Abstracts Lactobacillus Reuteri

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Randomised double blind placebo controlled trial on Lactobacillus reuteri DSM 17938: improvement in symptoms and bowel habit in functional constipation.

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Author information

Abstract

Dysbiosis may contribute to constipation and its symptoms, therefore probiotic administration could improve significantly gut health and functions. The aim of the study was to investigate the effects of a long-lasting administration of Lactobacillus reuteri DSM 17938 (LR DSM 17938) on symptoms and quality of life (QoL) score in patients with functional constipation (FC). 56 FC patients with normal colonic transit time and without anorectal disorders and pelvic floor dysfunctions completed the study. LR DSM 17938 was administered for 105 days in a randomised double-blind clinical trial (28 patients per arm). Individual and cumulative scores including the Constipaq, a modified Constipation Scoring System (CSS) that considers the patient assessment of constipation-QoL (PAC-QoL), were calculated during the preliminary visit (V0), at day 15 (end of the induction period with a LR DSM 17938 double dosage, 4×10^8 cfu), day 60 (intermediate evaluation) and day 105 (V4) after a standard dosage (2×10^8 cfu). At the end of treatment, the beneficial effect of LR DSM 17938 compared to placebo was significantly evident for symptoms related to gas content and dysbiosis (abdominal discomfort, pain and bloating), incomplete defecation and helps for defecation ($P<0.05$). At the end of the whole LR DSM 17938 treatment, a marked and positive effect on both the CSS single and the cumulative items was evident with the exception of unfruitful attempt and Bristol score. Present findings indicate that LR DSM 17938 has an effect on symptoms different from stool consistency, and they suggest that this probiotic can effectively be used in association therapy rather than as single-drug therapy in the management of FC.

KEYWORDS: *Constipaq; Lactobacillus reuteri DSM 17938; constipation; probiotics; symptoms*

Antiviral activity of Lactobacillus reuteri Protectis against Coxsackievirus A and Enterovirus 71 infection in human skeletal muscle and colon cell lines.

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BACKGROUND:

Recurrence of hand, foot and mouth disease (HFMD) pandemics continues to threaten public health. Despite increasing awareness and efforts, effective vaccine and drug treatment have yet to be available. Probiotics have gained recognition in the field of healthcare worldwide, and have been extensively prescribed to babies and young children to relieve gastrointestinal (GI) disturbances and diseases, associated or not with microbial infections. Since the faecal-oral axis represents the major route of HFMD transmission, transient persistence of probiotic bacteria in the GI tract may confer some protection against HFMD and limit transmission among children.

METHODS:

In this work, the antiviral activity of two commercially available probiotics, namely Lactobacillus reuteri Protectis (L. reuteriProtectis) and Lactobacillus casei Shirota (L. casei Shirota), was assayed against Coxsackieviruses and Enterovirus 71 (EV71), the main agents responsible for HFMD. In vitro infection set-ups using human skeletal muscle and colon cell lines were designed to assess the antiviral effect of the probiotic bacteria during entry and post-entry steps of the infection cycle.

RESULTS:

Our findings indicate that L. reuteri Protectis displays a significant dose-dependent antiviral activity against Coxsackievirus type A (CA) strain 6 (CA6), CA16 and EV71, but not against Coxsackievirus type B strain 2. Our data support that the antiviral effect is likely achieved through direct physical interaction between bacteria and virus particles, which impairs virus entry into its mammalian host cell. In contrast, no significant antiviral effect was observed with L. casei Shirota.

CONCLUSIONS:

Should the antiviral activity of L. reuteri Protectis observed in vitro be translated in vivo, such probiotics-based therapeutic approach may have the potential to address the urgent need for a safe and effective means to protect against HFMD and limit its transmission among children.

KEYWORDS: *Coxsackievirus; Enterovirus 71; Foot and mouth disease; Hand; Lactobacillus reuteri; Probiotics*

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Clinical and microbiological evaluation of the effect of Lactobacillus reuteri in the treatment of mucositis and peri-implantitis: A triple-blind randomized clinical trial.

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BACKGROUND AND OBJECTIVE:

Oral probiotics appear to improve the treatment of periodontal diseases but there is limited evidence on their efficacy in the treatment of peri-implant diseases. The objective of the present study was to evaluate, clinically and microbiologically, the effect of the oral probiotic, Lactobacillus reuteri Prodentis, as adjuvant to non-surgical mechanical therapy in implants with mucositis or peri-implantitis, placed in patients with a history of periodontal disease.

MATERIAL AND METHODS:

A randomized, controlled, parallel-design, triple-blind prospective clinical study was designed. Patients included in the study were partially edentulous and had implants with mucositis or peri-implantitis. Implants with radiographic bone loss of ≥5 mm and/or ≥50% of the implant length were excluded, and only one implant per patient was included. After non-surgical mechanical therapy, subjects were randomly assigned to take either 1 probiotic lozenge or 1 placebo lozenge every day for 30 days. Clinical measurements were taken in the whole mouth (general plaque index and general bleeding on probing) and at the implant site (probing pocket depth, plaque index and bleeding on probing) at baseline and 30 and 90 days Microbiological examination (to identify Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Porphyromonas gingivalis, Treponema denticola, Prevotella intermedia, Peptostreptococcus micros, Fusobacterium nucleatum, Campylobacter rectus and Eikenella corrodens) was performed at the same study time points that clinical measurements were made.

RESULTS:

A total of 44 patients - 22 with mucositis and 22 with peri-implantitis - randomly received treatment with either probiotic or placebo. The probiotic L. reuteri, together with mechanical therapy, produced an additional improvement over treatment with mechanical therapy alone, both in the general clinical parameters of patients with mucositis (bleeding on probing) and at the level of implants with mucositis (probing pocket depth) or peri-implantitis (bleeding on probing and probing pocket depth). However, L. reuteri had a very limited effect on the peri-implant microbiota because the only parameter in which a significant decrease was found was the bacterial load of P. gingivalis in implants with mucositis (P = .031).

CONCLUSIONS:

The administration of a daily lozenge of L. reuteri for 30 days, together with mechanical debridement of the whole mouth, improved the clinical parameters of implants with mucositis or peri-implantitis over a period of at least 90 days, but the microbiological effect was much more limited. Probiotics provide an alternative therapeutic approach to consider in the prevention and treatment of peri-implant diseases, but further long-term prospective studies with standardized variables are needed.

Proc Natl Acad Sci U S A. 2018 Mar 20;115(12):E2706-E2715. doi: 10.1073/pnas.1715016115. Epub 2018 Mar 5.

Structural basis for the role of serine-rich repeat proteins from Lactobacillus reuteri in gut microbe-host interactions.

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Lactobacillus reuteri, a Gram-positive bacterial species inhabiting the gastrointestinal tract of vertebrates, displays remarkable host adaptation. Previous mutational analyses of rodent strain *L. reuteri* 100-23C identified a gene encoding a predicted surface-exposed serine-rich repeat protein ($SRRP_{100-23}$) that was vital for *L. reuteri* biofilm formation in mice. SRRPs have emerged as an important group of surface proteins on many pathogens, but no structural information is available in commensal bacteria. Here we report the 2.00-Å and 1.92-Å crystal structures of the binding regions (BRs) of $SRRP_{100-23}$ and $SRRP_{53608}$ from *L. reuteri* ATCC 53608, revealing a unique β-solenoid fold in this important adhesin family. $SRRP_{53608}$-BR bound to host epithelial cells and DNA at neutral pH and recognized polygalacturonic acid (PGA), rhamnogalacturonan I, or chondroitin sulfate A at acidic pH. Mutagenesis confirmed the role of the BR putative binding site in the interaction of $SRRP_{53608}$-BR with PGA. Long molecular dynamics simulations showed that $SRRP_{53608}$-BR undergoes a pH-dependent conformational change. Together, these findings provide mechanistic insights into the role of SRRPs in host-microbe interactions and open avenues of research into the use of biofilm-forming probiotics against clinically important pathogens.

KEYWORDS: *Lactobacillus reuteri; SRRP; adhesin; biofilm; mucin*

Physiol Rep. 2018 Jan;6(2). doi: 10.14814/phy2.13514.

Lactobacillus reuteri strains protect epithelial barrier integrity of IPEC-J2 monolayers from the detrimental effect of enterotoxigenic Escherichia coli.

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Lactobacillus reuteri is an inhabitant of the gastrointestinal (GI) tract of mammals and birds and several strains of this species are known to be effective probiotics. The mechanisms by which L. reuteri confers its health-promoting effects are far from being fully understood, but protection of the mucosal barrier is thought to be important. Leaky gut is a state of abnormal intestinal permeability with implications for the pathophysiology of various gastrointestinal disorders. Enterotoxigenic Escherichia coli (ETEC) can invade the intestinal mucosa and induce changes in barrier function by producing enterotoxin or by direct invasion of the intestinal epithelium. Our

hypothesis was that L. reuteri can protect the mucosal barrier, and the goal of the study was to challenge this hypothesis by monitoring the protective effect of L. reuteri strains on epithelial dysfunction caused by ETEC. Using an infection model based on the porcine intestinal cell line IPEC-J2, it was demonstrated that pretreatment of the cells with human-derived L. reuteri strains (ATCC PTA 6475, DSM 17938 and 1563F) and a rat strain (R2LC) reduced the detrimental effect of ETEC in a dose-dependent manner, as monitored by permeability of FITC-dextran and transepithelial electrical resistance (TEER). Moreover, the results revealed that ETEC upregulated proinflammatory cytokines IL-6 and TNFα and decreased expression of the shorter isoform of ZO-1 (187 kDa) and E-cadherin. In contrast, pretreatment with L. reuteri DSM 17938 and 1563F downregulated expression of IL-6 and TNFα, and led to an increase in production of the longer isoform of ZO-1 (195 kDa) and maintained E-cadherin expression. Interestingly, expression of ZO-1 (187 kDa) was preserved only when the infected cells were pretreated with strain 1563F. These findings demonstrate that L. reuteri strains exert a protective effect against ETEC-induced mucosal integrity disruption.

KEYWORDS: *Lactobacillus reuteri ; Enterotoxigenic Escherichia coli (ETEC); IPEC-J2; mucosal integrity*

J Neurogastroenterol Motil. 2018 Jan 30;24(1):51-57. doi: 10.5056/jnm17059.

Is It Useful to Administer Probiotics Together With Proton Pump Inhibitors in Children With Gastroesophageal Reflux?

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BACKGROUND/AIMS:

Gastroesophageal reflux disease (GERD) is a frequent condition diagnosed in children and treated with proton pump inhibitors (PPI). Long-term PPI administration can alter intestinal bacterial population by suppressing the gastric acid barrier and may cause diarrhea. The aim of this study is to evaluate the prevalence of small intestinal bacterial overgrowth assessed by glucose hydrogen breath test among children that received 12 weeks of PPI with or without probiotics (*Lactobacillus reuteri* DSM 17938) associated, compared to controls.

METHODS:

Glucose hydrogen breath test was performed before PPI treatment and after 12 weeks of PPI treatment to 128 consecutive children with GERD (1-18 years old) and a control group (120 healthy children). The children with GERD were randomized into 2 groups: placebo group (64 who received PPI and placebo for 12 weeks) and probiotics group (64 who received PPI and probiotics for 12 weeks).

RESULTS:

After 12 weeks of treatment, dysbiosis was detected among 56.2% of children from placebo group (36/64), compared to 6.2% of children from the probiotics group (4/64, $P < 0.001$). Bacterial overgrowth was detected in 5% of controls (6/120). Probiotics group had a lower prevalence of dysbiosis, similar to controls ($P = 0.740$).

CONCLUSION:

Probiotics administration decreased the rate of dysbiosis among children treated with PPI.

KEYWORDS: *Breath tests; Child; Dysbiosis; Probiotics; Proton pump inhibitors*

Pediatrics. 2018 Jan;141(1). pii: e20171811. doi: 10.1542/peds.2017-1811.

Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis.

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CONTEXT:

Lactobacillus reuteri DSM17938 has shown promise in managing colic, but conflicting study results have prevented a consensus on whether it is truly effective.

OBJECTIVE:

Through an individual participant data meta-analysis, we sought to definitively determine if *L reuteri* DSM17938 effectively reduces crying and/or fussing time in infants with colic and whether effects vary by feeding type.

DATA SOURCES:

We searched online databases (PubMed, Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature, the Database of Abstracts of Reviews of Effects, and Cochrane), e-abstracts, and clinical trial registries.

STUDY SELECTION:

These were double-blind randomized controlled trials (published by June 2017) of *L reuteri* DSM17398 versus a placebo, delivered orally to infants with colic, with outcomes of infant crying and/or fussing duration and treatment success at 21 days.

DATA EXTRACTION:

We collected individual participant raw data from included studies modeled simultaneously in multilevel generalized linear mixed-effects regression models.

RESULTS:

Four double-blind trials involving 345 infants with colic (174 probiotic and 171 placebo) were included. The probiotic group averaged less crying and/or fussing time than the placebo group at all time points (day 21 adjusted mean difference in change from baseline [minutes] -25.4 [95% confidence interval (CI): -47.3 to -3.5]). The probiotic group was almost twice as likely as the placebo group to experience treatment success at all time points (day 21 adjusted incidence ratio 1.7 [95% CI: 1.4 to 2.2]). Intervention effects were dramatic in breastfed infants (number needed to treat for day 21 success 2.6 [95% CI: 2.0 to 3.6]) but were insignificant in formula-fed infants.

LIMITATIONS:

There were insufficient data to make conclusions for formula-fed infants with colic.

CONCLUSIONS:

L reuteri DSM17938 is effective and can be recommended for breastfed infants with colic. Its role in formula-fed infants with colic needs further research.

J Pediatr. 2018 Jan;192:171-177.e1. doi: 10.1016/j.jpeds.2017.08.062. Epub 2017 Sep 29.

Crying Time and RORγ/FOXP3 Expression in Lactobacillus reuteri DSM17938-Treated Infants with Colic: A Randomized Trial.

Savino F[1], Garro M[2], Montanari P[3], Galliano I[3], Bergallo M[3].

OBJECTIVES:

To evaluate crying time, retinoid-related orphan receptor-γ (RORγ) and forkhead box P3 (FOXP3) messenger RNA levels (transcription factors that can modulate T cell responses to gut microbes), and to investigate gut microbiota and fecal calprotectin in infants treated with Lactobacillus reuteri for infantile colic.

STUDY DESIGN:

A double-blind, placebo-controlled randomized trial was conducted in primary care in Torino from August 1, 2015 to September 30, 2016. Patients suffering from infantile colic were randomly assigned to receive daily oral L reuteri (1×10^8 colony forming unit) or placebo for 1 month. Daily crying times were recorded in a structured diary. FOXP3 and RORγ messenger RNA in the peripheral blood was assessed with real-time TaqMan reverse transcription polymerase chain reaction. Gut microbiota and fecal calprotectin were evaluated.

RESULTS:

After infants with colic were supplemented with L reuteri DSM 17938 for 30 days, crying times were significantly shorter among infants with colic in the probiotic group compared with infants in

the placebo group (74.67 ± 25.04 [IQR = 79] minutes /day vs 147.85 [IQR = 135] minutes /day [P = .001]). The FOXP3 concentration increased significantly (P = .009), resulting in decreased RORγ/FOXP3 ratios: 0.61 (IQR = 0.60) at day 0 and 0.48 (IQR = 0.28) at day 30 (P = .028). Furthermore, the probiotic increased the percentage of Lactobacillus (P = .049) and decreased fecal calprotectin (P = .0001).

CONCLUSIONS:

Infants with colic treated with L reuteri for 30 days had a significantly decreased crying time and an increased FOXP3 concentration, resulting in a decreased RORγ/FOXP3 ratio. The treatment reduced fecal calprotectin.

J Pediatr. 2017 Dec;191:170-178.e2. doi: 10.1016/j.jpeds.2017.07.036. Epub 2017 Sep 29.

Lactobacillus reuteri for Infants with Colic: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial.

Fatheree NY[1], Liu Y[1], Taylor CM[2], Hoang TK[1], Cai C[3], Rahbar MH[4], Hessabi M[5], Ferris M[2], McMurtry V[2], Wong C[6], Vu T[6], Dancsak T[7], Wang T[1], Gleason W[1], Bandla V[1], Navarro F[1], Tran DQ[1], Rhoads JM[8].

OBJECTIVE:

To assess the safety of probiotic Lactobacillus reuteri strain Deutsche Sammlung von Mikroorganismen (DSM) 17938 with daily administration to healthy infants with colic and to determine the effect of L reuteri strain DSM 17938 on crying, fussing, inflammatory, immune, and microbiome variables.

STUDY DESIGN:

We performed a controlled, double-blinded, phase 1 safety and tolerability trial in healthy breast-fed infants with colic, aged 3 weeks to 3 months, randomly assigned to L reuteri strain DSM 17938 (5×10^8 colony-forming units daily) or placebo for 42 days and followed for 134 days.

RESULTS:

Of 117 screened infants, 20 were randomized to L reuteri strain DSM 17938 or placebo (sunflower oil) (in a 2:1 ratio) with 80% retention. Eleven of the 20 (55%) presented with low absolute neutrophil counts (<1500/mm^3), which resolved in all subjects by day 176.

L reuteri strain DSM 17938 produced no severe adverse events and did not significantly change crying time, plasma bicarbonate, or inflammatory biomarkers. Fecal calprotectin decreased rapidly in both groups. In the infants with dominant fecal gram negatives (Klebsiella, Proteus, and Veillonella), resolution of colic was associated with marked decreases in these organisms.

CONCLUSIONS:

Daily administration of L reuteri strain DSM 17938 appears to be safe in newborn infants with colic, including those with neutropenia, which frequently coexists. A placebo response of 66% suggests that many infants with colic will have resolution within 3 weeks.

Medicine (Baltimore). 2017 Dec;96(51):e9375. doi: 10.1097/MD.0000000000009375.

Efficacy of Lactobacillus reuteri DSM 17938 for infantile colic: Systematic review with network meta-analysis.

Gutiérrez-Castrellón P[1], Indrio F[2], Bolio-Galvis A[3], Jiménez-Gutiérrez C[4], Jimenez-Escobar I[5], López-Velázquez G[6].

BACKGROUND:

5% to 40% of infants cry excessively, usually accompanied by fussiness and excessive of gas. There are no uniform criteria for treatment of infantile colic. Lactobacillus reuteri DSM 17938 has been used with promising results. The objective of this network-meta-analysis (NMA) is to compare the efficacy of L reuteri DSM 17938 with other interventions for infantile colic.

METHODS:

RCTs, published between 1960 and 2015 for the treatment of infantile colic were included. Primary outcome was duration of crying after 21 to 28 days of treatment. Different databases were searched. Information was analyzed using control group as central axis. A random effect model was used. Hedges standard mean difference (SMD) and odds ratio (OR) were calculated. A SUCRA analysis was performed to evaluate superiority for each intervention.

RESULTS:

32 RCTs were analyzed, including 2242 patients. Studies with L reuteri DSM 17938 versus Ctrl., Diet versus Ctrl. and Acupuncture versus Ctrl. were the most influential studies in the NMA. L reuteri DSM 17938 [WMD -51.3 h (CI95% -72.2 to -30.5 h), P .0001] and dietetic approaches [WMD -37.4 h (CI95% -56.1 to -18.7 h), P .0001] were superior compared to the other treatments.

CONCLUSIONS:

L reuteri DSM 17938 and some dietetic approaches are better to other interventions for treatment of infantile colic.

Sci Rep. 2017 Nov 8;7(1):15047. doi: 10.1038/s41598-017-15404-7.

Impact of Lactobacillus reuteri colonization on gut microbiota, inflammation, and crying time in infant colic.

Nation ML[1], Dunne EM[1,2], Joseph SJ[1], Mensah FK[1,3,2], Sung V[1,3,2], Satzke C[1,2], Tang MLK[4,5,6].

Infant colic is a distressing condition of unknown etiology. An aberrant gastrointestinal microbiota has been associated, and Lactobacillus reuteri supplementation has been shown to reduce crying and/or fussing time ('crying time') in some infants with colic. The relationship between L. reuteri gut colonization and crying time has not been examined. We investigated the relationship between L. reuteri colonization and fecal microbiota (microbial diversity and Escherichia coli), intestinal inflammation, and crying time in infants with colic, using a subset of 65 infants from the Baby Biotics trial, which randomized healthy term infants aged <13 weeks with infant colic to receive probiotic L. reuteriDSM 17938 (1×10^8 colony forming units) or placebo daily for 28 days. We observed an overall reduction in median crying time, regardless of L. reuteri colonization status (n = 14 colonized). There were no differences in E. coli colonization rates or densities, microbial diversity or intestinal inflammation by L. reuteri colonization status. We found that L. reuteri density positively correlated with crying time, and E. coli density negatively correlated with microbial diversity. As density of L. reuteri was associated with increased crying time, L. reuterisupplementation may not be an appropriate treatment for all infants with colic.

J Med Microbiol. 2017 Oct;66(10):1416-1420. doi: 10.1099/jmm.0.000591. Epub 2017 Sep 13.

Isolates of Lactobacillus plantarum and L. reuteri display greater antiproliferative and antipathogenic activity than other Lactobacillus isolates.

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PURPOSE:

Lactic acid bacteria (LAB) have been associated with many beneficial effects in human digestive physiology. The aim of this study was to evaluate such effect, including attachment, antiproliferation and anti-pathogenic/antibacterial/antimicrobial properties of LAB isolated from healthy humans.

METHODOLOGY:

Thirteen isolates, obtained from fecal samples of healthy individuals, were identified by phenotypic and molecular methods. Human colon adenocarcinoma cell line HT-29 and the cell proliferation kit II (XTT) assay were used for examination of the Lactobacillusadherence and antiproliferative activity, respectively. In addition, the inhibitory effect of Lactobacillus isolates against pathogenic bacteria was examined.

RESULTS:

Out of 13 Lactobacillus isolates, 5 (38%) isolates were non-adhesive, 4 (31%) were adhesive and 4 (31%) were strongly adhesive. Amongst the isolated lactobacilli, L. reuteri showed the highest

degree of inhibitory effect against the attachment of the enteropathogens. The XTT assay showed that 3 different isolates had the strongest antiproliferative activity with the maximum effect observed by L. plantarum isolates.

CONCLUSION:

Our results described that different Lactobacillus species isolated from normal fecal samples had different degrees of antiproliferative and anti-pathogenic/antibacterial/antimicrobial activities. However, no isolates showed all of the examined properties concurrently, suggestive that a combination of Lactobacillus species is needed for an active biological defense system.

KEYWORDS:

HT-29 cells; Lactobacillus spp; XTT assay; healthy human; probiotic

PLoS One. 2017 Jun 8;12(6):e0178868. doi: 10.1371/journal.pone.0178868. eCollection 2017.

Effect of probiotic Lactobacillus on lipid profile: A systematic review and meta-analysis of randomized, controlled trials.

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Author information

Abstract

OBJECTIVE:

To assess the efficacy of probiotic Lactobacillus on serum lipids using a meta-analysis of randomized, controlled trials.

METHODS:

Fifteen studies containing 15 trials, with 976 subjects were included. The pooled WMD was calculated by random effects model.

RESULTS:

Probiotic Lactobacillus consumption significantly reduced TC by 0.26mmol/l (95% CI, -0.40 to -0.12) and LDL-C by 0.23mmol/l (95% CI, -0.36 to -0.10). Subgroup analysis of trials found significantly reduction of TC using L. plantarum and reduction of LDL-C using L. plantarum or L. reuteri. No significant effects were found on TG and HDL-C levels after supplementation with probiotic Lactobacillus. While, subgroup analysis found significantly beneficial effects on TG and HDL-C by consuming synbiotic food, containing L. sporogenes and inulin.

CONCLUSION:

Consuming probiotic Lactobacillus, especially L. reuteri and L. plantarm, could reduce TC and LDL-C significantly. The study also suggested significantly beneficial effects on TG and HDL-C by consuming synbiotic food, containing L. sporogenes and inulin.

A Randomized, Double-blind, Placebo-controlled Pilot Study of Lactobacillus reuteri ATCC 55730 for the Prevention of Antibiotic-associated Diarrhea in Hospitalized Adults

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Journal of Clinical Gastroenterology: October 2011 - Volume 45 - Issue 9 - p 785–789
doi: 10.1097/MCG.0b013e3182166a42

Goals The purpose of the study was to evaluate Lactobacillus reuteri for the prevention of antibiotic-associated diarrhea (AAD) in hospitalized adults.

Background AAD is a problem in hospitalized adults, contributing to increased length of stay, cost, and mortality. Probiotics have been proposed as a way to prevent AAD. L. reuteri decreases acute infectious diarrhea in children; however, L. reuteri has never been evaluated for the prevention of AAD.

Study In a randomized, double-blind, placebo-controlled pilot study, in-patients receiving antibiotics were given L. reuteri 1×108 colony-forming units twice daily or an identical placebo for 4 weeks. Stool frequency, consistency, and gastrointestinal symptoms were monitored during the 4-week treatment period and during a 2-week follow-up period.

Results A total of 31 patients were enrolled. Eight patients were excluded in the data analysis because of length of study participation less than 14 days. Mean age was 51±18 years; 63% were female and 37% male. Most frequent primary diagnosis was pneumonia (20%), followed by abscess (10%), chronic obstructive pulmonary disease (6.7%), and bronchitis (6.7%). Thirteen patients received L. reuteri and 10 received placebo. Patients treated with L. reuteri had a significantly lower frequency of diarrhea compared with placebo (50% in the placebo group vs. 7.7% in the probiotic group, P=0.02). There were no differences in the frequency or severity of gastrointestinal symptoms.

Conclusions In this placebo-controlled, pilot study, L. reuteri twice daily for 4 weeks significantly decreased AAD among hospitalized adults. L. reuteri was safe and well tolerated.

Lactobacillus reuteri (DSM 17938) in Infants with Functional Chronic Constipation: A Double-Blind, Randomized, Placebo-Controlled Study

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The Journal of Pediatrics Volume 157, Issue 4, October 2010, Pages 598-602

Objectives: To evaluate the beneficial effects of Lactobacillus reuteri (DSM 17938) in infants with functional chronic constipation.

Study design: A double-blind, placebo-controlled, randomized study was conducted from January 2008 to December 2008 in 44 consecutive infants at least 6 months old (mean age ± SD, 8.2 ± 2.4 SD; male/female, 24/20) admitted to the Gastrointestinal Endoscopy and Motility Unit of the Department of Pediatrics, University "Federico II" of Naples, with a diagnosis of functional chronic constipation. The 44 infants with chronic constipation were randomly assigned to 2 groups: group A (n = 22) received supplementation with the probiotic ***L reuteri*** (DSM 17938) and group B (n = 22) received an identical placebo. Primary outcome measures were frequency of bowel movements per week, stool consistency, and presence of inconsolable crying episodes, recorded in a daily diary by parents.

Results: Infants receiving ***L reuteri*** (DSM 17938) had a significantly higher frequency of bowel movements than infants receiving a placebo at week 2 (***P*** = .042), week 4 (***P*** = .008), and week 8 (***P*** = .027) of supplementation. In the ***L reuteri*** group, the stool consistency was reported as hard in 19 infants (86.4%) at baseline, in 11 infants (50%) at week 2, and in 4 infants (18.2%) at weeks 4 and 8. However, there was no significant difference between ***L reuteri*** and placebo groups in the stool consistency at all weeks (***P*** = .63, week 2; ***P*** = .38, week 4; ***P*** = .48, week 8). Similarly, there was no statistically difference in the 2 groups in the presence of inconsolable crying episodes. No adverse effects were reported.

Conclusions: The administration of ***L reuteri*** (DSM 17938) in infants with chronic constipation had a positive effect on bowel frequency, even when there was no improvement in stool consistency and episodes of inconsolable crying episodes. Because of their safety profile, probiotics may be an attractive option in the treatment of functional constipation.

Decreased gum bleeding and reduced gingivitis by the probiotic Lactobacillus reuteri.

Krasse P , Carlsson B , Dahl C , Paulsson A , Nilsson A , Sinkiewicz G

Swedish Dental Journal [01 Jan 2006, 30(2):55-60]

The primary aim of this study was to assess if the probiotic Lactobacillus reuteri could be effective in the treatment of gingivitis and further to evaluate the influence of the probiotic on plaque and the lactobacilli population in the saliva. A randomised, placebo-controlled, double blind study was performed over 2 weeks. Fifty-nine patients with moderate to severe gingivitis were included and given one of two different Lactobacillus reuteri formulations (LR-1 or LR-2) at a dose of 2 x 10(8) CFU per day, or a corresponding placebo. At baseline (day 0) gingival index and plaque index were measured on two surfaces and saliva for lactobacilli determination was collected. The patients were instructed how to brush and floss efficiently and study treatment was started.The patients returned on day 14 for final assessment of gingivitis and plaque and saliva was collected. 20 patients were randomised to LR-1, 21 to LR-2 and 18 to placebo. Gingival index fell significantly in all 3 groups ($p < 0.0001$). LR-1, but not LR-2 improved more than placebo ($p < 0.0001$). Plaque index fell significantly in LR-1 ($p < 0.05$) and in LR-2 ($p < 0.01$) between day o and day 14 but there was no significant change in the placebo group. At day 14, 65% of the patients in LR-1 were colonised with Lactobacillus reuteri and 95% in the LR-2 group. Lactobacillus reuteri was efficacious in reducing both gingivitis and plaque in patients with moderate to severe gingivitis.

Human-derived probiotic Lactobacillus reuteri demonstrate antimicrobial activities targeting diverse enteric bacterial pathogens

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Lactobacillus reuteri is a commensal-derived anaerobic probiotic that resides in the human gastrointestinal tract. *L. reuteri* converts glycerol into a potent broad-spectrum antimicrobialcompound, reuterin, which inhibits the growth of gram-positive and gram-negative bacteria. In this study, we compared four human-derived *L. reuteri* isolates (ATCC 55730, ATCC PTA 6475, ATCC PTA 4659 and ATCC PTA 5289) in their ability to produce reuterin and to inhibit the growth of different enteric pathogens *in vitro*. Reuterin was produced by each of the four *L. reuteri* strains and assessed for biological activity. The minimum inhibitory concentration(MIC) of reuterin derived from each strain was determined for the following enteric pathogens: enterohemorrhagic *Escherichia coli*, enterotoxigenic *E. coli*, *Salmonella enterica*, *Shigella* sonnei and Vibrio *cholerae*. We also analyzed the relative abilities of *L. reuteri* to inhibit enteric pathogens in a pathogen overlay assay. The magnitude of reuterin production did not directly correlate with the relative ability of *L. reuteri* to suppress the proliferation of enteric pathogens. Additional

antimicrobial factors may be produced by *L. reuteri*, and multiple factors may act synergistically with reuterin to inhibit enteric pathogens.

Lactobacillus reuteri DSM 17938 for the Management of Infantile Colic in Breastfed Infants: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective **To determine whether administration of *Lactobacillus reuteri* (*L reuteri*)** DSM 17938 is beneficial in breastfed infants with infantile colic.

Study design Eighty infants aged <5 months with infantile colic (defined as crying episodes lasting 3 or more hours per day and occurring at least 3 days per week within 7 days prior to enrollment), who were exclusively or predominantly (>50%) breastfed were randomly assigned to receive L *reuteri* DSM 17938 (108 colony-forming units) (n = 40) or an identically appearing and tasting placebo (n = 40), both orally, in 5 drops, 1 time daily, for 21 days. The primary outcome measures were the treatment success, defined as the percentage of children achieving a reduction in the daily average crying time ≥50%, and the duration of crying (minutes per day) at 7, 14, 21, and 28 days after randomization.

Results The rate of responders to treatment was significantly higher in the probiotic group compared with the placebo group at day 7 (P = .026), at day 14 (relative risk (RR) 4.3, 95% CI 2.3-8.7), at day 21 (RR 2.7, 95% CI 1.85-4.1), and at day 28 (RR 2.5, 95% CI 1.8-3.75). In addition, throughout the study period, the median crying time was significantly reduced in the probiotic group compared with the control group.

Conclusion Exclusively or predominantly breastfed infants with infantile colic benefit from the administration of L *reuteri* DSM 17938 compared with placebo.

Probiotic Lactobacillus reuteri suppress proinflammatory cytokines via c-Jun

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Background: Differential immunoregulatory capabilities of probiotic *Lactobacillus* were explored in the context of pediatric Crohn's disease. Experimental strategies addressed molecular mechanisms of tumor necrosis factor (TNF) suppression in activated macrophages by transcriptional regulation.

Methods: Secreted factors produced by probiotic *Lactobacillus reuteri* strains were harvested and tested with human monocytes and macrophages. Quantitative immunoassays and real-time reverse-transcriptase polymerase chain reaction (RT-PCR) were used to examine relative quantities of human cytokines and TNF mRNA, respectively, and reporter assays assessed transcriptional regulation of TNF by probiotics. DNA-protein macroarrays interrogated probiotic-mediated effects on transcription factor activation. Finally, enzyme-linked immunosorbent assays (ELISAs) and immunoblots examined the involvement of the specific transcription factor AP-1 and its components.

Results: Probiotic *L. reuteri* strain ATCC PTA 6475 demonstrated the ability to potently suppress human TNF production by lipopolysaccharide-activated monocytes and primary monocyte-derived macrophages from children with Crohn's disease. Quantities of the chemokine MCP-1/CCL2 were also reduced by probiotic *L. reuteri* strain ATCC PTA 6475 in macrophages of children in remission. Quantitative real-time RT-PCR and luciferase reporter assays showed that transcriptional regulation of human TNF was a primary mechanism of probiotic-mediated immunomodulation. Probiotic *L. reuteri* suppressed TNF transcription by inhibiting activation of MAP kinase-regulated c-Jun and the transcription factor, AP-1.

Conclusions: Human TNF and MCP-1 suppression by probiotic *L. reuteri* was strain-dependent, and the activation of c-Jun and AP-1 represent primary targets for probiotic-mediated suppression of TNF transcription. This report emphasizes the clonal nature of immunoprobiosis and delineation of a specific immunomodulatory mechanism for probiotic strain selection in future inflammatory bowel disease-oriented clinical trials.
(Inflamm Bowel Dis 2008)

Lactobacillus reuteri DSM 17938 in Infantile Colic: A Randomized, Double-Blind, Placebo-Controlled Trial

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OBJECTIVE: To test the efficacy of *Lactobacillus reuteri* on infantile colic and to evaluate its relationship to the gut microbiota.

STUDY DESIGN: Fifty exclusively breastfed colicky infants, diagnosed according to modified Wessel's criteria, were randomly assigned to receive either *L reuteri* DSM 17 938 (10^8 colony-forming units) or placebo daily for 21 days. Parental questionnaires monitored daily crying time and adverse effects. Stool samples were collected for microbiologic analysis.

RESULTS: Forty-six infants (*L reuteri* group: 25; placebo group: 21) completed the trial. Daily crying times in minutes/day (median [interquartile range]) were 370 (120) vs 300 (150) (*P* = .127) on day 0 and 35.0 (85) vs 90.0 (148) (*P* = .022) on day 21, in the *L reuteri* and placebo groups, respectively. Responders (50% reduction in crying time from baseline) were significantly higher in the *L reuteri* group versus placebo group on days 7 (20 vs 8; *P* = .006), 14 (24 vs 13; *P* = .007), and 21 (24 vs 15; *P* = .036). During the study, there was a significant

increase in fecal lactobacilli (*P* = .002) and a reduction in fecal Escherichia coli and ammonia in the *L reuteri* group only (*P* = .001). There were no differences in weight gain, stooling frequency, or incidence of constipation or regurgitation between groups, and no adverse events related to the supplementation were observed.

CONCLUSION: *L. reuteri* DSM 17 938 at a dose of 10^8 colony-forming units per day in early breastfed infants improved symptoms of infantile colic and was well tolerated and safe. Gut microbiota changes induced by the probiotic could be involved in the observed clinical improvement.

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Probiotics for Infantile Colic: A Randomized, Double-Blind, Placebo-Controlled Trial Investigating Lactobacillus reuteri DSM 17938

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Objective To investigate the effectiveness of *Lactobacillus reuteri* DSM 17938 for the treatment of infantile colic in breastfed Canadian infants, compared with placebo.

Study design A randomized, double-blind, placebo-controlled trial was conducted involving 52 infants with colic, according to modified Wessel criteria, who were assigned at random to receive *L reuteri* DSM 17938 (108 colony-forming units) (n = 24) or placebo (n = 28) for 21 days. Daily crying and fussing times were recorded in a structured diary, and maternal questionnaires were completed to monitor changes in infant colic symptoms and adverse events.

Results Total average crying and fussing times throughout the study (from baseline to day 21) were significantly shorter among infants with colic in the probiotic group compared with infants in the placebo group (1719 ± 750 minutes [29 ± 13 hours] vs 2195 ± 764 minutes [37 ± 13 hours]; *P* = .028) (relative risk, 0.78; 95% CI, 0.58-0.98). Infants given *L reuteri*DSM 17938 showed a significant reduction in daily crying and fussing times at the end of treatment period compared with those receiving placebo (median, 60 minutes/day [IQR, 64 minutes/day] vs 102 minutes/day [IQR, 87 minutes/day]; *P* = .045). On day 21, a significantly higher proportion of infants in the *L reuteri* DSM 17938 group responded to treatment with a ≥50% crying time reduction compared with infants given placebo (17 vs 6, *P* = .035; relative risk, 3.3; 95% CI, 1.55-7.03).

Conclusion Administration of *L reuteri* DSM 17938 significantly improved colic symptoms by reducing crying and fussing times in breastfed Canadian infants with colic.