

LACTOBACILLUS REUTERI ATCC 55730

A clinically proven probiotic

Eamonn Connolly

BioGaia AB, Stockholm, Sweden

INTRODUCTION

Lactobacillus reuteri ATCC 55730 is widely used as a probiotic in dairy foods. Milk supplemented with *L. reuteri* ATCC 55730 was first introduced in Sweden in 1991 under the BRA brand and currently, dairy products containing *L. reuteri* ATCC 55730 are sold in the US, Finland, Japan, Korea, Spain, Portugal and the UK. In 2000, chewable tablets containing *L. reuteri* ATCC 55730 were introduced in the US and these tablets have since been introduced into Europe, S. Africa and Asia. To date the equivalent of more than 200 million doses of 10s CFU *L. reuteri* ATCC 55730 have been sold through the various products described above (BioGaia internal market information) and no clinical infection or untoward side-effect involving *L. reuteri* has been reported. The FAO/WHO definition of a probiotic is a live microorganism which when administered in adequate amounts confers a health benefit to the host. *Lactobacillus reuteri* ATCC 55730 has been demonstrated to be a true probiotic as described below and the main supportive clinical data is described in this review.

Lactobacillus reuteri (*L. reuteri*), a distinctive species (1) originally described by Gerhard Reuter, in 1980 is a heterofermentative species that resides in the gastrointestinal (GI) tract of humans and all animals tested (2-5) and is considered to be one of the few true autochthonous (indigenous) *Lactobacillus* species in man (5). Members of the species *L. reuteri* have the ability to successfully inhibit the growth of pathogenic microorganisms by a combi-

nation of different mechanisms including excretion of lactic and acetic acids as well as other short chain fatty acids, hydrogen peroxide, antimicrobial substances and bacteriocins (3) and like other lactic acid bacteria, are able to convert milk sugar (lactose) into lactic acid. Axelsson et al. (6) reported that *L. reuteri* converted glycerol into a potent, broad-spectrum antimicrobial that was termed 'reuterin' which is a low molecular weight, neutral, water-soluble compound (3-hydroxy propionaldehyde) capable of inhibiting growth of species representing several bacterial genera including *Escherichia*, *Salmonella*, *Shigella*, *Proteus*, *Pseudomonas*, *Clostridium* and *Staphylococcus* as well as yeasts, fungi, protozoa and viruses (6).

Reuterin is excreted by *L. reuteri* during anaerobic growth in the presence of glycerol (7) and both of these conditions are satisfied in the human bowel. Chung et al. (8) showed that reuterin was synthesized under environmental conditions similar to those that exist in the GI tract and that reuterin synthesis was stimulated by contact with other bacteria found in the

Key Words

Lactobacillus reuteri
Clinical trials
Probiotic
Gastroenteritis
Colonization

Eamonn Connolly

Department of Research
BioGaia AB
Box 3242
SE-103 64 Stockholm
Sweden
tel +46.8.5552 9318
fax +46.8.5552 9301
email ec@biogaia.se

CEC Milan, Italy
tel +39.02.4152 943
fax +39.02.416 737
email info.nutrafoods@cec-editore.com
website www.cec-editore.com

VfCI Augsburg, Germany
tel +49.0821.325 830
fax +49.0821.3258 323
email fischer@sofw.com
website www.sofw.com

human gut, such as *E. coli*, *Salmonella typhimurium*, *Shigella*, *Proteus*, *Pseudomonas fluorescens*, *Staphylococcus epidermidis*, *Bacillus megaterium*, *Clostridium sporogenes*, *Pedococcus pentosaceus*, *Leuconostoc mesenteroides* and *Streptococcus cremoris*.

The β -hydroxy moiety of reuterin renders its aldehyde function reactive, capable of spontaneous reaction with available amino and sulfhydryl functional groups in the gut lumen. Thus, reuterin action is local and it is not systemically absorbed. The structure of another unique compound with antimicrobial effect produced by *L. reuteri*, reutericyclin (a tetramic acid), has recently been elucidated and reported (9,10). Reutericyclin has been shown to exert an inhibitory effect on several bacteria that are pathogenic to humans or considered as food contaminants, such as *Bacillus cereus*, *Stafylococcus aureus*, *Listeria* and *Entecococcus faecium*. Further studies have demonstrated that *L. reuteri* exerts a strong inhibitory action on GI tract pathogens, including *H. pylori* but that it is unique in that it does not negatively affect the normal, beneficial microflora (3,11-14). A true probiotic active in the GI tract must be shown to survive passage and to colonize its proposed site of action. *L. reuteri* ATCC 55730 not only tolerates the very low pH of the stomach, but also survives better than other lactobacilli directly isolated from the human stomach (14). Adherence to intestinal mucosa (3,14,15) and growth at the site of action are probiotic properties that have also been demonstrated for *L. reuteri* ATCC 55730 (see below). Thus, oral administration of *L. reuteri* ATCC 55730 in foods and dietary supplements delivers the live and active probiotic to the entire human GI tract.

The studies below refer to clinical work with *L. reuteri* ATCC 55730, unless otherwise indicated. This is the commercial probiotic strain used in all human *L. reuteri* product applications and is sometimes referred to in the literature under the synonyms '*L. reuteri* SD2112' (an earlier ATCC designation), '*L. reuteri* MM53' and '*L. reuteri* ING1'.

CLINICAL TRIALS

The main clinical studies performed with *L. reuteri* ATCC 55730 are presented in summary format in Table 1.

Adults

Wolf et al. (16) studied the safety and tolerance of *L. reuteri* ingestion in healthy adult males in a randomized, double-blinded placebo controlled trial (RTC). *L. reuteri* administration (1×10^{11} CFU/day) for 21 days significantly raised *L. reuteri* levels in the feces compared to placebo without any clinically significant safety issues. Wolf et al (17) further examined *L. reuteri* in immunocompromized individuals (with HIV infection) in a similarly controlled trial. Subjects were supplemented with *L. reuteri* (10^{10} CFU/day, 21 days) and again showed an increase in fecal levels of *L. reuteri* and safety was confirmed in this infection susceptible group. There are no reports of clinical infections with or isolation of *L. reuteri* in connection with any disease or pathological process in either animals or humans. Indeed, an excellent study recently reported on bacteremia in the Finnish population (18) did not detect any cases of *L. reuteri* in the circulation, although several other well-known *Lactobacillus* species were detected in the blood. These observations were made during a period when *L. reuteri* was widely consumed in Finland in dairy and juice products (approx. 1 million litres/year with 1×10^9 CFU *L. reuteri*/litre).

Children

Ruiz-Palacios et al. (19) established the tolerance of doses up to 1×10^{10} CFU/day of a probiotic mixture containing *L. reuteri*, *L. acidophilus* and *B. infantis* in children (12-36 m) and then went on to investigate the ability of the probiotic mix to prevent community-acquired diarrhoea in healthy children (20). Children received the probiotic mix (n=119) or placebo (n=120) for 14 weeks. The number of children with diarrhoea was significantly lower in the

Table 1 Main clinical studies with *Lactobacillus reuteri* ATCC 55730

Trial (ref)	Aim	Study design	Groups	Number of subjects	Duration	Main outcome
Wolf et al. (16)	Safety Healthy adults	R, DB, PC	Placebo <i>L. reuteri</i> (1x10 ¹¹ CFU/day)	15 15	21 days	No clinical safety or tolerance problems
Wolf et al. (17)	Safety Immunocompromised adults	R, DB, PC	Placebo <i>L. reuteri</i> (1x10 ¹⁰ CFU/day)	20 15	21 days	No clinical safety or tolerance problems
Ruiz-Palacios et al. (19)	Safety Children (1-3 years)	R, DB, PC	Placebo <i>L. reuteri</i> (1x10 ¹⁰ CFU/day)* <i>L. reuteri</i> (1x10 ⁸ CFU/day)* <i>L. reuteri</i> (1x10 ⁶ CFU/day)*	20 18 16 18	21 days	No clinical safety or tolerance problems
Ruiz-Palacios et al. (20)	Prevention of diarrhoea Children (1-3 years)	R, DB, PC	Placebo <i>L. reuteri</i> (5x10 ⁷ CFU/day)*	120 119	14 weeks	Probiotic significantly reduced incidence of diarrhoea
Guerrero et al. (21)	Prevention of diarrhoea Children (1-3 years)	R, DB, PC	Placebo Probiotic mix without <i>L. reuteri</i> ** Probiotic mix with <i>L. reuteri</i> (1.5x10 ⁸ CFU/day)**	130 129 129	16 weeks	<i>L. reuteri</i> -containing probiotic mix only significantly reduced incidence of diarrhoea
Shornikova et al. (22)	Treatment of acute gastroenteritis in children (0.5-3 years)	R, DB, PC	Placebo <i>L. reuteri</i> (1x10 ¹⁰⁻¹¹ CFU/day)	21 19	up to 5 days	<i>L. reuteri</i> significantly reduced duration of gastroenteritis
Shornikova et al. (23)	Treatment of acute rotavirus gastroenteritis in children (0.5-3 years)	R, DB, PC	Placebo <i>L. reuteri</i> (1x10 ¹⁰ CFU/day) <i>L. reuteri</i> (1x10 ⁷ CFU/day)	25 21 20	up to 5 days	High dose <i>L. reuteri</i> significantly reduced duration of gastroenteritis Low dose tendency to similar effect
Karvonen et al. (24)	Safety & colonisation Newborn term infants	R, DB, PC	Placebo <i>L. reuteri</i> (1x10 ⁹ CFU/day) <i>L. reuteri</i> (1x10 ⁷ CFU/day) <i>L. reuteri</i> (1x10 ⁵ CFU/day)	28 25 25 12	30 days from birth	No clinical safety or tolerance problems Significant reduction in watery stools with <i>L. reuteri</i>
Vesikari & Karvonen (submitted)	Safety & colonisation Newborn term infants Premature infants	R, DB, PC	Placebo <i>L. reuteri</i> (1x10 ⁸ CFU/day) Placebo <i>L. reuteri</i> (1x10 ⁹ CFU/day) <i>L. reuteri</i> (1x10 ⁷ CFU/day)	12 23 16 13 14	28 days from birth	No clinical safety or tolerance problems No clinical safety or tolerance problems
Weizman & Alsheikh (25)	Safety Infants (3-65 days)	R, DB, PC	Placebo <i>L. reuteri</i> (approx 10 ⁸ CFU/day)** <i>B. lactis</i> Bb12 (approx 1x10 ⁹ CFU/day)	17 17 16	60 days	No clinical safety or tolerance problems
Weizman et al. (27)	Prevention of infection Day-care children (4-10 months)	R, DB, PC	Placebo <i>L. reuteri</i> (3x10 ⁸ CFU/day)** <i>B. lactis</i> Bb12 (approx 1x10 ⁹ CFU/day)	58 65 71	12 weeks	<i>L. reuteri</i> superior in significantly reducing incidence of gastrointestinal infection
Valeur et al. (31)	Gastrointestinal colonization Healthy adults	Open	<i>L. reuteri</i> (4x10 ⁸ CFU/day)	19	28 days	<i>L. reuteri</i> colonizes the human stomach, duodenum and ileum

Abbreviations: R, randomised; DB, double-blind; PC, placebo-controlled

* also received *L. acidophilus* and *B. infantis* at constant dose** Probiotic mix contained *L. acidophilus* and *B. infantis*

*** Personal communication

probiotic group (29/119 vs 43/120) as was the incidence of diarrhoea per child (0.27 vs 0.42) compared to placebo. A second blinded RCT (21) compared the diarrhoea preventing effect of two probiotic blends; one group (n=129) was given a blend of *L. acidophilis* and *B. infantis* whilst a second (n=129) received the same blend plus 1.5×10^8 CFU *L. reuteri* ATCC 55730 per day for 16 weeks. The relative risk for diarrhoea compared to placebo (1.0, n=130) was significantly reduced to 0.67 for the *L. reuteri* fed group and to 0.75 (not significant) for the blend without *L. reuteri*, showing the direct effect of *L. reuteri* on infectious diarrhoea. In a recent study in India (Jangle et al, unpublished) children (aged 3-6y) in a rural area were given either *L. reuteri* (as tablets; n=160) at a dose of 10^8 CFU/day or placebo (n=158) for 35 days. Extensive blood safety data revealed no negative effects of *L. reuteri*.

Infants and neonates

Two randomized double-blind, placebo controlled studies examined the effects of *L. reuteri* on acute infectious diarrhoea in children (22,23) and in both studies *L. reuteri* was well-tolerated. In the first study, children received 10^{10} - 10^{11} CFU/d (n=19) or placebo (n=21). *L. reuteri* significantly reduced the duration of diarrhoea from 2.9 to 1.7 days. In the second study, the duration of 2.5 days of rotavirus-induced diarrhoea for placebo (n=25) was reduced to 1.9 days with a dose of 10^7 CFU/d (n=20) and to 1.5 days at 10^{10} CFU of *L. reuteri*/d (n=21). Notably, the lower dose gave almost the same efficacy as the higher dose. Karvonen et al. (24) studied further doses of *L. reuteri* between 10^5 - 10^9 CFU/d given to healthy neonates (as powder added to breast milk or infant

formula) from birth for 28 days. There was no evidence of adverse effects (GI symptoms) compared to placebo but there was a significant reduction in the incidence of watery stools in the treated infants. The same group has recently studied the safety and colonizing efficacy of an oil suspension of *L. reuteri* (doses 10^7 - 10^9 CFU per day) given from birth for 28 days in newborn (n=23 treated) and premature (n=27 treated) infants (Vesikari & Karvonen, submitted for publication). No safety issues were reported, the formulation was again well-tolerated by the infants and excellent fecal colonisation was observed from the oil formulation. A recent placebo-controlled, double blind clinical trial (25) has confirmed the safety of *L. reuteri* ATCC 55730-supplemented infant formula given to healthy infants (3-65 days of age) for 4 weeks.

The infant studies above, as well as a pre-clinical study in infant rhesus monkeys (26), are of particular interest with reference to the existing CODEX guidelines for use of live bacteria as fermentation aids for the acidification of infant formulas. These guidelines refer to clinical data from the late 1950's and perpetuate the idea that lactobacilli that produce D-lactic acid are unsuitable for use in infant formulas. However, the CODEX recommendations refer to acidifying agents used in fermenting milks in production as opposed to freeze-dried probiotic ingredients added to the final infant formula product. A review of the existing literature (Connolly, unpublished) and data from our own clinical trials with *L. reuteri*, clearly show that there is no evidence describing D(-)-lactic acidosis in healthy infants (or humans of any age), despite extensive use of probiotic D-lactic acid producing *Lactobacillus* supplements around the world. This is, of course, not a surprise since these bacteria are a natural contaminant of mother's milk and cannot be expected to adversely affect the newborn. Fortunately, the EU Scientific Committee on Foods has recognized this in their Opinion (http://europa.eu.int/comm/food/fs/sc/scf/outcome_en.html, see out199IF SCF May 2003_en.pdf, section XI) which will come into force early 2004 and safe and potentially very efficacious lactobacilli normally found in mothers milk will be acceptable for use as ingredients in infant formulas, irrespective of the lactic acid metabolic profile.

Recent clinical findings

Weizman et al. (27) have just presented data from a double-blind, placebo controlled trial in infant for-

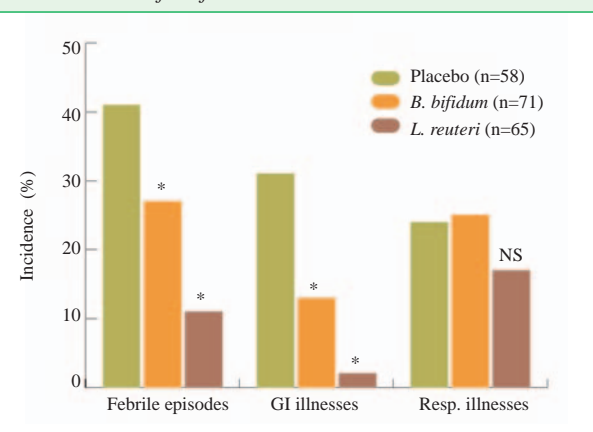
mulas supplemented with either *L. reuteri* ATCC 55730 (approx 10^8 CFU/day) or *B. bifidum* (Bb12) for 12 weeks. Infants given the probiotics showed less febrile episodes and fewer GI illnesses and infections than the placebo group (Fig 1) and the authors noted that *L. reuteri* ATCC 55730 was found to be superior to both placebo and supplementation with *Bifidobacterium lactis* (Bb12) in maintaining the gastro-intestinal health of the infants and reducing the use of visits to the doctor and prescription of antibiotics (27 and personal communication). Interesting new clinical data is being generated by Rosenfeldt et al. (28-30) with a mixture of *L. reuteri* (strain DSM 12246) and *L. rhamnosus* (19070-2) indicating amelioration of

rotavirus induced acute diarrhoea as well as potential effects on acute dermatitis. Unfortunately, the mixture of strains does not allow the determination of which of the bacterial strains has effect. BioGaia is currently sponsoring a major multicentre trial on the effect of supplementation of newborn infants with *L. reuteri* ATCC 55730 on the incidence of atopic allergy in the first two years of life, so new data should soon be available.

Further new clinical data (31) demonstrates in situ colonization of the human gastro-intestinal mucosa after dietary supplementation with *L. reuteri* ATCC 55730 tablets and subsequent immune responses at these sites. In this open clinical study, 10 healthy volunteers and 9 subjects with ileostomy underwent gastroscopy or ileoscopy and biopsies were taken from the stomach, duodenum or ileum before and after supplementation with 4×10^8 CFU live *L. reuteri* per day for 28 days.

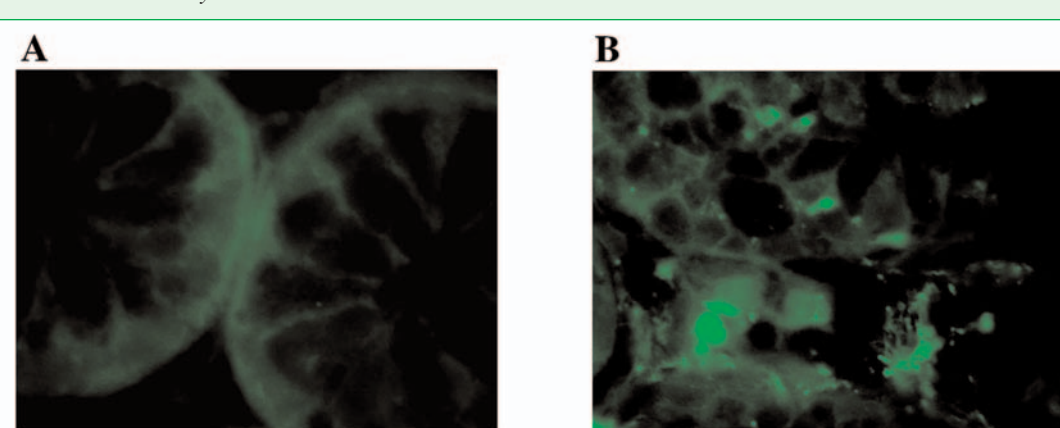
Biopsies were analysed for colonization (using fluorescent in situ hybridisation with a molecular beacon probe) and for immune cell populations. Endogenous *L. reuteri* was detected in the stomach of 1

Figure 1 Prevention of gastrointestinal infections and fever in infants given *L. reuteri* ATCC 55730 in infant formula



Full-term healthy infants were fed formula containing the *L. reuteri* ATCC 55730 or *Bifidobacterium* Bb12 for 12 weeks. The incidence (% of all illness episodes) of fever, infections of the GI tract and respiratory illnesses were recorded. $P < 0.001$ compared to placebo group. Adapted from data in Weizman et al (27)

Figure 2 FISH detection *L. reuteri* in situ in the human gastrointestinal tract after supplementation in healthy volunteers



Biopsies were taken from the gastric antrum of one subject before (A) and after (B) the daily administration of *L. reuteri* ATCC 55730 for 28 days. *L. reuteri* was detected using an *L. reuteri*-specific FISH molecular beacon probe. The appearance of *L. reuteri* after supplementation is clearly seen as bright green fluorescent colony-like formations.

subject and the duodenum of 3 subjects (of 10). After *L. reuteri* tablet supplementation, the stomachs of 8 and the duodenums of all subjects were colonized. Three ileostomy subjects (of 6 tested) had endogenous *L. reuteri* at baseline whilst all 6 displayed colonization after *L. reuteri* supplementation.

Our data (see examples *Fig 2*) provide the first clear and direct indication of colonization of the healthy human stomach, duodenum and ileum by any exogenously delivered probiotic. Colonization of the stomach and upper GI tract (the sites of *H. pylori* infection) by *L. reuteri* from the tablet supplement as well as the known ability of *L. reuteri* to kill *H. pylori* (14), encourages our continued investigations in this area. Emerging evidence suggests that the probiotic effects of *L. reuteri* may be related to its ability to modulate the immune system of the gastrointestinal tract. In the Valeur et al. (31) study, *L. reuteri* administration induced a significantly higher amount of CD4-positive T-lymphocytes in the ileal epithelium of the subjects. These findings in humans agree well with earlier observations in *Salmonella typhimurium* infected poultry (32), where *L. reuteri* supplementation led to an increased CD4:CD8 ratio in the ileum mucosa and a consequent dramatically improved survival of the chicks (3, 32). Further studies performed by our group have shown that ileal growth is stimulated by *L. reuteri* supplementation in the mouse with consequent reductions in *Salmonella*-induced inflammation and mortality (3; unpublished data). Mao et al. (33) studied methotrexate-induced enterocolitis in rats and found that *L. reuteri* could increase both ileal and colonic secretory IgA levels as well as CD4+ and CD8+ cell populations in the gut lamina

propria and that these changes were associated with decreased intestinal permeability, increased mucosal mass and recovery from enterocolitis (34). Ferreira et al. (35) have shown that activated T-lymphocytes in the human small intestinal lamina propria are involved in enhancing proliferation of intestinal epithelial cells and further *L. reuteri* (3) has been shown to stimulate mucosal growth in animals. *L. reuteri* is known to be a predominant indigenous species in the ileum (3) and thus, *L. reuteri* stimulation of T-helper cells in the human ileum may be a central mechanism of symbiosis for improving the health of the host gut and a key mechanism of action for this probiotic bacterium.

FUTURE PERSPECTIVES

Molecular investigation of the mechanisms by which *L. reuteri* ATCC 55730 exerts its effects has shown us that some probiotic effects are specific to strains of lactobacilli and that these cannot be extrapolated to the *Lactobacillus* species as a whole or to other *Lactobacillus* species. BioGaia has focussed much of its recent research on the selection of new probiotic strains of *L. reuteri* and other lactic acid bacteria species that have specific properties that enhance human health. Our development of new anti-inflammatory strains (36) as well as strains with strong effects on oral health and allergy prevention will provide the basis of the next generation of probiotics with targeted action in the field of maintaining human health.

SUMMARY

Lactobacillus reuteri (*L. reuteri*), one of the few true autochthonous (indigenous) *Lactobacillus* species in the gastrointestinal tract of man, is widely used for its probiotic properties as a food additive to improve gastrointestinal health. This review covers 12 major clinical trials documenting the safety and efficacy of *L. reuteri* ATCC 55730 over 600 supplemented subjects from adults to premature infants. Sound clinical data shows that *L. reuteri* ATCC 55730 administration significantly reduces the incidence and the severity of diarrhoea of different origins and reduces gastrointestinal illness and infections. The ability of *L. reuteri* ATCC 55730 to influence basic immune responses in the human gastrointestinal tract may be the basis for an improved protection against pathogen infection and further enhanced health of the host consuming this probiotic.

REFERENCES

- 1 **Kandler O, Stetter K, Kohl R (1980)**
Lactobacillus reuteri sp. nov. a new species
of heterofermentative lactobacilli
Zbl Bakt Hyg Abt Orig C1 264-9
- 2 **Mitsuoka, T (1992)**
In: *The Lactic Acid Bacteria in Health and Disease*.
Elsevier Applied Science, p 76
- 3 **Casas IA, Dobrogosz WJ (2000)**
Validation of the probiotic concept: *Lactobacillus reuteri* confers broad spectrum protection against disease in humans and animals
Microb Ecol Health Dis 12 247-285
- 4 **Kandler O, Weiss N (1986)**
Regular, nonsporing gram-positive rods.
In: *Bergey's Manual of Systematic Bacteriology (Volume 2)*
Sneath PH, Mair NS, Sharpe ME, Holt JG eds,
p 1208-1234
- 5 **Reuter, G (2001)**
The *Lactobacillus* and *Bifidobacterium* microflora of the human intestine: composition and succession
Curr Issues Intest Microbiol 2 43-53
- 6 **Axelsson L, Chung T, Dobrogosz W, Lindgren S (1989)**
Production of a broad spectrum antimicrobial substance by *Lactobacillus reuteri* *Microbial Ecology Health Disease* 2131-2136
- 7 **Talarico TL, Casas I, Chung TC, Dobrogosz WJ (1988)**
Production and isolation of reuterin, a growth inhibitor produced by *Lactobacillus reuteri*
Antimicrob Agents Chemother 32 1854-1858
- 8 **Chung TC, Axelsson L, Lindgren SE, Dobrogosz WJ (1989)**
In vitro studies on reuterin synthesis by *Lactobacillus reuteri*
Microb Ecol Health Dis 2 137-144
- 9 **Höltzel A, Gänzle MG, Nicholson GJ, Hammes WP, Jung G (2000)**
The first low molecular weight antibiotic from lactic acid bacteria: Reutericyclin, a new tetramic acid
Angew Chem Int Ed 39 2766-2768
- 10 **Gänzle MG, Höltzel A, Walter J, Jung G, Hammes WP (2000)**
Characterisation of reutericyclin produced by *Lactobacillus reuteri* LTH 2584
Appl Environ Microbiol 66 4325-4333
- 11 **Jacobsen C, Rosenfeldt Nielsen V, Hayford AE, Paerregaard A et al (1999)**
Screening of probiotic activities of forty-seven strains of *Lactobacillus* spp. by *in vitro* techniques and evaluation of the colonization ability of five selected strains in humans
Appl Environ Microbiol 65 4949-4956
- 12 **Lorca GL, Wadström T, Font de Valdez G, Ljungh Å (2001)**
Lactobacillus acidophilus autolysins inhibit *Helicobacter pylori* in vitro
Curr Microbiol 42 39-44
- 13 **Sinkiewicz, G, Casas I, Thorball J (2001)**
Inhibition of common pathogens by the probiotic *Lactobacillus reuteri* (*L. reuteri*)
Clin Nutr 20 66 (abstract no. 244).
- 14 **Johnson C, Dicksved J, Jonsson H, Roos S (2003)**
Anti *Helicobacter pylori* activity among lactic acid bacteria isolated from gastric biopsies and strains of *Lactobacillus reuteri*
Helicobacter 8 473
- 15 **Casas AI, Edens FW, Dobrogosz WJ (1997)**
Lactobacillus reuteri: an effective probiotic for poultry, other animals and humans.
In: *Lactic acid bacteria* Salminen S, von Wright A eds. Marcel Dekker, New York, p 475-518
- 16 **Wolf BW, Garleb K, Ataya D, Casas IA (1995)**
Safety and tolerance of *Lactobacillus reuteri* in healthy adults male subjects
Microbial Ecol Health Dis 8 41-50
- 17 **Wolf BW, Wheeler K, Ataya D, Garleb KA (1998)**
Safety and tolerance of *Lactobacillus reuteri* supplementation to a population infected with the human immunodeficiency virus
Food Chem Toxicol 36 1085-1094
- 18 **Salminen MK, Tynkkynen S, Rautelin H, Saxelin M, Vaara M, Ruutu P et al (2002)**
Lactobacillus bacteremia during a rapid increase in probiotic use of *Lactobacillus rhamnosus* GG in Finland
Clin Inf Dis 35 1155-1160
- 19 **Ruiz-Palacios GF, Tuz F, Arteaga, Guerrero ML, Dohnalek M, Hilty M (1996)**
Tolerance and fecal colonization with *Lactobacillus reuteri* in children fed a beverage with a mixture of *Lactobacillus* spp
Pediatr Res 39 1090

- 20 **Ruiz-Palacios G, Guerrero M, Hilty M (1996)**
Feeding of a probiotic for the prevention of community-acquired diarrhea in young Mexican children
Pediatr Res **39** 1089
- 21 **Guerrero M, Dohnalek M, Newton P, Kuznetsova O, Ruiz-Palacios G, Murphy T et al (1996)**
Effect of probiotic-containing beverages on incidence of diarrhoea. 1st World Congress of Pediatric Infectious Diseases, Dec. 1996, abstract 610 45-52
- 22 **Shornikova A, Casas IA, Isolauri E Mykkänen N, Vesikari T (1997)**
Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children
J Pediatr Gastroenterol Nutr **24** 399-404
- 23 **Shornikova A, Casas IA, Mykkanen H, Salo E, Vesikari T (1997)**
Bacteriotherapy with *Lactobacillus reuteri* in rotavirus gastroenteritis
Pediatr Infect Dis J **16** 1103-1107
- 24 **Karvonen A, Casas I, Vesikari T (2001)**
Safety and possible anti-diarrhoeal effect of the probiotic *Lactobacillus reuteri* after oral administration to neonates
Clin Nutr **20 (suppl 3)** 63
- 25 **Weizman Z, Alsheikh A (2003)**
Safety of infant formula supplemented with probiotics in early infancy
Clin Nutr **22 (suppl 1)** S69-70
- 26 **Kelleher SL, Casas I, Carbajal N, Lönnerdal B (2002)**
Supplementation of infant formula with the probiotic *Lactobacillus reuteri* and zinc: impact on enteric infection and nutrition in infant rhesus monkeys
JPGN **35** 162-168
- 27 **Weizman Z, Asli G, Alsheikh A (2003)**
Infant formula supplemented with probiotics reduces gastrointestinal infections rate in day care infants
Clin Nutr **22 (suppl 1)** S69
- 28 **Rosenfeldt V, Michaelsen KF, Jakobsen M, Nexmann Larsen C, Lange Moller P, Pedersen P et al (2002)**
Effect of probiotic *Lactobacillus* strains in young children hospitalized with acute diarrhea
Ped Inf Dis J **21** 411-416
- 29 **Rosenfeldt V, Michaelsen KF, Jakobsen M, Nexmann Larsen C, Lange Moller P, Tvede M et al (2002)**
Effect of probiotic *Lactobacillus* strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers
Ped Inf Dis J **21** 417-419
- 30 **Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen KF, Jeppesen DL, Valerius NH et al (2003)**
Effect of probiotic *Lactobacillus* strains in children with atopic dermatitis
J Allergy Clin Immunol **111** 389-395
- 31 **Valeur N, Engel P, Carbajal N, Connolly E, Ladefoged K (2004)**
Colonization and immunomodulation by *Lactobacillus reuteri* ATCC 55730 in the human gastrointestinal tract
Appl Environ Microbiol **70** 1176-1181
- 32 **Casas AI, Edens FW, Dobrogosz WJ (1997)**
Lactobacillus reuteri: an effective probiotic for poultry, other animals and humans.
In: *Lactic acid bacteria* Salminen S, von Wright A eds. Marcel Dekker, New York, p 475-518
- 33 **Mao Y, Yu JL, Ljungh A, Molin G, Jeppsson B (1996)**
Intestinal immune response to oral administration of *Lactobacillus reuteri* R2LC, *Lactobacillus plantarum* DSM 9843, pectin and oatbase on methotrexate-induced enterocolitis in rats
Microbial Ecol Health Dis **9** 261-270
- 34 **Mao Y, Nobaek S, Kasravi B, Adawi D, Stenram U, Molin G et al (1996)**
The effects of *Lactobacillus* strains and oat fibre on methotrexate-induced enterocolitis in rats
Gastroenterology **111** 334-344
- 35 **Ferreira R, Forsyth LE, Richman PL (1990)**
Changes in the rate of crypt epithelial cell proliferation and mucosal morphology induced by a T-cell-mediated response in human small intestine
Gastroenterology **98** 1255-1263
- 36 **Pena JA, Versalovic J (2003)**
Lactobacillus paracasei and *Lactobacillus reuteri* inhibit TNF-alpha production by *Helicobacter*-activated murine macrophages
Helicobacter **8** 365