Clinical Effects of Probiotics: A Pediatrician's Perspective

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TYKS TURUN YLIOPISTOLLINEN KESKUSSAIRAALA TURKU UNIVERSITY HOSPITAL

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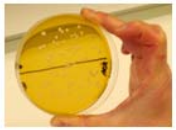


functional foods forum

The contents of the presentation

- Role of gut microbiota in the development of gut and its immune system
- Potential effects of probiotics on gut immune system
- Randomized clinical studies with probiotics
  - diarrhea
  - inflammatory bowel disease
  - irritable bowel syndrome
  - necrotizing enterocolitis (NEC)
  - allergic diseases
- Conclusions

Gut and its microbiota form immunologically active ecosystem

- Adult human gut harbours 1-2 kilograms of bacteria in the gut
- There are 10 x more prokaryotic cells in the gut than eukaryotic cells in the whole body
- The number of bacterial genes in the gut (microbiome) outnumber that of human genes (genome) by a factor of 100 - humans have been called 'supraorganisms'
- GALT (gut associated lymphatic tissue) forms a major part of the immune system (e.g. three fourths of the body's plasma cells are located in the GALT)

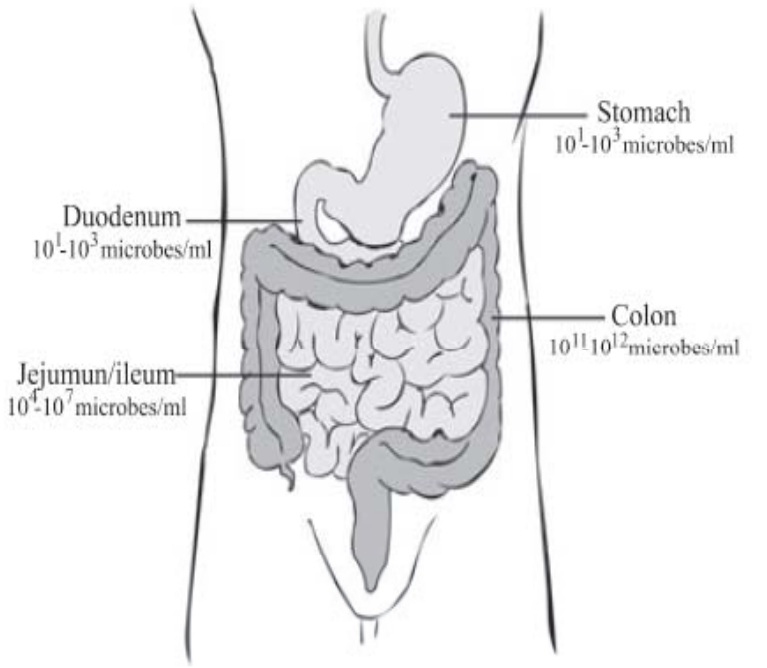


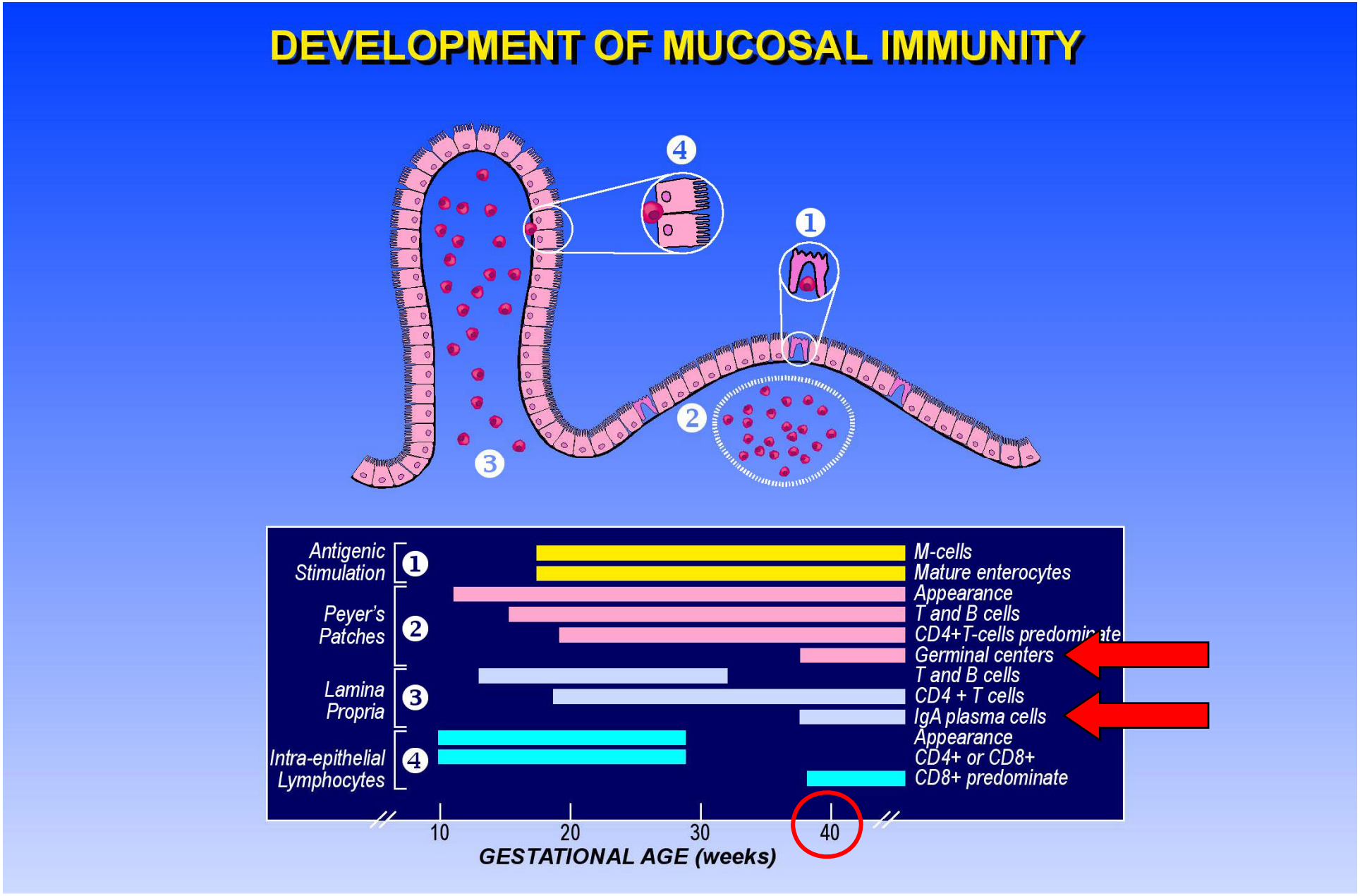
Figure 1. Bacterial densities increase throughout the gut, with highest concentrations found in the colon.

Figure from Allergy 2007;62:1223-36:

BUT…

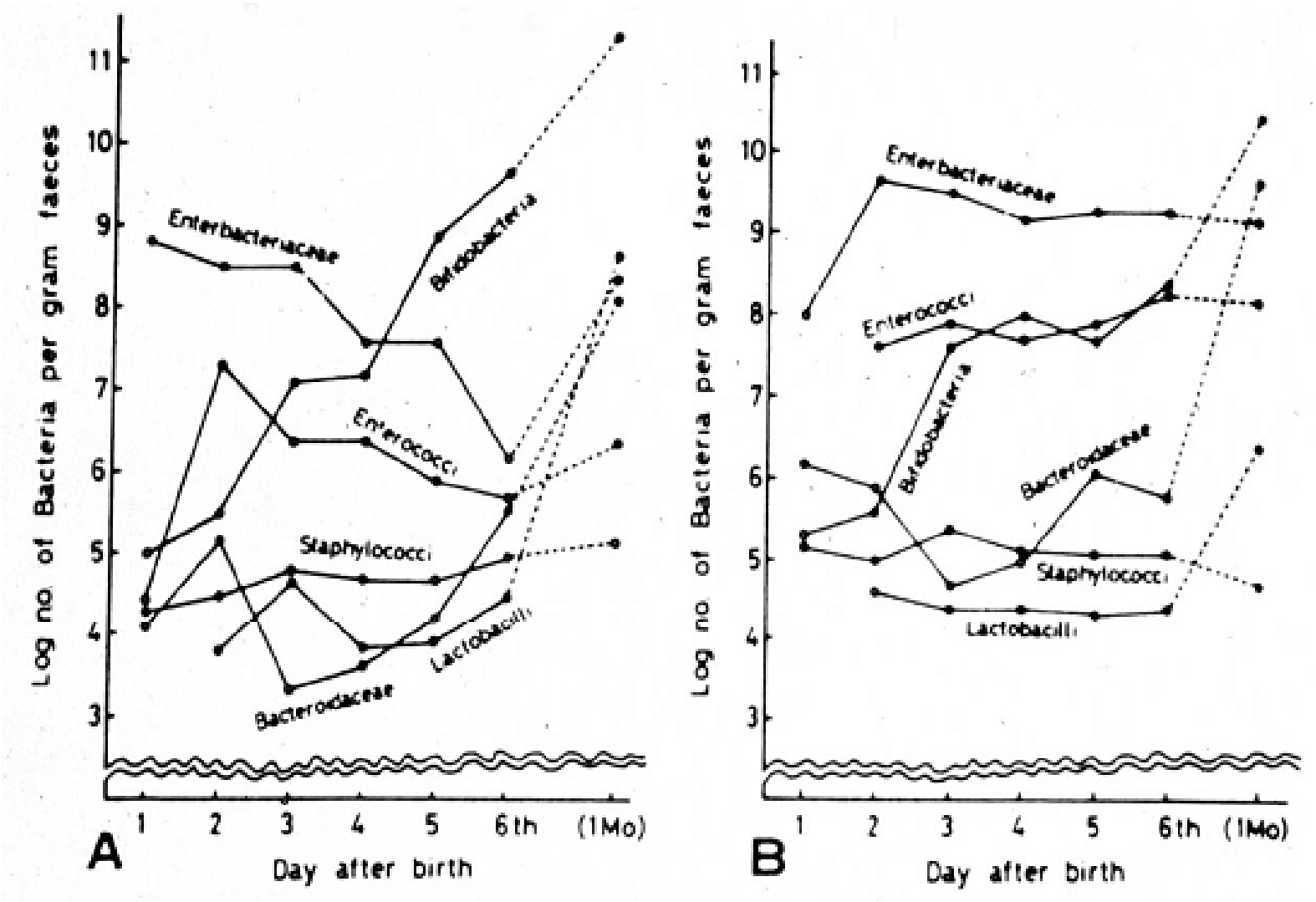
Development of mucosal immunity is immature at birth

(The figure is a generous courtesy from prof. Allan Walker, Harvard Medical School; modified from Walker WA and Sanderson I, 2003)



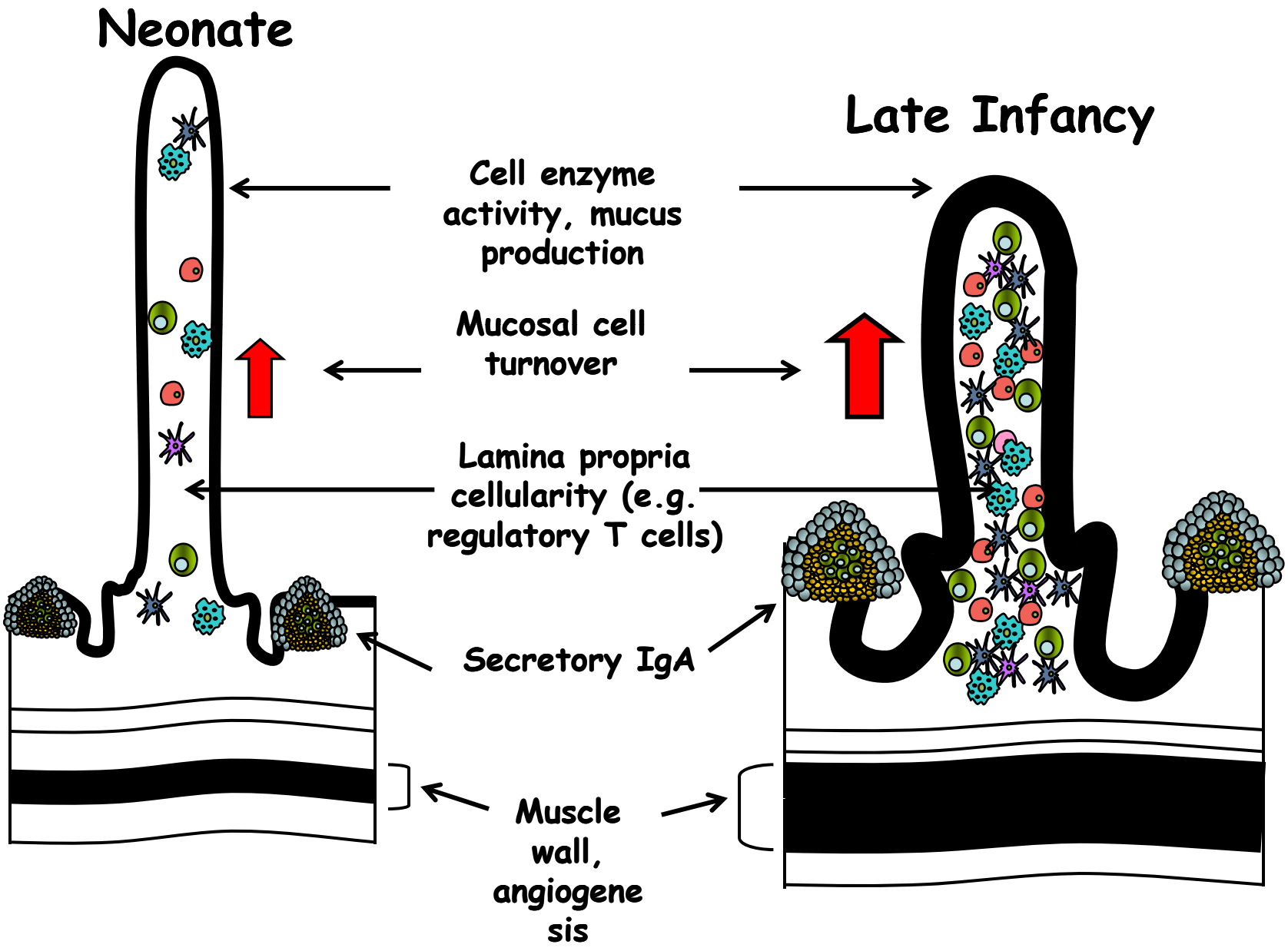
Gut microbiota develops after birth

Breast-fed infants **Formula-fed infants**



Pediatrics 1983;72:317-321

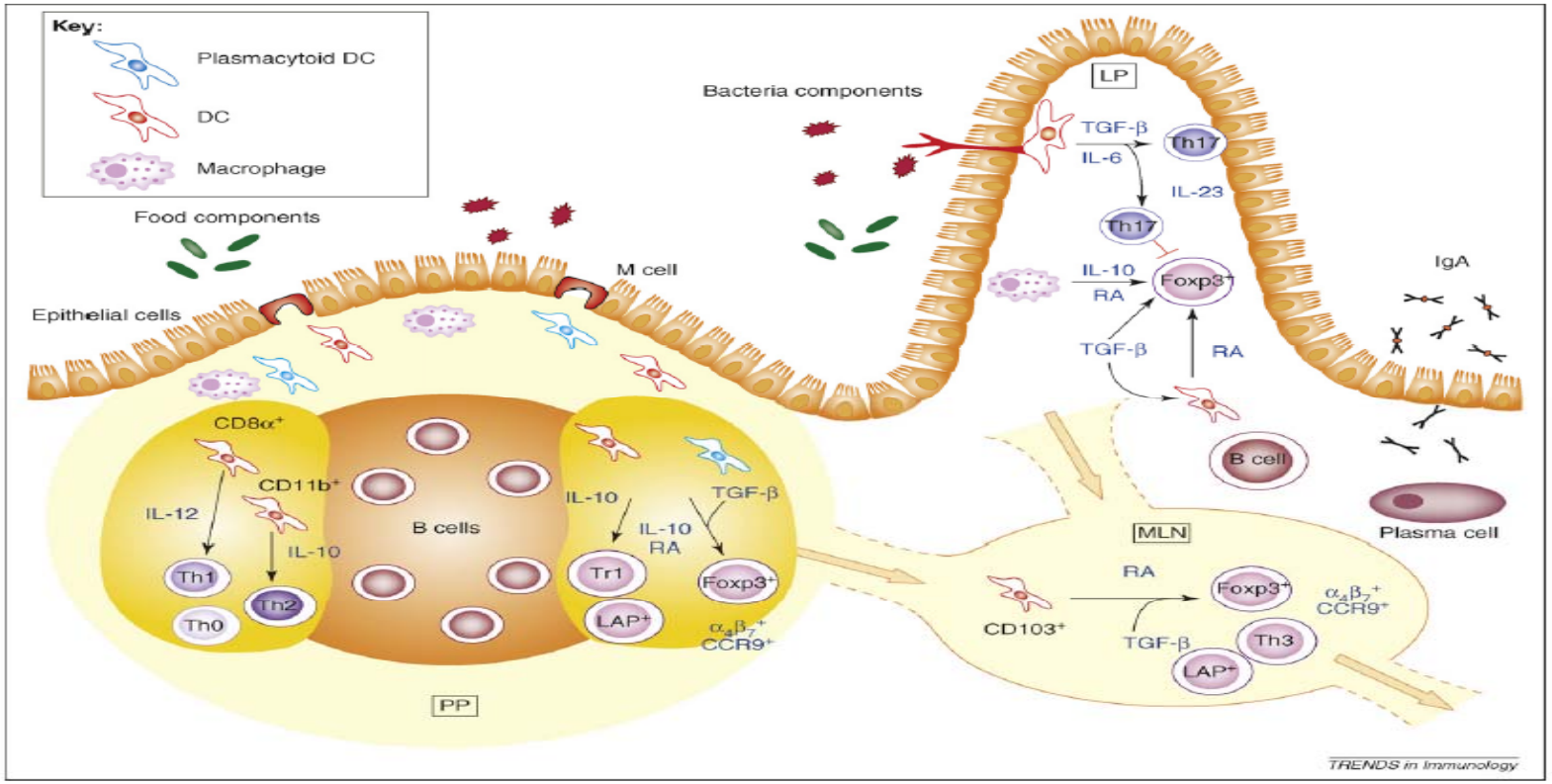
Development of the gut and its immune system is dependent on luminal microbial and dietary antigens (modified from Szepfalusi Z 2008)



Two functional arms of immune system in the aut

Review

Trends in Immunology Vol.29 No.11



(The figure from Tsuji NM and Kosaka A 2008)

- o Production ofsecretory IgA
- o Tolerance to luminal microbial and dietary antigens
  - regulatory T cells are mandatory for 1) oral tolerance and 2) prevention of both Th1- (found e.g. in diabetes mellitus) and Th2-skewed immune system (allergy)
  - development and function of regulatory T cells is dependent on gut microbiota

(Östman S et al. 2006, Ishikawa H et al. 2008)

Definition of probiotics

FAO/WHO (2001)

Probiotic bacteria are live microorganisms which when administered in adequate amounts confer a health benefit on the host

Lactobacilli and bifidobacteria have been a part of human diet for millenia

- Historian Plinius (76 BC) recommended sour milk products for treatment of diarrhea
- Nobel laureate Elie Metchnikoff (1908) claimed that yogurt promote health and longevity (autointoxication, Bulgarian bacillus)
- Frenchman Henry Tissier found bifidobacteria and showed their abundance in breastfed infants. He also recommended bifido-bacteria for treatment of diarrhea in infants (C R Soc Biol 1906)

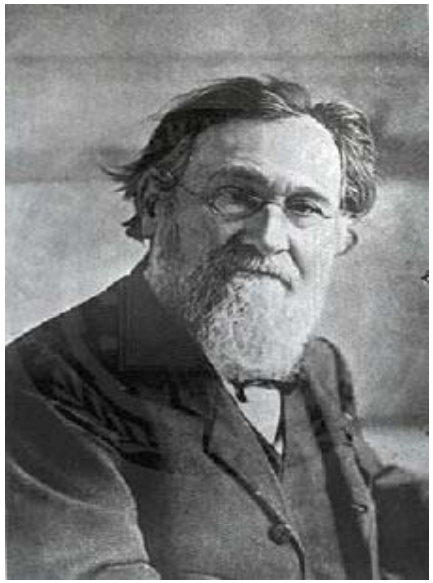


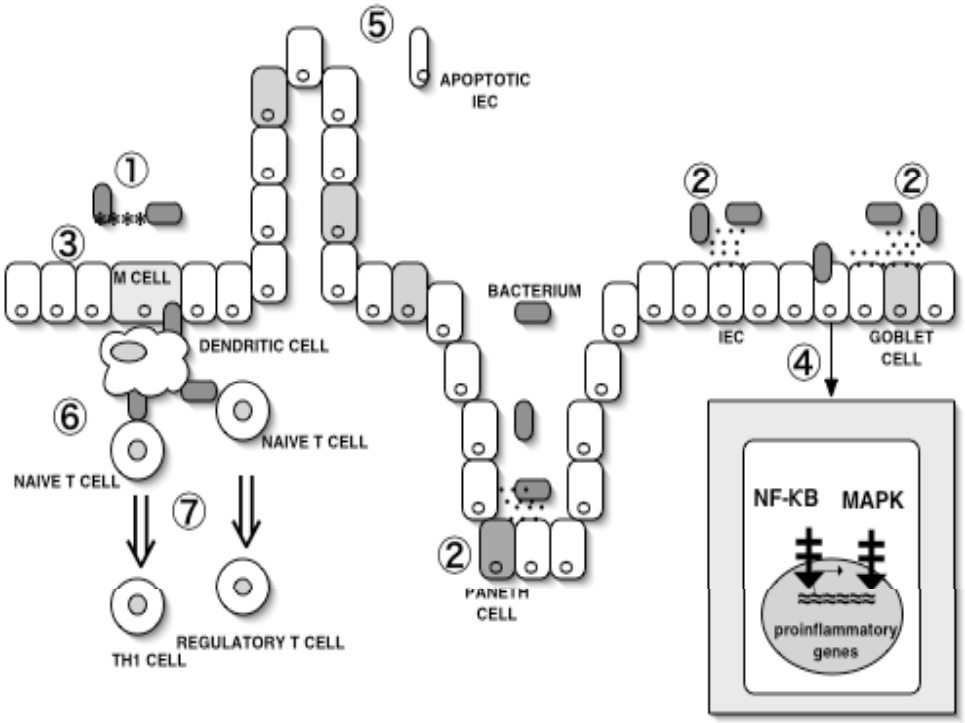
Figure from Wikipedia

Probiotics in the treatment and prevention of diarrhea in children (Szajewska H et al. 2005, 2006)

- Probiotics in acute diarrhea in children:
  - have a moderate effect that depends on the strain used (*Lactobacillus GG, Lactobacillus reuteri, Saccharomyces boulardii*) and dose.
  - help against watery viral diarrhea, especially one caused by rota virus
  - shorten the duration of illness approximately by one day if administered early in the course of disease
- *Saccharomyces boulardii, Lactobacillus rhamnosus GG* and *Bifibobacterium lactis + Streptococcuc thermophilus* prevent moderately antibiotic-associated diarrhea in children (NNT 7)

Potential mechanisms of action of probiotics in the gastrointestinal tract (Kalliomäki and Walker 2005)

1. Processing of enteral antigens
2. Inhibition of attachment of other bacteria to IEC
3. Enhancement of IEC's permeability barrier
4. Suppression of pro-inflammatory responses in IEC
5. Modulation of IEC's apoptosis
6. Maturation of dendritic cells with anti-allergic properties
7. Production of regulatory cytokines by immune cells in lamina propria



Proc Natl Acad Sci U S A. 2009 Feb 17;106(7):2371-2376. Epub 2009 Feb 3.

Differential NF-κB pathways induction by *Lactobacillus plantarum* in the duodenum of healthy humans correlating with immune tolerance

Peter van Baarlen[a,b,1,2], Freddy J. Troost[a,c,1], Saskia van Hemert[a,d], Cindy van der Meer[a,d], Willem M. de Vos[a,f], Philip J. de Groot[a,g], Guido J. E. J. Hooiveld[a,g], Robert-Jan M. Brummer[a,c], and Michiel Kleerebezem[a,d,e,3]

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Edited by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved December 18, 2008 (received for review October 3, 2008)

How do we acquire immune tolerance against food microorganisms and commensal bacteria that constitute the intestinal microbiota? We investigated this by stimulating the immune system of adults with commensal *Lactobacillus plantarum* bacteria. We studied the in vivo human responses to *L. plantarum* in a randomized double-blind placebo-controlled cross-over study. Healthy adults ingested preparations of living and heat-killed *L. plantarum* bacteria. Biopsies were taken from the intestinal duodenal mucosa and altered expression profiles were analyzed using whole-genome microarrays and by biological pathway reconstructions. Expression profiles of human mucosa displayed striking differences in modulation of NF-κB-dependent pathways, notably after consumption of living *L. plantarum* bacteria in different growth phases. Our in vivo study identified mucosal gene expression patterns and cellular pathways that correlated with the establishment of immune tolerance in healthy adults.

commensal bacteria | expression profiling | host–microbe interactions | pathway analysis

6 h after the consumption

Dose ≈ 2 x 10^{12}

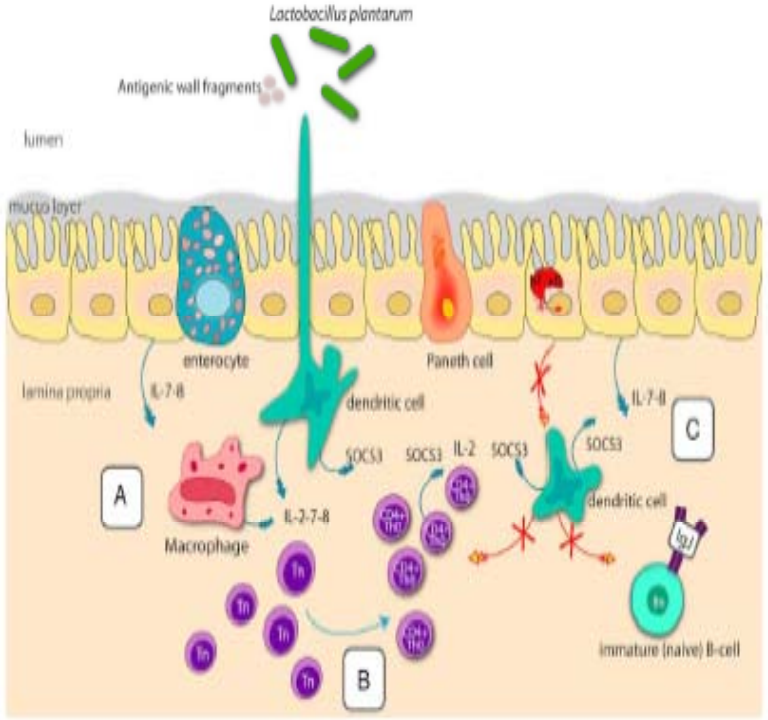
ingly, *L. plantarum* may induce innate or adaptive mouse immune responses, dependent on the viability of the bacteria (24).

Here, we describe the in vivo (immune) responses in humans after consumption of *L. plantarum* at the level of mucosal gene transcription, which comprehensively describes human responses to bacteria (26, 27). Mucosal transcriptional responses were determined in vivo in the duodenum, the proximal part of the small intestine, after 6 h consumption of *L. plantarum*, according to a randomized double-blind placebo-controlled cross-over design. Duodenal mucosa are the first small intestinal areas coming in contact with *L. plantarum*, minimizing the adaptive changes the bacteria might go through during passage of the intestinal tract. In addition, the duodenum is relatively accessible and does not require severely invasive sampling techniques. Finally, this intestinal region contains the lowest endogenous microbiota colonization level, ensuring that the measured responses are as specific as can be achieved. Considering the possible differential adjuvanticity response to different *L. plantarum* growth phases (24, 28) 3 preparations of bacteria were tested: (*i*) the logarithmic-phase of growth (exponentially growing; "midlog"), (*ii*) the stationary-phase of

Induction of NF-κB pathways was dependent on growth phase of the probiotic strain *Lactobacillus plantarum* WCFS1

- **Dead bacteria** (heat-killed in the stationary phase of growth) induced almost all NF-κB subunits but also 3 antagonists of NF-κB activity
- **Bacteria in the stationary phase** of the growth induced 2 NF-κB subunits and 3 antagonists of the NF-κB activity
- **Bacteria in the logarithmic-phase of growth** (expotentially growing; midlog) induced only 2 antagonists of the NF-κB activity
- None of the preparations led to infiltration of immune cells in the duodenal biopsies (immune tolerance).

Proc Natl Acad Sci U S A. 2009 Feb 17;106(7):2371-6.



Probiotics, inflammatory bowel disease and irritable bowel syndrome

(McFarland and Dublin 2008, Heilpern D and Szilagyi A 2008, Moayyedi P el al. 2008)

- **VSL#3*** has been effective in controlled clinical trials in preventing the onset of acute pouchitis in patients with newly formed surgical pouches and in maintaining remission following antibiotic treatment of acute pouchitis in patients with a history of refractory or recurrent pouchitis
- Probiotics decrease abdominal symptoms in adults with irritable bowel syndrome (NNT 4)
- A yoghurt containing a mix of 4 different probiotic strains (Lactobacillus rhamnosus GG, L. rhamnosus Lc705, Propionibacterium freudenreichii ssp. shermanii JS ja Bifidobacterium animalis ssp. lactis Bb12) decreased abdominal pain and distension and stabilized gut microbiota in patients with irritable bowel syndrome (Kajander et al. 2008).

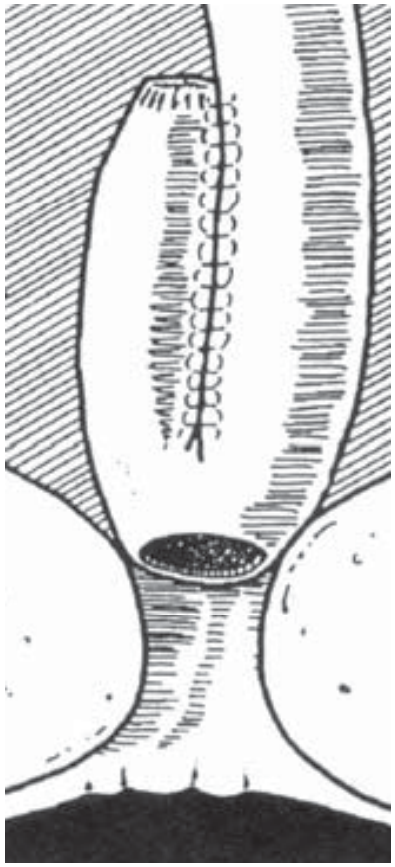


Figure from www.uoaa.org

* a mixture of four strains of lactobacilli: *Lactobacillus casei*, *L. plantarum*, *L. acidophilus* and *L. delbrueckii subsp. bulgaricus*, three strains of bifidobacteria: *Bifidobacterium longum*, *B. breve* and *B. infantis* and *Streptococcus salivarius* subsp.

Probiotics in the prevention of necrotizing entrocolitis (NEC)

(Deshpande G et al. 2007)

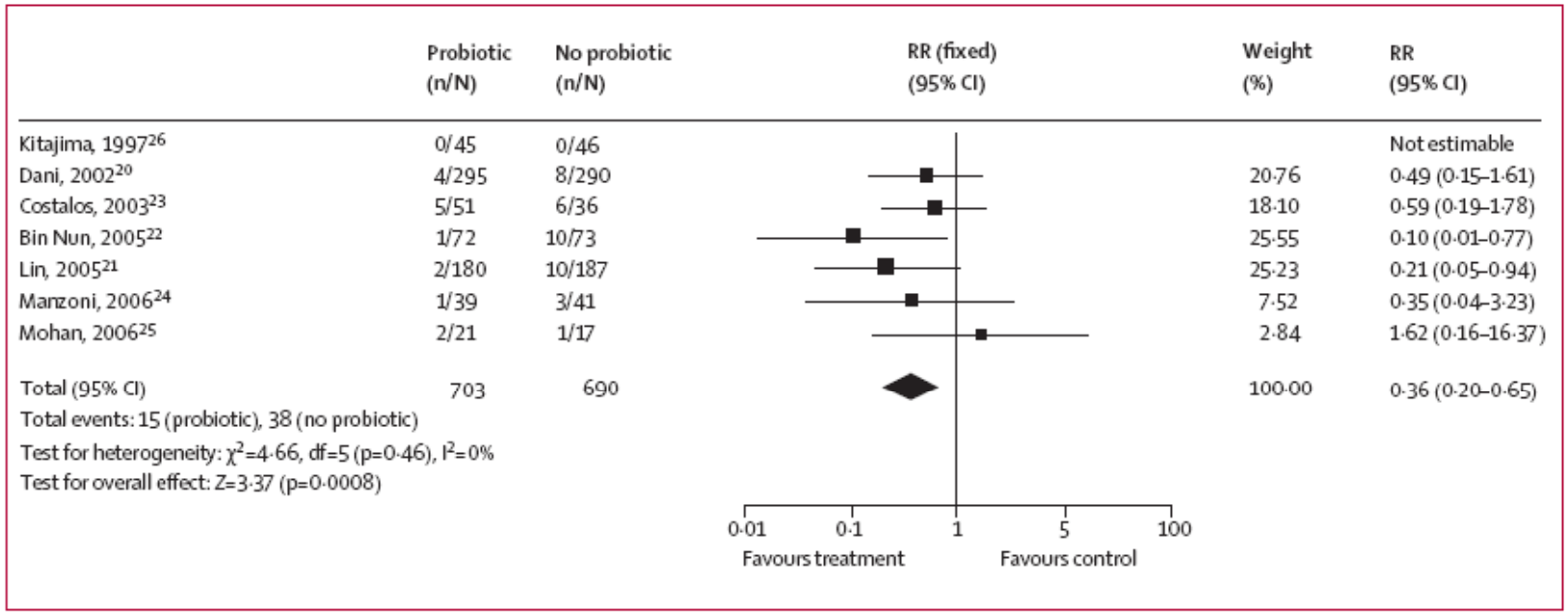


Figure 2: Effect of probiotics on necrotising enterocolitis of stage 2 or greater

Journal of Tropical Pediatrics Advance Access published October 8, 2008

Prophylactic Probiotics for Prevention of Necrotizing Enterocolitis in Very Low Birth Weight Newborns

by Moumita Samanta,[a] Mihir Sarkar,[a] Promit Ghosh,[b] Jayanta kr Ghosh,[a] Malay kr Sinha,[a] *and* Sukanta Chatterjee[a]
[a]*Department of Paediatrics, Medical College Kolkata, 88, College Street, Kolkata 700073, India*
[b]*Department of Community Medicine, Medical College Kolkata, 88, College Street, Kolkata 700073, India*

- Randomized, double-blind placebo-controlled clinical trial with a probiotic mixture (*Bifidobacterium infantis*, *Bifidobacteria bifidum*, *Bifidobacteria longum*, *Lactobacillus acidophilus*, each 2.5 x 10^9 CFU) twice a day
- The mixture was used from the beginning of enteral feedings till discharge (n=186)

The probiotic mixture had beneficial effects on feeding tolerance, duration of hospital stay, frequencies of death, NEC and sepsis

TABLE 3
Outcome variables after oral probiotics

Variables	Study group ($N=91$)	Control group ($N=95$)	*P*-value
Full enteral feeding (days)	13.76 ± 2.28	19.2 ± 2.02	<0.001
Hospital stay (days)	17.17 ± 3.23	24.07 ± 4	<0.001
Severity of NEC (Bell stage ≥ 2)	2.46 ± 0.51	2.6 ± 0.54	0.62
Death	4 (4.4)	14 (14.7)	0.032
NEC grade 2 or 3	5 (1.1)	15 (15.8)	0.042
Sepsis (culture proven)	13 (14.3)	28 (29.5)	0.020

Table from J Trop Pediatr. 2008 Oct 8. [Epub ahead of print]

Gut microbiota differences precede allergic manifestations (Kalliomäki 2009, in press)

Reference	Study population	Definition of allergy	Fecal analysis	Results
Kalliomäki 2001	76 newborns with family history of allergy - 22 became cases and 54 controls	One or more positive skin prick test at 12 months	Gas-liquid chromatography and bacterial culture at 3 weeks and 3 months, FISH at 3 weeks	**Different bacterial fatty acid profiles** at 3 weeks, no difference in colonization patterns Higher counts of clostridia and tendency to lower counts of bifidobacteria by FISH, lower ratio of bifidobacteria to clostridia by FISH
Björkstén 2001	44 newborns - 18 became cases and 26 controls	Atopic eczema and/or at least 1 positive skin prick test at 3, 6, 12, or 24 months	Bacteriological culture at 1 week and 1, 3, 6 and 12 months	Lower prevalence of bifidobacteria (during the 1st year) and enterococci (during the 1st month), lower counts of bacteroides (at 12 months), higher prevalence of *S. aureus* (at 6 months) and higher counts of clostridia (at 3 months)
Penders 2006	78 newborns (prospective nested case-control) - 26 became cases and 52 controls	Eczema (based on ISAAC-questionnaire) and specific IgE at least to 1 allergen at 12 months	PCR-DGGE and quantitative real-time PCR at 1 month	*E. coli* more prevalent in infants later developing atopic eczema, no difference in total bacterial profiles or in bifidobacterial counts or bifidobacterial species composition
Penders 2007	957 newborns - over 30% developed eczema and approximately 10% recurrent wheeze - over a quarter became sensitized (at least 1 antigen-specific IgE concentration > 0.3 IU/ml)	Eczema or atopic eczema or at least 1 positive antigen-specific IgE (>0.3 IU/ml) or recurrent (>3) wheeze during the first 2 years of life	Quantitative real-time PCR at 1 month	Higher counts and prevalence of *E.coli* in infants later developing eczema, higher prevalence of *C. difficili* in infants later developing eczema, recurrent wheeze and sensitization
Adlerberth 2007	324 newborns - 23% developed atopic eczema - 26% became sensitized	Atopic eczema, total and food-specific IgE levels at 18 months	Rectal cultures at 3 days, stool cultures at 1, 2 and 4 weeks and at 2, 6 and 12 moths	Neither atopic eczema nor food-specific IgE by 18 months of age were associated with time of acquisition of any particular bacterial group
Wang 2008	35 newborns - 15 became cases and 20 remained healthy	Atopic eczema at 18 months	Terminal restriction fragment length polymorphism (T-RFLP) and TTGE analysis of amplified 16S rRNA genes at 1 week	A reduced diversity of early gut microbiota of infants with atopic eczema

Probiotics in the treatment and prevention of allergic disease

Disease/Marker	Author and year	Participants	Type of probiotic(s)	Duration of intervention	Type of study	Outcome
Eczema/atopic eczema (AE)	Majamaa et al. 1997	27 infants	*Lactobacillus rhamnosus* GG (LGG)	1 month	R, DB, PC	Severity of AE decreased
Eczema/atopic eczema	Isolauri et al. 2000	27 infants	LGG or *B. bifidum* Bb-12	2 months	R, DB, PC	Severity of AE decreased
Eczema/atopic eczema	Rosenfeldt et al. 2003	43 children	*L. rhamnosus 19070 and L. reuteri DSM*	6 weeks	R, DB, PC	Extent but not severity of AE decreased
Eczema/atopic eczema	Viljanen et al. 2005	230 infants	LGG or a mixture of 4 probiotics	4 weeks	R, DB, PC	Severity of AE decreased only in IgE-associated eczema in LGG group
Eczema/atopic eczema	Weston et al. 2005	53 infants	*L. fermentum* VRI-033 PCC	8 weeks	R, DB, PC	Severity of AE decreased
Eczema/atopic eczema	Sistek et al. 2006	59 infants	*L. rhamnosus* and *B. lactis*	18 weeks	R, DB, PC	Severity of AE decreased only in children sensitised to food
Eczema/atopic eczema	Brouder et al. 2006	50 infants	LGG or *L. rhamnosus*	3 months	R, DB, PC	No effect
Eczema/atopic eczema	F□lster-Holst et al. 2006	54 infants	LGG	2 months	R, DB, PC	No effect
Eczema/atopic eczema	Gr□ber et al. 2007	102 infants	LGG	12 weeks	R, DB, PC	No effect
Asthma	Wheeler et al. 1997	15 adults	*L. acidophilus*	1 month	DB, CO	No effect on clinical parameters
Allergic rhinitis (AR)	Helin et al. 2002	36 adults	LGG	5.5 months	R, DB, PC	No effect
Allergic rhinitis	Wang et al. 2004	80 adults	*L. paracasei-33*	1 month	R, DB, PC	Quality of life improved
Allergic rhinitis	Peng et al. 2005	90 adults	*L. paracasei-33*	1 month	R, DB, PC	Quality of life improved
Allergic rhinitis	Ishida et al. 2005	49 adults	*L. acidophilus* L-92	8 weeks	R, DB, PC	Decrease in nasal symptoms
Allergic rhinitis	Xiao et al. 2006	44 adults	*B. longum* BB 536	13 weeks	R, DB, PC	Decrease in nasal symptoms
Allergic rhinitis	Tamura et al. 2007	109 adults	*L. casei* strain Shirota	10 weeks	R, DB, PC	No effect
Asthma and allergic rhinitis	Giovannini et al. 2007	187 children	*L. casei*	12 months	R, DB, PC	Decrease in rhinitis episodes
Serum ECP, Ig E, eosinopenia	Moreira et al. 2007	141 adults	LGG	4 months	R, DB, PC	No effect
Inflammatory markers in AR	Ivory et al. 2008	10 adults	*L. casei* strain Shirota	5 months	R, DB, PC	Decrease in antigen-specific IgE and antigen-induced cytokines
Prevention of AE	Kalliom□ki et al. 2001	132 infants	LGG	7 months perinatally	R, DB, PC	Incidence of eczema decreased during the first 2 years of life
Prevention of AE	Kalliom□ki et al. 2003	107 infants	same cohort	same cohort	same cohort	Incidence of eczema decreased during the first 4 years of life
Prevention of AE	Kalliom□ki et al. 2007	116 infants	same cohort	same cohort	same cohort	Incidence of eczema decreased during the first 7 years of life
Prevention of allergic disease	Kukkonen et al. 2007 Kuitunen et al. 2009 (in press)	925 infants	4 probiotic strains and galactoolico-saccharide (a prebiotic)	7 months perinatally	R, DB, PC	Incidence of eczema and AE decreased during the first 2 years of life. No effect at 5 years (except decrease in AE in cesarean-delivered children)
Prevention of AE	Taylor et al. 2007	188 infants	*L. acidophilus* (LAVRI-A1)	6 months postnatally	R, DB, PC	No effect on incidence of eczema, but increased allergic sensitisation
Prevention of allergic disease	Abrahamsson et al. 2007	188 infants	*Lactobacillus reuteri*	13 months perinatally	R, DB, PC	Less AE during the second year of life
Prevention of AE	Kopp et al. 2008	94 infants	LGG	7 months perinatally	R, DB, PC	No effect on AE or sensitisation, but increased risk for recurrent wheezy bronchitis
Prevention of AE	Wickens et al. 2008	474 infants	*L. rhamnosus* HN001 or *B. animalis* subs. *Lactis* strain HN019	7 months perinatally	R, DB, PC	Lactobacillus decreased risk of AE, whereas Bifidobacterium had no effect by 2 years. No effect on sensitisation
Prevention of AE	Soh et al. 2008 (in press)	253 infants	*B. longum* (BL999) and *L. rhamnosus*	6 months	R, DB, PC	No effect on eczema or sensitisation during the first year of life

Abbreviations: CO, cross-over; DB, double-blind; PC, placebo-controlled; R, randomized

Probiotics in the treatment of eczema/atopic eczema

Disease	Reference	n	Probiotic(s)	Duration	Type of study	Outcome
Eczema/atopic eczema (AE)	Majamaa et al. 1997	27 infants	*Lactobacillus rhamnosus* GG (LGG)	1 month	R, DB, PC	Severity of AE decreased
Eczema/atopic eczema	Isolauri et al. 2000	27 infants	LGG or *B. bifidum* Bb-12	2 months	R, DB, PC	Severity of AE decreased
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Eczema/atopic eczema	Viljanen et al. 2005	230 infants	LGG or a mixture of 4 probiotics	4 weeks	R, DB, PC	Severity of AE decreased only in IgE-associated eczema in LGG group
Eczema/atopic eczema	Weston et al. 2005	53 infants	*L. fermentum* VRI-033 PCC	8 weeks	R, DB, PC	Severity of AE decreased
Eczema/atopic eczema	Sistek et al. 2006	59 infants	*L. rhamnosus* and *B. lactis*	18 weeks	R, DB, PC	Severity of AE decreased only in children sensitised to food
Eczema/atopic eczema	Brouder et al. 2006	50 infants	LGG or *L. rhamnosus*	3 months	R, DB, PC	No effect
Eczema/atopic eczema	F□lster-Holst et al. 2006	54 infants	LGG	2 months	R, DB, PC	No effect
Eczema/atopic eczema	Gr□be et al. 2007	102 infants	LGG	12 weeks	R, DB, PC	No effect

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

Probiotics in the treatment of allergic rhinitis/asthma

Disease	Reference	n	Probiotics	Duration	Type of study	Outcome
Asthma	Wheeler et al. 1997	15 adults	*L. acidophilus*	1 month	DB, CO	No effect on clinical parameters
Allergic rhinitis (AR)	Helin et al. 2002	36 adults	LGG	5.5 months	R, DB, PC	No effect
Allergic rhinitis	Wang et al. 2004	80 adults	*L. paracasei-33*	1 month	R, DB, PC	Quality of life improved
Allergic rhinitis	Peng et al. 2005	90 adults	*L. paracasei-33*	1 month	R, DB, PC	Quality of life improved
Allergic rhinitis	Ishida et al. 2005	49 adults	*L. acidophilus* L-92	8 weeks	R, DB, PC	Decrease in nasal symptoms
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Allergic rhinitis	Tamura et al. 2007	109 adults	*L. casei* strain Shirota	10 weeks	R, DB, PC	No effect
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Serum ECP, Ig E, eosinopenia	Moreira et al. 2007	141 adults	LGG	4 months	R, DB, PC	No effect
Inflammatory markers in AR	Ivory et al. 2008	10 adults	*L. casei* strain Shirota	5 months	R, DB, PC	Decrease in antigen-specific IgE and antigen-induced cytokines

Abbreviations: CO, cross-over; DB, double-blind; PC, placebo-controlled; R, randomized

Probiotics in the prevention of allergic disease

Disease	Reference	n	Probiotics	Duration	Type of study	Outcome
Prevention of AE	Kalliomäki et al. 2001 Kalliomäki et al. 2003 Kalliomäki et al. 2007	132 infants 107 infants 116 infants	LGG	7 months perinatally	R, DB, PC	Incidence of eczema decreased during the first 2, 4, and 7 years of life
Prevention of allergic disease	Kukkonen et al. 2007 Kuitunen et al. 2009	925 infants 895 infants	4 probiotic strains and galactoolicosaccharide (a prebiotic)	7 months perinatally	R, DB, PC	Incidence of eczema and AE decreased during the first 2 years of life. No effect at 5 years (except decrease in AE in cesarean-delivered children)
Prevention of AE	Taylor et al. 2007	188 infants	*L. acidophilus* (LAVRI-A1)	6 months postnatally	R, DB, PC	No effect on incidence of eczema, but increased allergic sensitisation
Prevention of allergic disease	Abrahamsson et al. 2007	188 infants	*Lactobacillus reuteri*	13 months perinatally	R, DB, PC	Less AE during the second year of life
Prevention of AE	Kopp et al. 2008	94 infants	LGG	7 months perinatally	R, DB, PC	No effect on AE or sensitisation, but increased risk for recurrent wheezy bronchitis
Prevention of AE	Wickens et al. 2008	474 infants	*L. rhamnosus* HN001 or *B. animalis* subs. *Lactis* strain HN019	7 months perinatally	R, DB, PC	Lactobacillus decreased risk of AE, whereas Bifidobacterium had no effect by 2 years. No effect on sensitisation
Prevention of AE	Soh et al. 2008 (in press)	253 infants	*B. longum* (BL999) and *L. rhamnosus*	6 months	R, DB, PC	No effect on eczema or sensitisation during the first year of life

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

Conclusions

- All probiotics are not equal but effects are strain-specific
- Certain probiotic strains shorten the duration of viral diarrhea in children by approximately one day
- Probiotics have several properties that may assist in the development of immature mucosal immunity and gut microbiota after birth
- Prevention and treatment of allergic diseases with probiotics is an interesting and active field of research
- Preventive and therapeutic effects of certain probiotic strains on pouchitis have been promising
- Prevention of NEC in prematures and treatment of irritable bowel syndrome are potential future indications for probiotics
- Well-designed and -conducted clinical studies are needed to expand rationalized use of probiotics