

# EFFECT OF PROBIOTICS AND BREASTFEEDING ON THE *BIFIDOBACTERIUM* AND *LACTOBACILLUS/ENTEROCOCCUS* MICROBIOTA AND HUMORAL IMMUNE RESPONSES

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**Objective** To assess impact of probiotics and breastfeeding on gut microecology.

**Study design** Mothers were randomized to receive placebo or *Lactobacillus rhamnosus* GG before delivery, with treatment of the infants after delivery. We assessed gut microbiota, humoral immune responses, and measured soluble cluster of differentiation 14 (sCD14) in colostrum in 96 infants.

**Results** Fecal *Bifidobacterium* and *Lactobacillus/Enterococcus* counts were higher in breastfed than formula-fed infants at 6 months;  $P < .0001$  and  $P = .01$ , respectively. At 3 months, total number of immunoglobulin (Ig)G-secreting cells in breastfed infants supplemented with probiotics exceeded those in breastfed infants receiving placebo;  $P = .05$ , and their number correlated with concentration of sCD14 in colostrum. Total numbers of IgM-, IgA-, and IgG-secreting cells at 12 months were higher in infants breastfed exclusively for at least for 3 months and supplemented with probiotics as compared with breastfed infants receiving placebo;  $P = .005$ ,  $P = .03$  and  $P = .04$ , respectively. Again, sCD14 in colostrum correlated with numbers of IgM and IgA cells;  $P = .05$  in both.

**Conclusions** We found an interaction between probiotics and breastfeeding on number of Ig-secreting cells, suggesting that probiotics during breastfeeding may positively influence gut immunity. (*J Pediatr* 2005;147:186-91)

Epidemiological studies point to the early environment as a window of opportunity in shaping the infant's immune responder type.<sup>1</sup> During this early critical period, the gut immature immune system is confronted by increasing amounts of dietary and microbial antigens. It is not currently known how these antigens affect the maturational process of gut humoral immunity. The mother's gut mucosa modifies the structure of the dietary antigens as these are transferred to the infant via breast milk.<sup>2</sup> Gradually the child is given unmodified antigens in formulas and solid foods. In like manner, the establishment of gut microbiota is a gradual process, the first colonizers being enterobacteria, streptococci, and staphylococci, followed by bifidobacteria.<sup>3</sup> The early introduction of foreign dietary antigens and unbalanced gut microbiota, instead of a stepwise exposure, may be associated with a risk of chronic diseases such as allergic diseases, diabetes, or celiac disease later in life.<sup>1</sup> Probiotics have been documented to reduce the risk of gastrointestinal infection.<sup>4</sup> Breastfeeding promotes *Bifidobacterium* microbiota<sup>5</sup> and reduces the risk of infection and allergic diseases.<sup>6-8</sup>

The aim of this study was to assess the impact of probiotics and breastfeeding on gut microbiota composition as characterized by bifidobacteria and lactobacilli/enterococci and humoral immune responses as indirectly assessed by circulating immunoglobulin(Ig)-secreting cells (IgM, IgA, and IgG).

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See editorial, p 143, and related articles, p 192, and p 197.

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ELISPOT	Enzyme-linked immunospot assay	ISCs	Circulating immunoglobulin-secreting cells
FISH	Fluorescent in situ hybridization	sCD14	Soluble CD14
Ig	Immunoglobulin		

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**Table. The development of bifidobacteria and lactobacilli/enterococci and total bacterial counts in fecal samples (bacterial cells/g feces) in infants receiving probiotic or placebo analyzed by FISH at 3, 6, and 12 months of age**

Age (months)	(Bacterial cells/g feces)		Total cell count* ( $\times 10^9$ )
	Bifidobacteria* ( $\times 10^8$ )	Lactobacilli/enterococci* ( $\times 10^8$ )	
3 months			
Probiotic	14.0 (6.0-33.0)	2.2 (1.1-4.6)	7.0 (4.6-11.0)
Placebo	15.0 (7.3-30.0)	2.7 (1.5-4.6)	5.8 (3.8-8.7)
6 months			
Probiotic	12.0 (7.6-20.0)	2.3 (1.6-3.4)	4.1 (3.2-5.3)
Placebo	8.6 (4.4-17.0)	2.5 (1.6-3.8)	3.4 (2.8-4.5)
12 months			
Probiotic	1.2 (0.6-2.6)	0.9 (0.5-1.4)	2.4 (1.9-3.0)
Placebo	1.9 (0.9-4.0)	1.0 (0.6-1.7)	2.5 (2.0-3.1)

\*Geometric mean (95% CI).

## METHODS

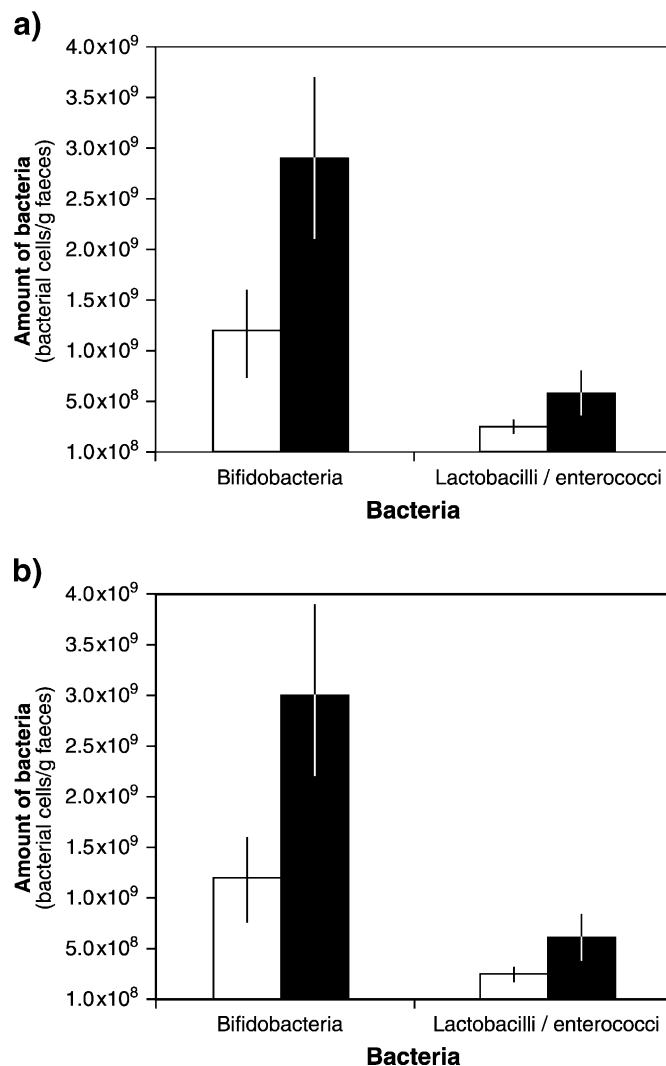
### Subjects and Study Design

The study population comprised 96 infants who had at least one close relative (mother, father, sibling) with atopic dermatitis, allergic rhinitis, or asthma. Children were recruited in antenatal clinics in the city of Turku, Finland. In a double-blind, placebo-controlled trial mothers were randomized to receive placebo (microcrystalline cellulose) or  $1 \times 10^{10}$  colony-forming units of *Lactobacillus rhamnosus* GG (ATCC 53103) once a day for 4 weeks before expected delivery, as described in detail elsewhere.<sup>9</sup> After the neonatal period, the assigned preparation was then given to the infants only. The contents of the capsule given to infants were administered by spoon after mixing in water. The duration of probiotic intervention after birth was 6 months. Mothers were encouraged to breastfeed their children at least up to 4 to 6 months of age. Parental smoking was discouraged, and feeding patterns of the infants were monitored.

The study protocol was approved by the Committee on Ethical Practice of Turku University Central Hospital, and infants were enrolled in the study after written informed consent was obtained from the mother before the prenatal intervention.

### Follow-up Visits and Sampling

The children were clinically examined at 3, 6, and 12 months of age by the same physician. The birth characteristics were evaluated; they included birth weight (g, mean and range) and the gestational age (weeks, mean and range). The diets of infants, recorded at all study visits, were classified as human milk, cow's milk-based adapted infant formula, or, in



**Figure 1 a, b.** The effect of exclusive breastfeeding on the bacterial counts (*Bifidobacterium* and *Lactobacillus/Enterococcus*) in fecal samples (bacterial cells/g feces) analyzed by FISH at 6 months of age. The white column indicates infants exclusively breastfed for <3 months, the black column infants exclusively breastfed for at least 3 months. The number of samples analyzed in *Bifidobacterium* group was 28 and 43, respectively. The number of samples analyzed in *Lactobacillus/Enterococcus* group was 28 and 43, respectively. **b.** The effect of partial breastfeeding on the bacterial counts (*Bifidobacterium* and *Lactobacillus/Enterococcus*) in fecal samples (bacterial cells/g feces) analyzed by FISH at 6 months of age. The white column indicates infants who have been partially breastfed for <6 months, the black column infants partially breastfed for at least 6 months. The number of samples analyzed in *Bifidobacterium* group was 31 and 40, respectively. The number of samples analyzed in *Lactobacillus/Enterococcus* group was 31 and 40, respectively.

a case of documented cow's milk allergy, a hypo-allergenic formula (extensively hydrolyzed or amino acid formula). The ages at introduction of formula and solid food were recorded. In addition, the duration of exclusive and partial breastfeeding was assessed. Exclusive and partial breastfeeding are reported separately as practiced elsewhere.<sup>10</sup> Exclusive breastfeeding refers to breast milk as a sole source of nutrition to the infant and partial breastfeeding means giving an infant some

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