr. 1999;135:564-568

Abstract: OBJECTIVE: The objective of this study was to determine the efficacy of Lactobacillus casei sps. rhamnosus (Lactobacillus GG) (LGG) in reducing the incidence of antibiotic-associated diarrhea when coadministered with an oral antibiotic in children with acute infectious disorders. STUDY DESIGN: Two hundred two children between 6 months and 10 years of age were enrolled; 188 completed all phases of the protocol. LGG, 1 x 10(10) - 2 x 10(10) colony forming units per day, or comparable placebo was administered in a double-blind randomized trial to children receiving oral antibiotic therapy in an outpatient setting. The primary caregiver was questioned every 3 days regarding the incidence of gastrointestinal symptoms, predominantly stool frequency and consistency, through telephone contact by blinded investigators. RESULTS: Twenty-five placebo-treated but only 7 LGG-treated patients had diarrhea as defined by liquid stools numbering 2 or greater per day. Lactobacillus GG overall significantly reduced stool frequency and increased stool consistency during antibiotic therapy by the tenth day compared with the placebo group. CONCLUSION: Lactobacillus GG reduces the incidence of antibiotic-associated diarrhea in children treated with oral antibiotics for common childhood infections.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Other
Reference number: 0600

Rautanen, et al. Management of acute diarrhoea with low osmolarity oral rehydration solutions and Lactobacillus strain GG. Arch.Dis.Child. 1998;79:157-160

Abstract: Two hypotonic oral rehydration solutions with osmolarities of 224 mosmol/l (Na+ 60 mmol/l, glucose 84 mmol/l) and 204 mosmol/l (Na+ 60 mmol/l, glucose 64 mmol/l), respectively, and oral treatment with Lactobacillus GG were evaluated in a double blind trial in children aged 6-36 months hospitalised for acute diarrhoea. Early administration of Lactobacillus GG at the start of oral rehydration resulted in the shortest duration of diarrhoea, best weight gain, and fastest correction of acidosis. A reduced osmolarity oral rehydration solution (224 mosmol/l) combined with early administration of Lactobacillus GG is an effective treatment for acute diarrhoea in young children; further reduction of osmolarity may not be beneficial.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 40 billion
Product formulation: Milk powder
Reference number: 0579

Majamaa, Isolauri. Probiotics: a novel approach in the management of food allergy. J.Allergy Clin.Immunol. 1997;99:179-185

Abstract: BACKGROUND: The gastrointestinal microflora is an important constituent of the gut mucosal defense barrier. We have previously shown that a human intestinal floral strain, Lactobacillus GG (ATCC 53103), promotes local antigen-specific immune responses (particularly in the IgA class), prevents permeability defects, and confers controlled antigen absorption. OBJECTIVE: The aim of this study was to evaluate the clinical and immunologic effects of cow's milk elimination without (n = 14) and with (n = 13) the addition of Lactobacillus GG (5 x 10(8) colony-forming units/gm formula) in an extensively hydrolyzed whey formula in infants with atopic eczema and cow's milk allergy. The second part of the study involved 10 breast-fed infants who had atopic eczema and cow's milk allergy. In this group Lactobacillus GG was given to nursing mothers. METHODS: The severity of atopic eczema was assessed by clinical scoring. The concentrations of fecal alpha 1- antitrypsin, tumor necrosis factor-alpha, and eosinophil cationic protein were determined as markers of intestinal inflammation before and after dietary intervention. RESULTS: The clinical score of atopic dermatitis improved significantly during the 1-month study period in infants treated with the extensively hydrolyzed whey formula fortified with Lactobacillus GG. The concentration of alpha 1-antitrypsin decreased significantly in this group (p = 0.03) but not in the group receiving the whey formula without Lactobacillus GG (p = 0.68). In parallel, the median (lower quartile to upper quartile) concentration of fecal tumor necrosis factor-alpha decreased significantly in this group, from 709 pg/gm (91 to 1131 pg/gm) to 34 pg/gm (19 to 103 pg/gm) (p = 0.003), but not in those receiving the extensively hydrolyzed whey formula only (p = 0.38). The concentration of fecal eosinophil cationic protein remained unaltered during therapy. CONCLUSION: These results suggest that probiotic bacteria may promote endogenous barrier mechanisms in patients with atopic dermatitis and food allergy, and by alleviating intestinal inflammation, may act as a useful tool in the treatment of food allergy.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 10 billion
Product formulation: Other
Reference number: 0564

Shornikova, et al. A trial in the Karelian Republic of oral rehydration and Lactobacillus GG for treatment of acute diarrhoea. Acta Paediatr. 1997;86:460-465

Abstract: In a controlled trial in Petrozavodsk, Karelia, the effects of oral rehydration and Lactobacillus strain GG (LGG) on recovery from acute diarrhoea (27% rotavirus, 21% bacterial aetiology) were studied in 123 children aged between 1 and 36 months of age. On admission to hospital, the patients were first randomized to receive either isotonic oral rehydration solution (ORS) with osmolarity 311 mosmol/l and sodium 90 mmol/l (WHO-ORS), or a hypotonic ORS with osmolarity 224 mosmol/l and sodium 60 mmol/l (Light-ORS), and thereafter randomized to receive either 5 x 10(9) colony forming units of LGG or a matching placebo. The two ORS performed equally for acute rehydration, and oral rehydration with either ORS was associated with a shorter duration of diarrhoea than intravenous rehydration (p = 0.036). Patients receiving LGG had a significantly shorter duration of watery diarrhoea [mean (SD) 2.7 (2.2) days] than those receiving the placebo [3.7 (2.8) days, p = 0.03]. LGG significantly shortened the duration of rotavirus diarrhoea but not diarrhoea with confirmed bacterial aetiology.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 0,25 billion
Product formulation: Unknown
Reference number: 0912

Gronlund, et al. Lactobacillus GG supplementation does not reduce faecal colonization of Klebsiella oxytoca in preterm infants. *Acta Paediatr*, *86*(4), 440–441, (1997)

Abstract: NA

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: NA
Reference number: 0608

Malin, et al. Dietary therapy with Lactobacillus GG, bovine colostrum or bovine immune colostrum in patients with juvenile chronic arthritis: evaluation of effect on gut defence mechanisms. Inflammopharmacology 1997:219-236

Abstract: The effect of dietary therapy with a human Lactobacillus strain GG (ATCC 53103), bovine colostrum, or bovine immune colostrum with specific antibodies against anaerobic intestinal bacteria on gut defence mechanisms were studied in juvenile chronic arthritis. Thirty patients with juvenile chronic arthritis were randomly allocated to receive a freeze-dried powder of Lactobacillus GG, or bovine colostrum, or bovine immune colostrum, for a two-week period. Immunologic and non-immunologic gut defence mechanisms were indirectly investigated in blood and faecal samples. In patients receiving Lactobacillus GG, the median (interquartile range) frequency of immunoglobulin-secreting cells, determined by enzyme-linked immunospot assay, increased in the IgA class from 1840 (690-2530) to 3480 (1030-13 170)/10(6) cells; p=0.02. Likewise the median (interquartile range) frequency of specific antibody-secreting cells against dietary antigens increased during the Lactobacillus GG therapy in the IgM class from 3.8 (1.4-5.0) to 11.2 (5.0-30.0)/10(6) cells; p=0.02. In addition, Lactobacillus GG therapy decreased the median (interquartile range) activity of faecal urease, which has been associated with mucosal tissue damage, from 40.3 (21.7-54.3) to 28.6 (24.5-49.4) nmol. min(-1) (mg protein)(-1); p=0.10, while, in patients receiving bovine colostrum, faecal urease activity increased (from 42.2 to 80.6; p=0.04). All findings were transient. We suggest that gut defence mechanisms are disturbed in juvenile chronic arthritis and we further suggest that orally administered Lactobacillus GG has a potential to reinforce the mucosal barrier mechanisms in juvenile chronic arthritis.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: NA
Product formulation: Yougurt
Reference number: 1051

Malin, et al. Increased bacterial urease activity in faeces in juvenile chronic arthritis: evidence of altered intestinal microflora? Br.J.Rheumatol. 1996;35:689-694

Abstract: The intestinal microflora was indirectly evaluated in juvenile chronic arthritis (JCA) by analysing enzyme activities--urease, beta-glucosidase and beta-glucuronidase--in faeces. In 18 out of 26 JCA patients, the illness had been diagnosed during the past year. The control group was composed of eight age-matched control patients and 18 family members of JCA patients (3-36 yr). The mean [95% confidence interval (CI)] urease activity, but not the activities of beta-glucosidase and beta-glucuronidase, in faeces from the JCA group differed from that in the control group: 32.3 (26.6-38.1) nmol/min/mg protein vs 24.0 (16.8-31.6), P = 0.07. The difference was more marked in a comparison of JCA patients with family members (P = 0.03). In a subgroup of subjects, the effect of 10 days oral bacteriotherapy with Lactobacillus GG on faecal enzyme activities was then investigated (n = 8 JCA patients, n = 8 control patients). This short-term oral bacteriotherapy reduced the increased urease activity in faeces of JCA patients. Keeping in mind the small number of subjects, it may be inferred from the present results that the increased urease activity in JCA is specific for the disease, suggesting altered intestinal microflora in JCA.

Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: NA
Reference number: 0672

Malin, et al. Promotion of IgA immune response in patients with Crohn's disease by oral bacteriotherapy with Lactobacillus GG. Ann.Nutr.Metab. 1996;40:137-145

Abstract: The effect of oral bacteriotherapy with human Lactobacillus casei strain GG (10(10) colony-forming units twice daily for 10 days) was investigated in Crohn's disease and in juvenile chronic arthritis which are chronic inflammatory diseases associated with impaired mucosal barrier function. During oral bacteriotherapy, the gut immune response was indirectly assessed by solid-phase enzyme-linked immunoassay in 14 children with Crohn's disease, in 9 with juvenile chronic arthritis, and in 7 controls. The immunostimulatory effect of Lactobacillus GG was specific for Crohn's disease, irrespective of its activity: the mean (95% confidence interval) number of specific antibody secreting cells in the IgA class to beta-lactoglobulin increased significantly from 0.2 (0.04-1.3) to 1.4 (0.3-6.0)/10(6) cells and to casein from 0.3 (0.1-1.4) to 1.0 (0.2-4.8)/10(6) cells. The results indicate that orally administered Lactobacillus GG has the potential to increase the gut IgA immune response and thereby to promote the gut immunological barrier. Consequently, Lactobacillus GG could provide an adjunct nutritional therapy for Crohn's disease.

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Research field: Infant & Children's Nutrition and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 100 billion
Product formulation: NA
Reference number: 0620

Isolauri, et al. Improved immunogenicity of oral D x RRV reassortant rotavirus vaccine by Lactobacillus casei GG. Vaccine 1995;13:310-312

Abstract: In a search for new strategies to improve oral vaccination, the effect of orally administered Lactobacillus casei strain GG (LGG) in conjunction with D x RRV rhesus-human reassortant live oral rotavirus vaccine was tested in 2-5-month-old infants. Infants who received LGG showed an increased response with regard to rotavirus-specific IgM secreting cells, measured using an ELISPOT technique, on day 8 after vaccination. In infants receiving LGG or placebo, respectively, a rotavirus IgM seroconversion was detected in 26/27 (96%), versus 23/27 (85%) cases (p = 0.15) and rotavirus IgA seroconversion was detected in 26/28 (93%) versus 20/27 (74%) cases (p = 0.05). These findings suggest that LGG has an immunostimulating effect on oral rotavirus vaccination. The clinical significance of LGG-enhanced immune responses to oral vaccines should be further evaluated.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Other
Reference number: 0566

Majamaa, et al. Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. J.Pediatr.Gastroenterol.Nutr. 1995;20:333-338

Abstract: We compared different lactic acid bacteria for their effect on the immune response to rotavirus in children with acute rotavirus gastroenteritis. After initial oral rehydration, 49 children aged 6 to 35 months with rotavirus gastroenteritis randomly received either Lactobacillus casei subsp. casei strain GG (LGG), L. casei subsp. rhamnosus (Lactophilus), or a combination of Streptococcus thermophilus and L. delbruckii subsp. bulgaricus (Yalacta) twice daily for 5 days. Serum antibodies to rotavirus, total number of immunoglobulin-secreting cells (ISC), and specific antibody-secreting cells (sASC) to rotavirus were measured at the acute stage and at convalescence. The mean (SD) duration of diarrhea was 1.8 (0.8) days in children who received LGG, 2.8 (1.2) days in those receiving Lactophilus, and 2.6 (1.4) days in those receiving Yalacta ($F = 3.3$, $p = 0.04$). The ISC response was comparable in the three study groups, but the rotavirus-specific immune responses were different. LGG therapy was associated with an enhancement of IgA sASC to rotavirus and serum IgA antibody level at convalescent stage. We conclude that certain strains of lactic acid bacteria, particularly LGG, promote serum and intestinal immune responses to rotavirus, and thus may be important in establishing immunity against rotavirus reinfections.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health and Immune Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20-200 billion
Product formulation: Other
Reference number: 0582

Kaila, et al. Viable versus inactivated lactobacillus strain GG in acute rotavirus diarrhoea. Arch.Dis.Child. 1995;72:51-53

Abstract: The effect of viable or heat inactivated human Lactobacillus casei strain GG on rotavirus immune responses in patients with rotavirus diarrhoea was assessed. Rotavirus serum IgA enzyme immunoassay antibody responses were higher in infants treated with viable L casei strain GG than in those treated with inactivated L casei strain GG. There was a significant difference at convalescence with rotavirus specific IgA secreting cells found in 10/12 infants receiving viable but only 2/13 infants receiving inactivated L casei strain GG. The results indicate that viable L casei strain GG stimulate rotavirus specific IgA antibody responses, theoretically significant in the prevention of reinfections.

Research field: Infant & Children's Nutrition, Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20 billion
Product formulation: Freezedried powder
Reference number: 0567

Isolauri, et al. Oral bacteriotherapy for viral gastroenteritis. Dig.Dis.Sci. 1994;39(12):2595-2600

Abstract: The effect of orally administered lactobacilli on acute rotavirus diarrhea was tested in 42 well-nourished children ages 5-28 months. After oral rehydration, the patients were randomized to a study group, receiving human Lactobacillus casei strain GG 10(10) colony-forming units twice daily for five days, or a control group not given lactobacilli. Lactobacillus GG was found in the feces in 83% of the study group. The diarrheal phase was shortened in that group. Dietary supplementation with lactobacilli significantly influenced the bacterial enzyme profile: urease activity during diarrhea transiently increased in the control group but not in the study group; F = 8.6, P = 0.01. No intergroup differences were found in beta-glucuronidase, beta-glucosidase, and glycocholic acid hydrolase levels. We suggest that rotavirus infection gives rise to biphasic diarrhea, the first phase being an osmotic diarrhea and the second associated with overgrowth of specifically urease-producing bacteria. Oral bacteriotherapy appears a promising means to counteract the disturbed microbial balance.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 0.2 billion
Product formulation: Milk powder
Reference number: 0603

Stansbridge, et al. Effects of feeding premature infants with Lactobacillus GG on gut fermentation. Arch.Dis.Child. 1993;69:488-492

Abstract: The study aimed to find out whether gut colonisation of premature babies with a probiotic, Lactobacillus GG, modified enteric carbohydrate fermentation. Twenty preterm infants were randomised to receive Lactobacillus GG 10(8) colony forming units twice a day for two weeks or to a control group. Faecal short chain fatty acids (SCFAs), ethanol, and urinary 2,3-butanediol, were measured in parallel with microbiological studies. Lactobacillus GG colonised nine babies. From 1-28 days of age faecal SCFAs did not differ significantly from controls. Median and ranges were (treated and controls, respectively): acetic acid: 173 (trace-799), 166 (trace-700); propionic acid: 44 (trace-169), 37 (11-229); butyric acid: 31 (5-107), 37 (2-118) mumol/g dry weight. Ethanol was detected in more faecal samples from treated babies (65% v 37%), and at higher concentration (6.3 (trace-40) v 3.3 (0.6-8.8; one 229) mumol/g). 2,3-Butanediol was found in 66% of urine samples from treated babies and 58% from controls. On 83% of these occasions Klebsiella sp, Enterobacter sp, or Serratia sp were cultured from faeces. Lactobacillus GG had no obvious adverse effects on nutritionally important SCFAs. The small increase in ethanol excretion is unlikely to have clinical significance.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 0.2 billion
Product formulation: Milk powder
Reference number: 0596

Millar, et al. Enteral feeding of premature infants with Lactobacillus GG. Arch.Dis.Child. 1993;69:483-487

Abstract: The objectives of this study were to determine whether or not the probiotic Lactobacillus GG can colonise the immature bowel of premature infants and if so, does colonisation result in a reduction of the size of the bowel reservoir of nosocomial pathogens such as enterobacteriaceae, enterococci, yeasts or staphylococci, and does colonisation with Lactobacillus GG have any effect on the clinical progress and outcome. Twenty preterm infants with a gestational age of 33 weeks or less who were resident on a neonatal unit were studied from the initiation of milk feeds until discharge. The infants were randomised to receive either milk feeds or milk feeds supplemented with Lactobacillus GG 10(8) colony forming units twice a day for two weeks. The clinical features of the two groups of infants were similar. Orally administered Lactobacillus GG was well tolerated and did colonise the bowel of premature infants. However, colonisation with Lactobacillus GG did not reduce the faecal reservoir of potential pathogens and there was no evidence that colonisation had any positive clinical benefit for this particular group of infants.

Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20-200 billion
Product formulation: Fermented milk
Reference number: 0561

Kaila, et al. Enhancement of the circulating antibody secreting cell response in human diarrhea by a human Lactobacillus strain. Pediatr.Res. 1992;32:141-144

Abstract: Human Lactobacillus sp strain GG (Lactobacillus GG) administered during acute rotavirus diarrhea has been shown to promote clinical recovery. To elucidate the immune mechanisms behind such a favorable outcome, the ELISPOT (solid phase enzyme-linked immunospot) assay of Ig- and specific antibody-secreting cells among circulating lymphocytes was used, giving indirect evidence of the immunologic events in the gut. After rehydration, 39 children with acute rotavirus diarrhea, mean age 16 (SD 6) mo, randomly received either a Lactobacillus GG fermented milk product (study group) or a pasteurized yogurt (placebo group). The duration of diarrhea was significantly shorter in the study group than in the placebo group [mean 1.1 (SD 0.6) versus 2.5 (SD 1.4)d, p = 0.001]. Lactobacillus GG therapy was associated with a significantly enhanced nonspecific humoral response during the acute phase of the infection, reflected in the IgG, IgA, and IgM Ig-secreting cell numbers. At convalescence, 90% of the study group versus 46% of the placebo group had developed an IgA specific antibody-secreting cell response to rotavirus (p = 0.006). The results indicate that Lactobacillus GG promotes recovery from rotavirus diarrhea via augmentation of the local immune defense. Furthermore, specific IgA response to rotavirus is endorsed, which is possibly relevant in protection against reinfections.

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Research field: Infant & Children's Nutrition and Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 20-200 billion
Product formulation: Freezedried powder
Reference number: 0560

Isolauri, et al. A human Lactobacillus strain (Lactobacillus casei sp strain GG) promotes recovery from acute diarrhea in children. Pediatrics 1991;88:90-97

Abstract: To determine the effect of a human Lactobacillus strain (Lactobacillus casei sp strain GG, Gefilac) on recovery from acute diarrhea (82% rotavirus), 71 well-nourished children between 4 and 45 months of age were studied. After oral rehydration, the patients randomly received either Lactobacillus GG-fermented milk product, 125 g (10(10-11) colony-forming units) twice daily (group 1); Lactobacillus GG freeze-dried powder, one dose (10(10-11) colony-forming units) twice daily (group 2); or a placebo, a pasteurized yogurt (group 3) 125 g twice daily; each diet was given for 5 days, in addition to normal full diet otherwise free of fermented dairy products. The mean (SD) duration of diarrhea after commencing the therapy was significantly shorter in group 1 (1.4 [0.8] days) and in group 2 (1.4 [0.8] days) than in group 3 (2.4 [1.1] days); F = 8.70, P less than 0.001. After rehydration, each dietary group maintained a positive weight trend. The urinary lactulose-mannitol recovery ratios (means [95% confidence intervals]) on admission were 0.09 (0.03, 0.24) in group 1, 0.12 (0.07, 0.22) in group 2, and 0.08 (0.04, 0.18) in group 3; no significant alterations in intestinal permeability were observed at retesting after 2 days of realimentation. The result indicates that early nutritional repletion after rehydration causes no mucosal disruption and is beneficial for recovery from diarrhea. It is further suggested that Lactobacillus GG in the form of fermented milk or freeze-dried powder is effective in shortening the course of acute diarrhea.

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Research field: Gastrointestinal Health
Study type: Human study
Probiotic strain: L. rhamnosus LGG®
Dosage CFU/day: 2 billion
Product formulation: Other
Reference number: 0556

Oksanen, et al. Prevention of travellers' diarrhoea by Lactobacillus GG. Ann.Med. 1990;22:53-56

Abstract: A placebo-controlled double-blind study was conducted on the efficacy of Lactobacillus GG in preventing travellers' diarrhoea. Altogether 820 persons travelling on holiday to southern Turkey to two destinations were randomized into two groups receiving either Lactobacillus GG or placebo in identical sachets. On the return flight each participant completed a questionnaire indicating the incidence of diarrhoea and related symptoms during the trip. Of the original group 756 (92%) subjects completed the study acceptably. The overall incidence of diarrhoea was 43.8% (331 cases). The total incidence of diarrhoea in the placebo group was 46.5% and in the Lactobacillus GG 41.0% indicating an overall protection of 11.8%. Protection rates varied between two different destinations with the maximum protection rate reported as 39.5%. Among older age groups there was significantly less diarrhoea when compared to younger travellers. Lactobacillus GG appeared to be effective in reducing the occurrence of travellers' diarrhoea in one of the two destinations with no side effects.