



Emerging Probiotic Research: A Guide to the Use of Probiotics in Clinical Practice

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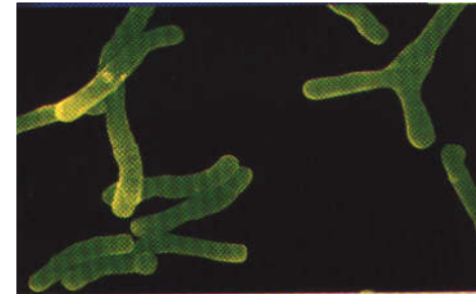
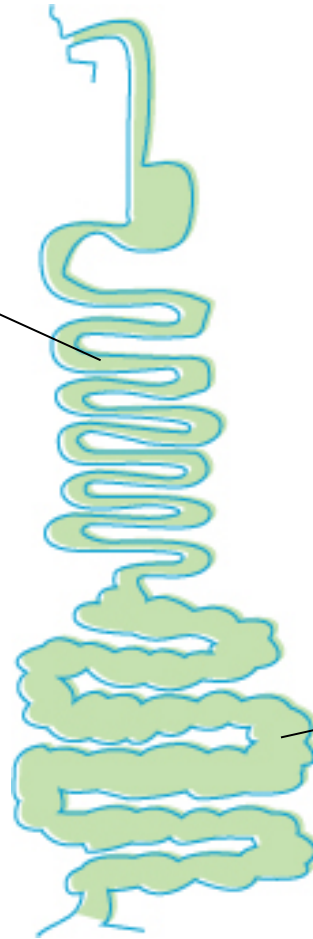
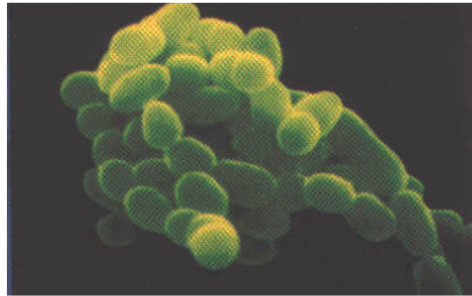
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Probiotics

- ***WHO Definition:***
 - ***“Live microorganisms, which when administered in adequate amounts, confer a health benefit on the host.”***

Two Main Families of Probiotics

Lactobacilli
(mostly reside
in small
intestine)

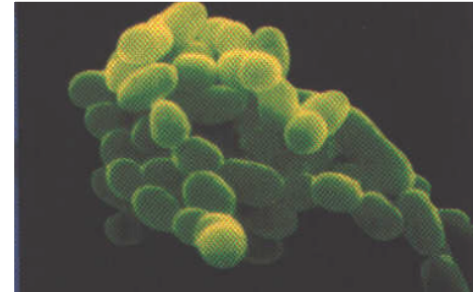
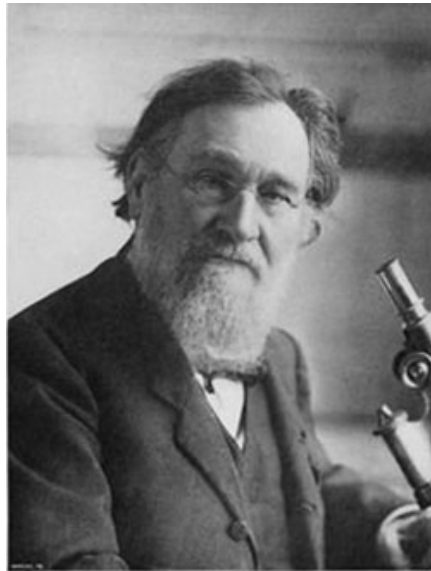


Bifidobacteria
(mostly reside in
large intestine)

Lactobacilli

“Ingested *lactobacilli* can displace toxin-producing bacteria, promoting health and prolonging life.”

***Elie Metchnikoff – 1908
(The Prolongation of Life)***



Bifidobacteria

- ***Bifidobacterium* was first isolated in 1899 from a healthy breast-fed infant at the Pasteur Institute in France by Henry Tissier.**
- ***Originally placed in the same genus with Lactobacillus, it was given its own genus in the 1960s.***



Probiotic Species

- **Lactobacillus**

- *L. acidophilus, L. bulgaricus, L. brevis, L. casei, L. fermentum, L. helveticus, L. plantarum, L. rhamnosus, L. salivarius, L. johnsonii, L. paracasei, L. reuteri*

- **Bifidobacterium**

- *B. bifidum, B. infantis, B. longum, B. breve, B. lactis*

- ***Saccharomyces boulardii***

Species vs. Strain



Genus

Species

Strain

- ***Species:*** each has common characteristics
- ***Strains:*** Each has its own characteristics/
health benefits (often proprietary)



Mechanisms of Action

- ***Competition with microbial pathogens for receptor sites***
- ***Production of antimicrobial substances and weak acids***
- ***Competitive consumption of nutrients***
- ***Increased production of mucin***



Benefits of Probiotics

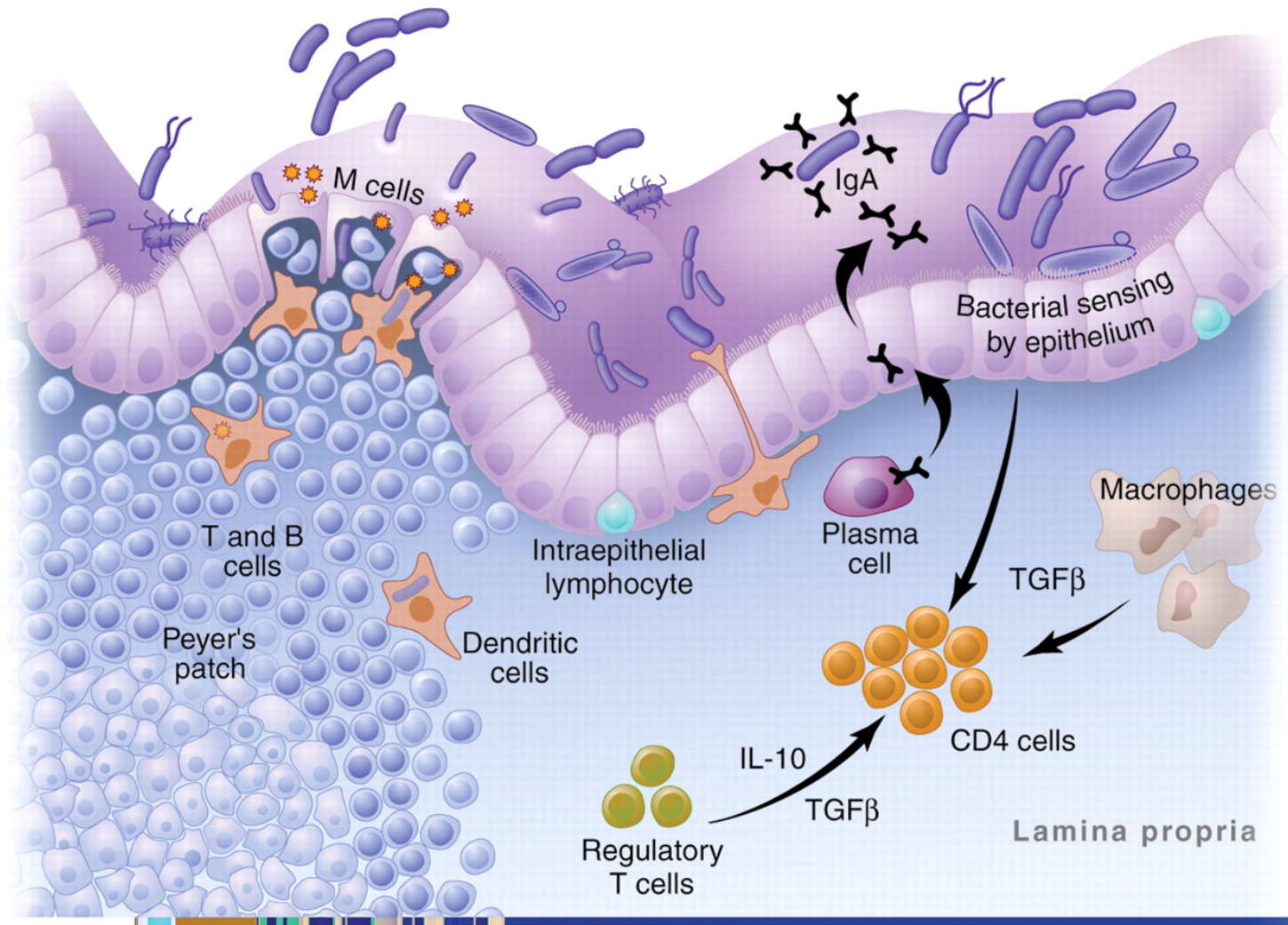
- ***Decreased intestinal inflammation/enhanced mucosal integrity (normalization of gut permeability)***
- ***Lessened systemic antigenic exposure/allergic sensitization (non-allergic children have higher concentrations of *Lactobacilli* and *Bifidobacteria*)***
- ***Increased local immune activity (IgA, GALT, IFN)***
- ***Systemic immune modulation***

Anti-inflammatory/ Immunomodulatory Effects

- ***Some probiotic strains have been shown *in vitro* and *in vivo* (animal studies) to induce Th1 production and downregulate some proinflammatory cytokines and Th2-mediated allergic responses. Also noted has been a decrease in IgE levels.***
- ***Effect on toll-like receptors – essential to innate defense against pathogens and trigger adaptive immune responses.***
- ***Additionally, by influencing cell adhesion and cell-cell signaling in the gut, probiotics appears to strengthen the integrity of the gut mucosa.***

Nutrition Reviews 2006;64:1-14.

Gut and Immune System Communication





Probiotics in Pediatrics

Development of Gut Flora

- ***The human gut is germ free at birth. Microbial colonization begins at birth when the infant swallows microflora from the vaginal fluid at delivery.***
- ***Factors influencing the gut flora of an infant include:***
 - ***Mode of delivery – vaginal vs. caesarean***
 - ***Breast fed vs. Formula fed***
 - ***Genetics***

Int J Pharm 2006;20:37-48.



Probiotics in Pediatrics

Development of Gut Flora, cont.

- ***Development of GALT begins shortly after birth.***
 - ***An adult-type pattern of stable indigenous gut microflora is established over first few months and years of life concomitantly with the development of GALT as the most important part of the adaptive immune system.***
- ***All infants are initially colonized by *E. coli* and *Streptococci*, followed by the establishment of anaerobic bacteroides, *Bifidobacterium* and *Clostridium* by the end of the first week of life.***
 - ***Caesarean delivered infants are colonized with more anaerobic bacteria, especially bacteroides, than vaginally delivered infants.***



Probiotics in Pediatrics

Breast-fed vs. Formula-fed Infants

- ***The flora of breast-fed infants contains more bacteroides, Clostridia and enterobacteria. Lactic acid bacteria is one of the dominating microbes while formula-fed infants have more diverse flora that develops more rapidly than breast-fed infants.***
- ***IgA and lysozyme in breast milk prevent the growth of some bacteria and breast milk appears to have prebiotic properties (contains GOS).***
- ***The feces of breast fed infants mainly contain lactic and acetic acid compared to acetic and proprionic acid in formula-fed infants who also have higher fecal ammonia and potentially harmful bacterial products.***

Int J Pharm 2006;20:37-48.

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Prenatal/Neonatal Applications

- ***Necrotizing enterocolitis (prevention)***
- ***Prevention of atopic disease in at-risk infants (e.g., atopic dermatitis)***
- ***Candida spp. colonization (prevention)***

Prevention of Necrotizing Enterocolitis

- ***Cochrane Review Meta-analysis – 2008***
 - ***Nine eligible randomized studies with 1425 preterm infants <37 weeks gestational age and <2500 g birth weight***
 - ***Enteral probiotics supplementation significantly reduced the incidence of severe NEC (stage II or more) [typical RR 0.32 (95% CI 0.17, 0.60)] and mortality [RR 0.43 (95% CI 0.25, 0.75)]***
 - ***The included trials found no cases of systemic infection due to the probiotic strains used in the supplements***

Prevention of Atopic Dermatitis

- ***159 pregnant women (or their partner) with at least one first-degree relative with a history of atopic dermatitis, allergic rhinitis, or asthma (this included mother, father, or older sibling) and their infants postnatally.***
- ***132 women and their infants completed the study at the end of the two years. Lactobacillus GG—two capsules daily for 2 to 4 weeks before expected delivery. After delivery, breastfeeding mothers continued to take the capsules; otherwise, infants were given the contents of the capsules mixed with water. The duration of postnatal supplementation was six months.***

Prevention of Atopic Dermatitis, cont.

- ***Two Year Follow-up***
 - *Frequency of AD was 46% in the placebo group compared to 23% in the probiotic group (Lancet 2001;357:1076-79).*
- ***Four Year Follow-up***
 - *Frequency of AD was 46% in the placebo group compared to 26% in the probiotic group (Lancet 2003;361:1869-71).*
- ***Seven Year Follow-up***
 - *Cumulative risk of developing AD was significantly lower in the probiotic group (42.6%) compared to the placebo group (66.1%) (J Allergy Clin Immunol 2007;119:1019-21).*

Prevention of Atopic Dermatitis Update

- ***DB, PC trial with 188 children. Mothers given *L. reuteri* (1 x 10⁸cfu/day) or placebo from gestational week 36 until delivery. Infants continued from birth until 12 months. One year follow-up. Cumulative incidence of AD was the same in both groups but the probiotic group had less IgE-associated AD in the 2nd year (8% vs. 20%; p = 0.02) (*J Allergy Clin Immunol* 2007;119:1174-80).***
- ***Newborns of women with allergy were given *L. acidophilus* (LAVARI-A1; 3 x 10⁹cfu/day) or placebo for 6 months. There was no reduction in the incidence of AD compared to placebo (*J Allergy Clin Immunol* 2007;119:184-91).***

Prevention of Atopic Dermatitis Update, cont.

- **DB, PC trial with 474 infants. Mothers took either *L. rhamnosus* HN001 (6×10^9 cfu/day), *B. lactis* HN019 (9×10^9 cfu/day), or placebo from 35 weeks gestation until 6 months if breastfeeding or the same dose to the infant if weaned. Infants in the *L. rhamnosus* group had a significantly ($p = 0.01$) reduced incidence of AD at 24 months but not the *B. lactis* group (*J Allergy Clin Immunol* 2008;122:788-94).**
- **DB, PC trial with 102 infants. Mothers took a combination probiotic product (*B. bifidum*, *B. lactis*, *Lactococcus lactis* [Ecologic® Panda]; 3×10^9 cfu/day) or placebo or the last 6 weeks of pregnancy and to the child for 12 months. The incidence of AD was reduced significantly in the first 3 months of life in the probiotic group but only slightly beyond that (*Allergy* 2009 DOI: 10.1111/j.1398-9995).**



Pediatrics

Gastrointestinal Applications

- ***Acute Infectious Diarrhea***
- ***Antibiotic-Associated Diarrhea (prevention)***
- ***Recurrent *C. difficile* Diarrhea (treatment or prevention)***
- ***Colic***
- ***Constipation***
- ***Irritable Bowel Syndrome***
- ***Ulcerative Colitis***
- ***Helicobacter pylori Infection***

Combination of *L. rhamnosus* Strains Shortens Duration of Infectious Diarrhea

- **In a DBPCT, 87 children (2 mths - 6 years old) with infectious diarrhea were rehydrated orally or intravenously and then realimentation was initiated. Children were then randomized to receive either 1.2×10^{10} CFU of a freeze-dried mixture of three *L. rhamnosus* strains or placebo b.i.d. for 5 days.**
- **Etiology of diarrhea was identified in 53 of 87 children: 39 had rotavirus infection, 5 had adenovirus gastroenteritis, and 9 showed the presence of bacterial organisms (e.g., *Salmonella enteritidis*, *E. coli*).**

Combination of *L. rhamnosus* Strains Infectious Diarrhea, cont.

- ***Considering all cases combined, the duration of diarrhea was not significantly shorter than those in the control group.***
- ***However, the duration of diarrhea in children with rotavirus infection taking probiotics was significantly shorter than those receiving placebo ($p = 0.03$). In patients below the age of 12 mths with rotavirus infection, those treated with probiotics had a significant reduction in the duration of diarrhea compared to controls ($p = 0.001$).***
- ***When the intervention started before the 72nd hour of diarrhea, probiotic-treated children had a significantly shorter duration of illness than controls. If after, then there was no difference.***

Aliment Pharmacol Ther 2006;23:247–53.

***Saccharomyces boulardii* – Treatment of Acute Diarrhea**

- **200 children (3 mths-7 years old) with acute diarrhea for a minimum of 24 hours before admission to the trial but not for longer than 7 days were given either placebo or *S. boulardii* -- 250 mg/day diluted with water or juice for 5 days. Patients were given oral rehydration therapy and normal food for their age.**
- **No sig. differences in the first 24 hours. The number of stools showed a significant reduction in the *S. boulardii* group after day 2 ($p = 0.003$) and day 3 ($p = 0.002$). The duration of diarrhea was significantly reduced in children receiving *S. boulardii* compared to placebo ($p = 0.03$). Diarrhea persisted over 14 days in four children in the placebo group compared to only one in the *S. boulardii* group.**

Acute Diarrhea, cont.

- ***Large randomized, controlled study (n = 662) in India with children with acute watery diarrhea. Use of L. GG did not decrease the frequency or duration of diarrhea and vomiting (J Ped Child Health 2007;43:837-42).***
- ***Another Indian study looked at the efficacy of LGG (60 million cfu bid) in children (n = 235) with persistent diarrhea (14 or more days). The mean duration was significantly lower in the treatment group compared to controls (5.3 vs. 9.2 days) (J Gastroenterol 2007;41:756-60).***

Probiotics for Pediatric Antibiotic-Associated Diarrhea

- ***Meta-analysis initiated by the CARE (Complementary and Alternative Research and Education) Program at Stollery Children's Hospital, University of Alberta***
- ***Six studies (n = 707 patients) considered – combined results showed a significant benefit vs. placebo***
- ***However, ITT analysis was nonsignificant overall***
- ***Reviewers call for greater attention to drop-out rates and subjects lost to follow-up in future studies as well as greater standardization of organisms used and also dose-response studies***

CMAJ 2006;175:377-83.

Chronic Constipation

- ***45 children under age 10 years with chronic constipation were randomized to receive *L. caseirhamnosus*(Lcr35, 8 x 10⁸cfu/day), MgO (50 mg/kg/day), or placebo twice daily for 4 weeks.***
- ***Children who received either Lcr35 or MgO had a significantly higher defecation frequency ($p = 0.03$), higher percent of treatment success ($p = 0.01$), less use of glycerin enema ($p = 0.04$), and less hard stool ($p = 0.01$) compared to placebo. There was no difference between the Lcr35 and MgO groups in efficacy on the above. Abdominal pain was less frequent in the Lcr35 group compared to both the MgO and placebo groups ($p = 0.03$).***

Ped International 2007;49:485-90.

Ulcerative Colitis

- ***Placebo-controlled, randomized trial with 29 new diagnosed pediatric UC patients (1.7-16.1 years old). Dose of VSL#3 was weight based (450-1,800 billion/day). All children were also treated with prednisone (induction treatment) and 5-ASA (maintenance treatment). Treatment was for 1 year.***
- ***Remission was achieved in 13 patients treated with VSL#3 (92.8%) and IBD therapy compared to 3 in the placebo group (21.4%). Three patients (21.4%) in the VSL#3 group relapsed in 1 year compared to 11 (73.3%) in the placebo group ($p = 0.014$). At 6 and 12 months, or at time of relapse, endoscopic and histological scores were significantly lower in the VSL#3 group ($p < 0.05$).***

VSL#3 – 300 billion bacteria/g – contains *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. casei*, *L. bulgaricus*, *S. thermophilus*

Am J Gastroenterol 2009;104:437-44.



Adult

Gastrointestinal Applications

- ***Antibiotic-associated diarrhea***
- ***Recurrent *C. difficile****
- ***Irritable bowel syndrome***
- ***Inflammatory bowel disease***
- ***Helicobacter pylori* – adjunctive use**
- ***Functional constipation***
- ***Colorectal tumors***

Dysbiosis in IBS and IBD

- ***Small intestinal bacterial overgrowth (SIBO) postulated to be a causative factor in IBS. 75% improvement in IBS after eradication of SIBO (JAMA 2004;292:852-8).***
- ***Colonic microflora of 57 patients with active IBD was compared to 46 healthy controls. Diversity of bacterial microflora significantly less in the IBD patients with notable loss of normal anaerobic bacteria such as *Lactobacillus* spp. (Gut 2004;53:685-93).***

Probiotics for IBS Meta-Analysis

- ***14 randomized DBPCT identified as sufficient for review (4-26 weeks in duration); two were pediatric studies; strains used varied from 1 to 8 (VSL #3).***
- ***With the exception of one trial, the data suggests a modest improvement in overall symptoms. Seven trials found a significant reduction in abdominal pain; five for flatulence and four for bloating.***
- ***Authors suggest future trial focus on the type and optimal dose of probiotics and subgroups of patients most likely to respond.***

***B. infantis* for IBS**

- ***In a DBPCT, 75 IBS patients (ages 18 – 73 years) were randomized to receive either 1×10^{10} cfu of *L. salivarius* UCC4331 or *B. infantis* 35624 in a malted milk drink or placebo q.d. for 8 weeks.***
- ***The composite Likert score was significantly lower for those treated with *B. infantis* compared to placebo ($p < 0.05$) during treatment and for one week after treatment stopped. Likert scores for bloating and abdominal pain were also significantly decreased in the *B. infantis* 35624 group ($p < 0.05$). Bowel movement difficulty decreased significantly for weeks 2 to 6 during the treatment with *B. infantis* 35624 ($p < 0.05$).***

***B. infantis* for IBS, cont.**

- ***The composite VAS score significantly decreased in weeks 2 – 9 in the *B. infantis* 35624 group compared to placebo ($p < 0.05$). Treatment with *B. infantis* 35624 resulted in significantly lower scores for bowel movement difficulty and composite Likert and composite VAS scores compared to *L. salivarius* UCC4331 ($p \leq 0.05$).***
- ***At baseline the IL-10 / IL-12 ratio was significantly different in volunteers with IBS compared to healthy controls. Treatment with *B. infantis* 35624 significantly increased the IL-10 / IL-12 ratio ($p = 0.001$), which approximated the IL-10 / IL-12 levels detected in the control group at baseline (values not reported).***

***Gastroenterol* 2005;128:541–51.**

***B. infantis* for IBS, cont.**

- ***Follow-up DBPC trial with 362 IBS patients. Randomized to placebo or 1×10^6 , 1×10^8 , or 1×10^{10} cfu *B. Infantis* 35624 for 4 weeks.***
- ***The 1×10^8 dose was clinically superior to placebo and the other doses for the primary efficacy variable of abdominal pain as well as bloating, bowel dysfunction, incomplete evacuation, straining, and passage of gas.***
- ***No significant adverse events were recorded.***

Am J Gastroenterol 2006;101:1581-90.

Lactobacillus GG & Ulcerative Colitis Delays Relapses

- ***In an open-label study, 187 patients (mean age of 33 years) with UC that were in remission for no longer than 12 months based on laboratory and endoscopic examinations. Patients were randomized to one of the following treatment groups:***
 - ***1) Lactobacillus GG (LGG)— 18×10^9 cfu/day;***
 - ***2) Mesalazine—800 mg t.i.d.;***
 - ***3) LGG plus mesalazine (same doses as above) – treatment for 12 months.***
- ***Patients maintaining clinical remission after 6 and 12 months of treatment was 91% and 85%, respectively, for the LGG group, 87% and 80 % for the mesalazine group, and 94% and 84% for the combined treatment group. These differences were not statistically significant.***

Lactobacillus GG & Ulcerative Colitis Delays Relapses, cont.

- ***Patients in the mesalazine group had the tendency to relapse earlier than the LGG group or the combination treatment group. These differences were significant (LGG, $p = 0.01$; combination treatment, $p = 0.03$).***
- ***The difference between the LGG group and the combination group did not reach statistical significance. No significant side effects to any of the treatments were reported.***

Probiotics

Reduce side effects of *H. pylori* treatment

- **85 male and female patients with a diagnosis of *H. pylori* infection - all were treated with a combination of rabeprazole, clarithromycin, and tinidazole for one week.**
- **During the 7-day treatment period and for 7 days after patients were randomized to additionally receive one of the following:**
 - **(1) a combination of *L. acidophilus* and *B. lactis* (approx. 10 billion organisms per day);**
 - **(2) *Lactobacillus GG* (approx. 12 billion organisms per day);**
 - **(3) *S. boulardii* (approx. 10 billion organisms per day);**
 - **(4) placebo.**

Probiotics

Reduce side effects of *H. pylori* treatment, cont.

- ***The incidence of diarrhea was significantly lower in all three probiotic groups compared to the placebo group. The risk of diarrhea during week one for individuals treated with probiotics versus placebo was significantly lower as was the incidence of taste disturbance in all probiotic groups compared to placebo.***
- ***Overall tolerability of treatment was significantly superior in all treatment groups compared to placebo.***

Am J Gastroenterol 2002;97:2744-49.

Probiotics improve outcome in treatment of *G. lamblia*

- **65 adult patients with giardiasis were treated as follows: Group 1 (17 were symptomatic) was treated with 750 mg of metronidazole t.i.d. and 250 mg of encapsulated *Saccharomyces boulardii* b.i.d. for 10 days. Group 2 (15 were symptomatic) were treated with just metronidazole and placebo for 10 days.**
- **At the end of the 2nd week, *G. lamblia* cysts were detected in 6 cases (17.1%) in group 2 compared to no cases in group 1. The proportion of patients with clearance of microscopic findings after two weeks as 100% in group 1 compared to 82% in group 2 ($p = 0.027$).**



Pediatrics

Misc. Indications

- ***Atopic Dermatitis – treatment***
- ***Wellness/Prevention of ARIs***

Treatment of Atopic Dermatitis

- ***Double-blind, placebo-controlled crossover trial using *L. reuteri* and *L. rhamnosus* for children with moderate to severe atopic dermatitis. Marked decrease in gastrointestinal symptoms and decreased gastrointestinal permeability with probiotic therapy (*J Pediatr* 2004;145:612-6).***
- ***An earlier pediatric study found that eczema improves with combination of *L. reuteri* and *L. rhamnosus* (*J Allergy Clin Immunol* 2003;11:389–95).***
- ***Infants with AD (3-12 months) treated with *L. GG* or placebo for 12 weeks. No therapeutic effect for the probiotic treatment (*Allergy* 2007;62:1270-6).***

Lactobacillus GG - Reduces Symptoms of Atopic Dermatitis in IgE-sensitized Infants

- 230 infants (ages 1.4-11.9 months) with symptoms that suggested cow's milk allergy (CMA), one of which had to be atopic eczema/dermatitis syndrome (AEDS) – received either *L. GG* (5×10^9 CFU) mixed with food b.i.d; a MIX group, which were treated with *L.GG*, *L. rhamnosus* LC705 (5×10^9 CFU), *B. breve shermanii* JS (2×10^9 CFU) b.i.d; or placebo.
- *L. GG* reduced mean SCORAD significantly greater than placebo in a subgroup of infants with IgE-associated AEDS (-26.1 vs. -19.8, respectively; $p = 0.036$). The MIX group showed no difference compared to placebo in this subgroup.

Lactobacillus fermentum

Reduces Severity of Atopic Dermatitis

- ***In an 8-week DBPC, 56 children aged 6-18 months with moderate or severe AD (SCORAD index score of ≥ 25) were treated with 1 billion cfu of *L. fermentum* VR1-003 PCC or placebo b.i.d.***
- ***Compared to baseline, the reduction in SCORAD index was significant in the probiotic group ($p = 0.03$) but not the placebo group ($p = 0.83$) - difference between the two groups did not reach statistical significance ($p = 0.06$). Significantly more children receiving probiotics ($n = 24$, 92%) had a SCORAD index that was better than baseline at week 16 compared with the placebo group ($n = 17$, 63%) ($p = 0.01$). At the completion of the study, more children in the probiotic group had mild AD ($n = 14$, 54%) compared to the placebo group ($n = 8$, 30%).***

Probiotics/Pediatrics

Wellness – Prevention of ARIs

- **326 children (3-5 years of age) were randomized to receive either *L. acidophilus* NCFM (1×10^{10} cfu/day; $n = 110$), *L. acidophilus* combined with *B. animalis subsp lactis* BI-07 (1×10^{10} cfu/day; $n = 112$), or placebo ($n = 104$) for 6 months.**
- **Compared to the placebo group, the following was found:**
 - **Reduced fever incidence – single probiotic (53%; $p = 0.0085$); combination (72.7%; $p = 0.0009$)**
 - **Reduced coughing incidence – single (41.4%; $p = .027$); combination (62.1%; $p = 0.005$)**
 - **Reduced rhinorrhea – single (28.2%; $p = 0.68$) combination (58.8%; $p = 0.03$)**
 - **Fever, coughing, and rhinorrhea duration was decreased significantly by 32% in the single strain group ($p = 0.0023$) and 48% in the combination ($p < 0.001$)**



Probiotics/Pediatrics Wellness – Prevention of ARIs, cont.

- ***Incidence of antibiotic use was reduced by 68.4% in the single strain group ($p = 0.0002$) and 84.2% in the combination group ($p < 0.0001$)***
- ***There was a significant reduction in absences from day care in both probiotic groups compared to the placebo group—31.8% in the single strain group ($p = 0.002$) and 27.7% in the combination group ($p < 0.001$)***

Pediatrics 2009;124:e172-e179.



Probiotics

Female Genitourinary

- ***Bacterial vaginosis***
- ***Vulvovaginal candidiasis***

Bacterial Vaginosis

- ***In a DBPCT, 125 premenopausal women (18-44 years old) with diagnosed BV received oral metronidazole (550 mg b.i.d.) from days 1 to 7 and then randomized to receive one capsule of *L. rhamnosus* GR-1 (2.5×10^9) and *L. reuteri* RC-14 (2.5×10^9) or placebo orally b.i.d. from days 1 to 30.***
- ***In the antibiotic/probiotic group, 88% of women were cured compared to 40% in the antibiotic/placebo group ($p < 0.001$). Of the remaining antibiotic/probiotic subjects (12%), none had BV, but had mild irritative symptoms, no discharge or odor, a weakly positive sialidase score and intermediate Nugent score. This contrasted with the remaining 34 antibiotic/placebo subjects, of which half had BV and the other half had an intermediate status.***

Bacterial Vaginosis

- ***100 women (mean age 34 years) with bacterial vaginosis were treated with 2% vaginal clindamycin cream for 7 days and then randomized to receive capsules (vaginally inserted) containing either placebo or a combination of *L. gasseri* and *L. rhamnosus*(10⁹cfu per capsule) for 10 days. The above was repeated for 3 cycles.***
- ***Treatment with the probiotic combination did not improve the efficacy of BV treatment during the first month of treatment.***
- ***However, women initially “cured” were followed for 6 menstrual cycles or until relapse within that time. At the end of 6 months, 64.9% of the probiotic-treated group were still BV-free compared to 46.2% in the placebo group (p = 0.027).***

BMC Women's Health 2008;8:3 (doi: 10.1186/1472-6874-8-3)

Vulvovaginal Candidiasis

- ***RDBPCT with 55 women diagnosed with VVC. All were treated with a single dose of fluconazole (150 mg) and two oral capsules of either placebo or a combination of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (1×10^9 of each organism per capsule) once daily for 28 days.***
- ***At 4 weeks, the probiotic group exhibited cure of VVC as determined by having no vaginal discharge, itching and/or burning, dyspareunia and/or dysuria and negative culture compared to the placebo group ($p < 0.05$). The probiotic treated group showed significantly less vaginal discharge (10.3% vs. 34.6%; $p = 0.03$) and lower presence of yeast detected by culture (10.3% vs. 38.5%; $p = 0.014$).***

Letters Applied Microbiol 2009;48:269-74.

Intestinal Microflora Changes in the Elderly

- ***Distinct changes occur in the composition of the intestinal microflora in the elderly.***
- ***There is a decline in the number of protective anaerobes with increased age, including bacteroides and bifidobacteria as well total SCFA.***
- ***These changes in intestinal bacteria, and changes in diet and digestive physiology, such as intestinal transit time, may result in increased putrefaction and greater susceptibility to gastroenteritis, *C. difficile*(especially following antibiotic treatment), and possibly a decline in cellular immunity.***

J Applied Microbiol 2007;102:1178-86.

Probiotics Enhance Immune Function in the Elderly

- ***30 healthy elderly volunteers (63-84 years old) participated in a 3-stage dietary intervention trial lasting 9 weeks. During the middle 3 weeks, subjects received *B. lactis* HN019 (5×10^{10} or 5×10^9 cfu per day) in skim milk.***
- ***After consumption of *B. lactis* HN019, there were notable increases in total, helper (CD4⁺), and activated (CD25⁺) T lymphocytes and natural killer cells. The ex vivo phagocytic capacity of mononuclear and polymorphonuclear cells and the tumoricidal activity of NK cells were also elevated after *B. lactis* consumption. The greatest changes were noted in subjects who had poor pretreatment immune responses. The response was the same for both doses.***

Am J Clin Nutr 2001;74:833-9.

Probiotic Safety

- ***Risk of translocation exists and probiotic-related sepsis has been reported in the literature. Proposed risk factors for probiotic sepsis (according to one source):***
- ***Major risk factors***
 - ***Immunocompromised, including a debilitated state or malignancy***
 - ***Premature infants***
- ***Minor risk factors***
 - ***Central venous catheter***
 - ***Impaired intestinal epithelial barrier, e.g., diarrheal illness, intestinal inflammation***
 - ***Administration of probiotics by jejunostomy***
 - ***Probiotics with properties of high mucosal adhesion or known pathogenicity***
 - ***Cardiac valvular disease***

Am J Clin Nutr 2006;83:1256-64.

Probiotic Safety, cont.

- ***A group of Finnish researchers reviewed 89 cases of *Lactobacillus* bacteremia -- all of them adults (*Clin Infect Dis* 2004;38:62-9). The primary predisposing factors to bacteremia were immunosuppression, prior to prolonged hospitalization, and prior to surgical interventions. Detailed species characterization from blood cultures was available for 53% of these cases. Cases of bacteremia, as well as mortality, were usually associated with severe underlying comorbidities--82% of cases were classified as having either ultimately or rapidly fatal diseases.***
- ***Bacteremia with *S. boulardii* has also been reported***
- ****L. reuteri* is one organism that has been demonstrated to be safe in HIV-positive individuals(*Food Chem Toxicol* 1998;36:1085-96) as has the combination of *L. reuteri* RC-14 and *L. rhamnosus* GR-1 (*J Clin Gastroenterol* 2008; 42:239-43).***



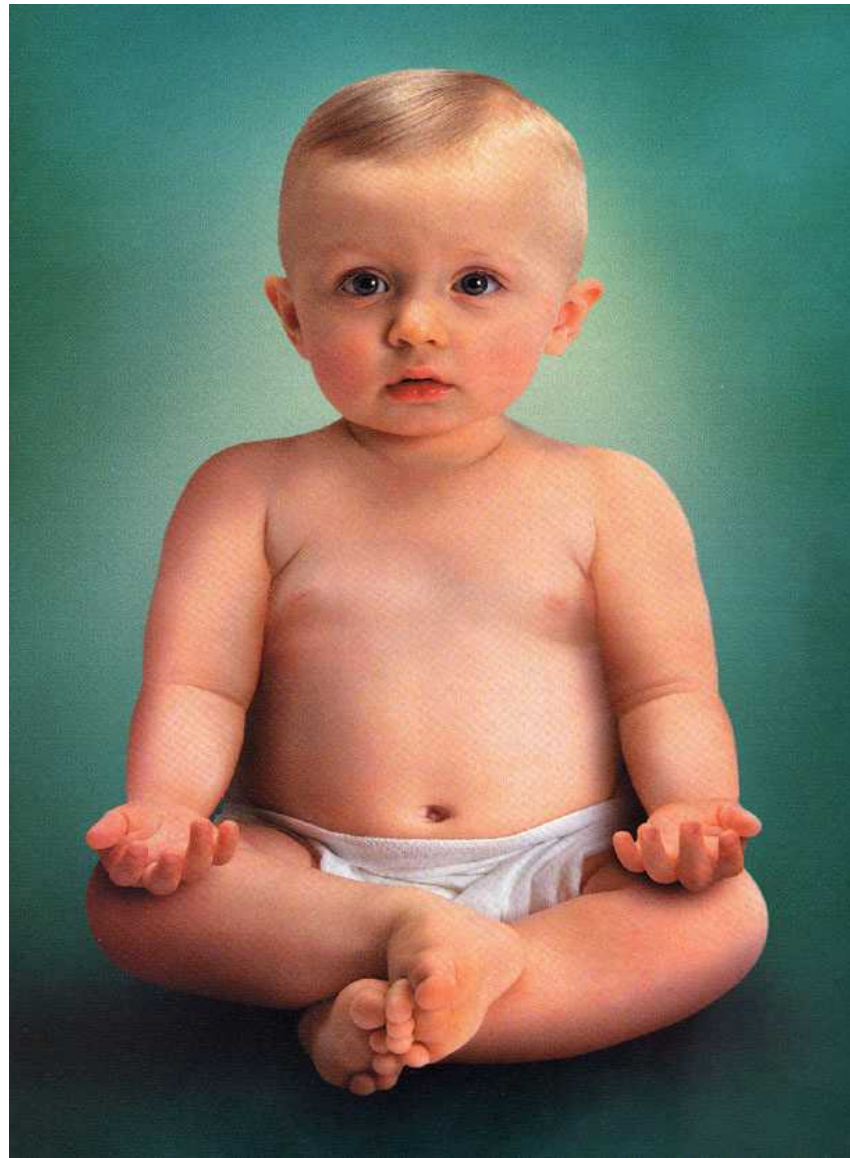
Probiotic Safety, cont.

- ***Despite concerns stated in previous slide, new data has found the following:***
 - ***Probiotics actually decrease translocation of some pathogenic bacteria***
 - ***Probiotics have now been extensively studied in very low birth weight infants with no safety issues***
- ***Bottom line is probiotic supplements are safe for a broad spectrum of the population.***



International Scientific Association for Probiotics and Prebiotics

- ***“Pick quality packaging and a trusted manufacturer”***
 - ***“Live bacteria – through the end of shelf life”***
 - ***“Packaging should ensure an effective level of live bacteria through the ‘best buy’ or expiration date”***



Questions?