Interdisciplinary Journal of Microinflammation

Cantani, Interdiscip J Microinflammation 2014, 1:2
http://dx.doi.org/10.4172/ijm.1000127

Research Article Open Access

Immunological Properties of Breast Milk: A Prospective Study in 589 Children

Cantani A*

Department of Pediatrics, Allergy and Clinical Immunology Division, University of Rome "La Sapienza", Rome, Italy

Abstract

Background: Normal neonates are equipped with a limited immunocompetence, therefore they need breast milk (BM), which represent an excellent immune protection for the neonate during the critical period of intestinal vulnerability, due to a great variety of functionally interactive immunological, antibacterial, antiviral, anti-inflammatory and immunomodulating factors. Evidence suggests that the protection afforded by human milk to the recipient infant is greatest when breast-feeding is exclusive and of substantial duration.

Material and methods: In this update of an old topic, we shall review its role in atopy prevention as an introduction to the immunological and non-immunological components of BM and colostrum, and the spectrum and mechanisms of the protection of host defenses. Accordingly, we analyzed the propensity for breastfeeding in 289 children with respiratory disease and in 300 control children. Results: The net result is that a high proportion of atopic children (273/289) were breastfed from their mothers and for a longer period of time.

Conclusion: This is the best demonstration that breastfeeding is the most effective single nutritional strategy that has been identified for the prevention of the atopic march in vulnerable infants. Therefore we stress that breast-feeding can prevent or ameliorate allergies, although some authors have emphasized the increased hazard of sensitization in breast-fed infants.

Keywords: Atopy prevention; Breast milk; Colostrum; Neonate; Breastfeeding; Essential fatty acids; Nucleotides; Atopic march

Breast Milk in the Allergy Prevention

There is a continuous flow of studies stressing the effectiveness of exclusive breastfeeding (associated or not with soy protein formulas (SPF) and/or hydrolysate formulas (HFs), along with food and inhalant allergens avoidance) in decreasing the prevalence of allergic diseases in genetically at risk neonates [1]. The protective effects of breastfeeding are indeed a positive natural selection process [2]. The allergy-preventive importance of BM has been evaluated by both prospective and retrospective studies [3-5]. We have prepared a partial list of both types of studies (Tables 1 and 2) [3-5], which show that the protective value of BM is confirmed by 37/41 (90.3%) of prospective, and by 4/9 (44.4%) retrospective studies (p=0.001, Fisher=0.005). Therefore the studies showing either no differences or an increase of allergic disease in breast-fed in comparison with the bottle-fed children total to 8/40. As was pointed out [4-9] in some cases the infants were breastfed for less than 3 months (47% of children in one study) [10], sometimes less than 6 weeks [11-16]. Solid foods were introduced very early in the infants' diet (75% of cases at the 4th month in another study) [13] with foreseeable effects [17-19], e.g. the start of the atopic march.

As regards the importance of environmental controls, as we proposed and applied together with dietary manipulations (Table 3 and 4) since 1983 [4], Arshad et al. [5] confirm these measures, demonstrating that they are highly effective in reducing the prevalence of allergic disease: 14% vs 40% according to the employment or not of environmental controls in babies, who were all fed either with BM or a soy HF.

In our studies the figures are quite similar according to the dietary manipulations (breast or SPF in the study group, cow's milk-CM-in the controls) associated with the environmental controls. The results showed that 51/244 children developed atopic symptoms during the follow-up: when we consider together the study group, only 14.5% (26/179) compared to 38.5 (25/65) of the control group developed atopic manifestations during the follow-up [4] (p ≤0.0000), thus confirming that dietary and environmental measures are able to significantly prevent atopy onset in high-risk babies, at least until the age of 3 years and 8 months. Similar results we obtained in a multicenter study comprising 2270 infants. At the last follow-up [20-23], 732 children are 3 years old, 98 (13%) have two or more relatives, 634 (87%) have one relative affected by atopic disease. 242/732 (33%) were exclusively breast feed until the 6th month of life, 139/732 (19%) received exclusively SPF, 212/732 (29%) received BM and SPF supplement, and 139/732 (19%) were CM formula feed. The prevalence of atopic disease was 13% (77/593 of the study group vs. 48/139=34.5% of the controls, p=0.0000).

In this prospective study in high-risk babies we have verified how many of them were breastfed, in comparison with the children of the control group.

Patients and Methods

In order to explore how long a baby genetically at risk of atopy is breastfed, we have enrolled into this prospective study 289 children, 169 males and 120 females, aged 3.5 to 7.5 years. These children attended the Allergy and Clinical Immunology Division of the Pediatric Department of Rome University, because they were affected by respiratory allergy, previously diagnosed with family history, SPTs and IgE antibodies. As controls there were 300 children comparable for age and sex with no respiratory illness recruited from our outpatient clinic.

***Corresponding author:** Cantani A, Division of Pediatric Allergy and Immunology, Roma University "La Sapienza", Italy, Tel: 0644230256; E-mail: acantani13@gmail.com

Received November 17, 2014; **Accepted** December 07, 2014; **Published** December 09, 2014

Citation: Cantani A (2014) Immunological Properties of Breast Milk: A Prospective Study in 589 Children. Interdiscip J Microinflammation 1: 127. doi:10.4172/ijm.1000127

Authors Diseases	Ref	Year	No. of Cases	Alimentation of significance	Data in bracket=OR	Duration of BM	F-U (y)	Effect on atopic	Results in the study group (1st No.) Compared to controls (2nd No.)
Chandra [6]	6	1979	37	37	BM	>5 m	2	⇓ AD	10.8/56.7 p <0.001, Asthma 2.7/21.6 p <0.01
Saarinen et al. [7]	7	1979	54	105	BM	6 m	3	⇓ AD	0/18 p <0.05, FA 4/24 p < 0.05
Ziering et al.[8]	8	1979	25	25	BM	6 m	2	⇓ AD	32/64 p = 0.0235
Kaufman and Frick [9]	9	1981	38	56	BM	6 w	2	⇓ Asthma	5.3/17.9 p <0.05
Hide and Guyer [10]	10	1981	204	62	BM	6 m	1	⇓AD	7.9/8.9, Asthma 11.8/11.3 NS ^
Gruskay [11]	11	1982	48	201	BM	3 m	15	⇓ AD	8.3/12 Asthma 8.3/15,4 AR 8/10.4 NS
Juto et al. [12]	12	1982	54	11	BM	>1 m	1	⇓ Asthma Atopy	0.06 ± 0.3/1.3 ± 2.1 p <0.001 1.4 ± 1.8/3.2 ± 4.5, p <0.05
Businco et al. [34]	4	1983	49	41	BM +SM	6 m	2	⇓ Atopy	18/37 Fisher = 0.0381
Fergusson et al. [56]	13	1983	199	911	BM	4 m	4	⇑/= Asthma	8.5/6.6 NS
Kajosaari and Saarinen [14]	14	1983	70	65	BM	6 m	1	⇓ FA	7/37, AD 14/35 p <0.001 – 0.01
Pratt 15]	15	1984	19	58	BM	>3 m	5	⇓ AD	15.8/37.9 p <0.05
Hide and Guyer [16]	16	1985	115	52	BM	6 m	4	=AD	14.8/17.3, Asthma 10.4/11.5 NS
Moore et al.[17]	17	1985	224	35	BM	3 m	1	⇓ AD	13/20 p <0.05
Chandra et al. [18]	18	1986	35	20	BM	3 m	1	⇓ AD	14/60 Fisher = 0.0046
Vandenplas and Sacre [19]	19	1986	47	228	BM	3 m	0,4	⇓ Atopy	8.5/39.9 p = 0.0001
Miskelly et al. [20]	20	1988	189	293	BM +SM	± 3 m	1	⇓Asthma	21.7/42.7, p <0.001
Hattevig et al. [21]	21	1989	65	50	BM +CH	± 3 m	1, 5	⇓ AD	10.8/28 p = 0.033
Chandra et al. [22]	22	1989	97	40	BM	± 6 m	1, 5	⇓ AD	22/70 p <0.001
Chandra et al. [23]	23	1989	72	72	BM	± 4 m	1, 5	⇓ AD	18/30 Asthma 0/4.5 AR 1.5/7.5 p<0.05
Lucas et al. [24]	24	1990	38	37	BM	5 w	2	⇓ AD	6/15 (3.6), Asthma 8/11 (1,6), Atopy 13/24 (3.6)
Chandra and Hamed [25]	25	1991	60	68	BM	4 m	1, 5	⇓ AD	20/35.8 p = 0.0484
Arshad and Hide [37]	5	1992	420	747	BM	3 m	1	⇓Asthma	6.7/12 p < 0.01
Sigurs et al. [26]	26	1992	65	60	BM +CH	± 3 m	4	⇓ AD	29.2/50 p = 0.0038
Burr et al. [27]	27	1993	179	274	BM	± 3 m	7	⇓ Asthma	59/74 p <0.001 AD, AR NS
Halken et al. [28]	28	1993	20	75	BM	6 m	1,5	⇓ CMA	0/20 Fisher 0.0207
Kajosaari [29]	29	1994	51	62	BM	6 m	5	⇓ AR	20/37 p = 0.04, Asthma 8/15 NS
Høst et al. [30]	30	1995	88	75	BM +CH	6 m	5	⇓ CMA/CMI	5.7/20 p = 0.0055
Saarinen and Kajosaari [31]	31	1995	48	102	BM	<1->6 m	17	⇓ Atopy	42/65 p = 0.02, grave 8/54 p <0.0001 AD p = 0.03, FA p = 0.02 , Asthma p = 0.01
Chandra [32]	32	1997	60	68	BM	4 m	5	⇓ AD, Asthma	AD = 10/29.9 p = 0.0057, Asthma 6.6/23.9 p = 0.0079
With environmental controls									
Matthew et al. [33]	33	1977	23	19	BM+SM	3 m	1	⇓ AD	13/47.4 Fisher 0.0171
Businco et al. [34]	34	1987	179	65	BM +SM	6 m	3,6	⇓ AD ⇓Atopy	4.5/15.4 p = 0.0039, Asthma 7.2/20 p = 0.0073 14.5/38.5 p = 0.0001
Savilahti et al. [35]	35	1987	142	31	BM	6-9 m	1	⇑ Atopy	38/13 NS
Zeiger et al. [36]	36	1989	103	185	BM +CH	± 6 m	2	⇓ AD, FA	7.2/20.1 p = 0.005
Arshad et al. [37]	37	1992	58	62	BM +IS	9 m	1	⇓ AD	4/12 (>3), FA 3/7 (>3), Asthma 7/19(>4)
Halken et al. [38]	38	1992	105	85	BM +CH/SPH	≥ 3 m	1,5	⇓ Atopy Asthma	32/74 p <0.01, AD 14/31 p <0.01, 13/37 p <0.01, FA 6/17 p <0.05
Zeiger et al. [39]	39	1992	103	185	BM +CH	± 6 m	4	⇓ Atopy, FA, AR	at 12 months p ≤ 0.05 – 0.01
Bardare et al. [40]	40	1993	145	196	BM +SM	6 m?	1	⇓ Atopy	13.3/28.9 p = 0.0044
Bruno et al.[41]	41	1993	114	14	BM +SM	6 m	4,3	⇓ Atopy	11/21 p = 0.001
Hide et al. [42]	42	1994	58	62	BM+IS	9 m	2	⇓ Atopy Asthma	29.3/58.1 p <0.05, AR 3.4/11.3 p < 0.1, (SPT+) 6.9/22.6 p = 0.0162
Machado et al.[43]	43	1994	333	87	BM+SM	6 m	4	⇓ Atopy	17/32 p = 0.0028
Zeiger et al. [44]	44	1995	53	106	BM+CH	± 6 m	7	⇓FA	10/22 p = 0.06 ***
Hide et al. [45]	45	1996	58	62	BM+SH	9 m	4	⇓ Atopy	32.7/54.8 (2.73) AD 13.8/24.2 (3.4),
Total 41445089 NB Hide and Guyer [16] have re-examined the 1981 group [10], Burr et al [27] that of 1988 [20], Chandra and Hamed [25] that of 1989 [23], concluded by Chandra at the 5th year [32], Kajosaari [23] that of 1983 [14], Zeiger et al. [39,44] that of 1989 [36] and 1992 [39], Saarinen and Kajosaari [31] that of 1979 [7], Hide et al. [45] the study of Arshad et al. [37], Sigurs et al. [26] that of Hattevig et al. [21]; the number shown represents the total of children whatever studied (excluding from total the "re-examined"=12.8%=10.587). For abbreviations and symbols see Table 2.									

Table 1: Prevention of Atopy based on BM: Results of Prospective Studies according to the publication year.

Authors	No. of Cases		Alimentation of S group	Duration of BM (s, m)	F-U (y)	Effect on atopic diseases (as above)
	S	C				
Grulee and Sanford [3]	200	61	BM	9 m	0,75	⇓ AD0.2/3.5 p ≤ 0.0000
Halpern et al.[46]	193	349	BM, SM, CM	2 w	7	= Atopy 11.1/19.9 NS
Koivikko [47]	73	486	BM	≥6 m	1	⇓ Asthma p <0.0005 = AD
Blair [48]	80	59	BM	≥2 m	20	⇓ Asthma 25/64 p <0.05
Kramer and Moroz [49]	59	102	BM	≥2 m	0.8	= AD 41.5/31.1 NS
Gordon et al. [50]	112	85	BM	≥ 3 m	2	= AD, Asthma 22/15 NS
Golding [51]	221	1567	BM	≥ 3 m	5	⇓ AD 1.6/6.6 p <0.001 =Asthma 0.2/1.4 NS
Magnusson [52]	48	142	BM +SM	≥ 3 m	1.5	= Atopy 16.7/21.1 NS
Wjst et al. [53]	484	2352	BM	2 m	1	= Asthma, AR NS

Table 2: Prevention of Atopy based on BM: Results of Retrospective Studies according to the publication year.

- Absolutely no smoking in the house
- Strict environmental controls for the elimination of house dust
- No pets in the house
- Day-care centers attendance delayed to after 3 years of age

Table 3: DIetary manipulations followed by the study group.

Components	Properties
sIgA 240 µg/mg/day until 3rd day, ~20 µg/mg/day from 15 days to 6 months	Does not activate complement, suppresses PMN chemotaxis, blocks adhesion of microbial pathogens, prevents infections, limits the allergenic penetration
IgM about 100 mg/day	Activates complement, forms antibodies against bacteria and virus, retains opsonic activity after traversing the intestinal canal
IgG about 70 mg/day	Activates complement, has heat-stable opsonic activity, blocks toxins and virus
IgG subclasses	Anti-infective activity
IgD	Forms antibodies against bacteria
α-2-glycoprotein associated with pregnancy	Inhibits the lymphocytes, lymphocyte blastogenesis, ADCC, and immunoglobulin productions
Antioxidants: ascorbic acid, cysteine, ß-carotene, α tocopherol	Contrast superoxide production
Arylsulphatase	Degrades leukotrienes
Catalase	Degrades H_2O_2
Cytokines [95,97,103,105]: IFN-γ (0,5 UI/ml)	Increases chemotaxis and opsonization, enhances Th1 and antagonizes Th2 cells
IFN-γ (0,5 UI/ml)	Increases chemotaxis and opsonization, enhances Th1 and antagonizes Th2 cells
IL_1 (1 ng/ml)	Activates T lymphocytes
IL_6 (50 pg/ml)	Enhances IgA production and favors oral tolerance
IL_{10} (3.000 pg/ml)	Carries on anti-inflammatory activity in the infants' gut, has effects opposed to those of IFN-γ on Th1 e Th2 cells
M-CSF, GM-CSF	Induces macrophage differentiation
TGF-ß (1.000 ng/ml)	Enhances isotype switching to B_{IgA+} cells and favors oral tolerance
TNF-α (500 pg/ml)	Induces proliferation of epithelial cells from G-CSF; activates macrophage motility and SC production
Glycoproteins, glycolipids	Antiviral activity, offer protection against bacterial colonization
fibronectins	membrane protein, mediates cell interactions and adhesion plasma protein with opsonic functions
Histaminase	Catabolize histamine
Inhibitors of proteases	Reduce inflammation
α-1-antichimotripsina	Degrades the enzymes active in the inflammatory reactions
α-1-antitripsina	
Inhibitors of viruses	
Lactoferrin	Inhibits complement and inflammation, is bacteriostatic and iron-binding factor
Lipids	Inhibits superoxide production, disrupt enveloped virus
Lysozyme	Inhibits PMN chemotaxis and free radicals formation, antibacterial activity
Macrophagesc	Have sIgA, produce lysozyme and PGE_2 which reduces intestinal permeability
Modulators of growth	

EGF	Enhances maturation of epithelial cells: levels in "mature" BM 20-111 ng/ml, versus pasteurized CM 155 ng/ml [101]
NGF	neuropeptides: GIP, bombesin, cholecystokinin, gastrin, etc
taurine	
Oligosaccharides	Receptors for certain microbes, block their attachment to mucosal sites
Prostaglandins	Inhibit degranulation of neutrophils, activation of lymphocytes, are cytoprotec¬tive, promote intestinal and cellular integrity, release brush border enzymes
Protein binding B_{12}	Antibacterial activity, is bacteriostatic
Receptor analogues	Anti-infective activity, protection of mucosal barrier
Evaluation of BM immune activity	
Poor or absent cellular reactivity	
Absence of basophils, mast-cells, eosinophils, platelets	
T lymphocytes respond weakly to allogenic cells	
Poor activity of NK cells and of ADCC	
Slow motility of neutrophils	
Active cellular reactivity	
Macrophages: contain IgA, produce IFN and lysozyme, modulate phagocytosis, epithelial growth, immunoregulation	
Neutrophils: contain IgA, regulate chemotaxis, phagocytosis	
B lymphocytes: Ig synthesis	
T lymphocytes: cellular immunity, produce IFN, modulate cytotoxicity, immunoregulation	
* Features denoting that BM lymphocytes are activated (99)	
T cells: IFN-γ, CD45RO, CD25, HLA-DR ↑	
macrophages: motility ↑ CD11b ↑ CD62L ↓	
neutrophils: chemotactic response ↓ CD11b ↑ CD62L ↓	
* Number of lymphocytes and other cells/mm^3 (mean ± SD) (94,98,100)	
Total lymphocytes = 1.196.7± 358.7	
B lymphocytes = 376.2 ± 138.1	
T lymphocytes = 222.3 ± 251, CD4 = 504.2 ± 155.3, CD8 = 318.4 ± 98.6; CD4/CD8 = 1.6 ± 0.15	
Macrophages = 2.325.5 ± 660.5	
Neutrophils = 948.9 ± 368.3	
* Determinants (% of positive cells ± SD) [93,96)	
CD3 (T lymphocytes)	25.6 ± 14.9
TcR αß	24.5 ± 15.6
TcR γδ	4.0 ± 3.6
CD4	13.6 ± 8.7
CD8	12.2 ± 7.0
CD14 (macrophages)	64.0 ± 18.2
CD19 (B lymphocytes)	10.2 ± 5.3
CD103	4.7 ± 1.6
IL_2R	10.5 ± 4.6
ADCC = antibody dependent cell mediated cytotoxicity, EGF = epidermal growth factor, GIP = gastric inhibitory peptide, NGF = nerve growth factor, TGF-ß = transforming growth factor-ß, TNF = tumor necrosis factor Data from references 92-105	

Table 4: Environmental measures given to the study group.

In particular we asked the accompanying parent(s) of the 589 children whether they were breastfed, and in case of positive response, which was the duration of breastfeeding. The parents of all children gave their informed consent. Data were analyzed using the X2 method.

Results

Analysis males versus females p=0.0001. The mothers of the study group have breastfed 273/289 off springs (94.5%) of cases (p=0.0225) for 136 days (mean 125, range 33-211) p=0.0001. The control children were breastfed in 89.6% of cases, for a mean of 98 days (mean 80 days, range 10-110). In both groups breastfeeding was not always exclusive.

Discussion

The mothers of children at genetic risk were much more motivated, and have breastfed their children for a significantly longer period of time than the mothers of the control babies. A basic knowledge of controversial results in studies on atopy prevention, examining the prospective versus the retrospective ones has been outlined in Table 5 [24-34]. On the contrary, the prospective preventive studies have largely confirmed the high value of breastfeeding alone or associated with dietary manipulations, along with environmental controls in the prevention of allergic disease in at risk babies. It was already stressed elsewhere that postponing the atopy development leads to a lessening of the severity of the clinical manifestations, and even to atopy avoidance forever [34-46].

However, there are very sophisticated measures to cast doubt on the "completeness" of BM, such as indirectly throwing discredit on breast-feeding. There are some controversies and the reader can conclude that the above studies have yielded conflicting results, and that the ability of breastfeeding to delay the onset or to reduce the severity of allergic

1. Selection criteria (atopic or non-atopic parents)
2. Methods used to diagnose the atopic disease (parental diagnosis, general practitioners, pediatricians, allergists, dermatologists, questionnaires)
3. Lack of supportive immunologic data
4. Lack of statistical analysis of data
5. Social demographic characteristics
6. Sex of babies
7. Drop-out rates
8. Small number of subjects (possible type 2 error)
9. Exclusive nature and duration of breast-feeding
10. Dietary restriction in mothers (cow's milk, egg)
11. Age of solid food introduction
12. Type of solid foods
13. Maternal and child compliance
14. Attendance at day care facilities
15. Environmental measures (smoking, dust, pets)
16. Duration of the follow-up
17. Prospective versus retrospective studies
Modified from reference 57

Table 5: Possible causes of controversial results in studies on atopy prevention.

disease is only equivocal. For example Vandenplas [47-58] affirms that although the majority of studies suggest that exclusive breastfeeding exerts a protective effect, a number of other studies fails to show this assumption and points out that breastfeeding is associated with a decrease in the subsequent risk of atopic disease. In addition, breastfeeding has been associated even with a rise in prevalence of atopic diseases, and a possible interference with normal growth [59]. There are further, direct measures to comply this effect, such as advertising infant formulas in hospitals [60] or the use of HFs in the Maternity Hospitals and even for atopyprevention in at risk infants [61].

In addition we refer to the necessity stressed by several authors of supplementing the diet of breastfeeding mothers with essential fatty acids (EFAs) and/or administering EFAs to children with atopic dermatitis (AD). Since 1929 we have learned that a deficit of EFAs may be the cause of skin lesions in animals [62] and in atopic children compared with healthy controls [63]. EFAs are polyunsaturated fatty acids that cannot be synthesized by vertebrates and must therefore be obtained from the diet. Dietary EFAs and their derived compounds are important structural components of cell membranes. They are the principle determinants of membrane fluidity and affect the activity of a number of membrane-associated enzymes [64].

These eicosanoids play an important role in immunological and inflammatory processes both as effector signals and as immunoregulatory mediators [65-69]. Increased proportions of LA and decreased proportions of its derived fatty acids have been found in the plasma of AD patients [70-73]. Supplementation of the diet in these patients with g-linolenic acid (GLA) in the form of evening primrose oil produces a tendency towards normal of the EFA (essential fatty acids) profile and an improvement in symptoms [74-77].

Another possible drawback of BM resides in the so-called BM allergy, starting from the supplements of CM formulas occasionally given to full term healthy neonates in nurseries, even in breast-fed babies. The amount of CM proteins in such supplements is enormous compared with the extremely low amount provided by BM [78]. We know that 40 ml of BM contains an amount of ß-lactoglobulin (ßLG) of 0.012ng/l [78], whereas 40 ml of CM contains 1610ng/l of ßLG! As a consequence of these occasional supplements, sensitization may occur in a predisposed baby, and the minute amount of CM proteins of BM may subsequently act as a booster dose, triggering allergic reactions. The results of several studies support this hypothesis: CM allergy (CMA) was significantly more common in babies who received supplements of CM formulas early in life in comparison to fully breastfed babies [30,79,80]. All the fully breastfed babies who developed CMA received feedings of CM formula in the nurseries and none of the fully breast fed babies without supplements of CM formula developed CMA [30].

Lindfors et al. [81] have documented that children with skin prick tests (SPT) and specific IgE antibodies against egg all were fed CM during the first days of life. Total IgE levels at the 5th day of life were significantly correlated with the amount of early post natal CM supplementation (p=0.013) [82], maintaining the significativity until the age of 12 months mainly in at risk babies [83]. This data confirms the studies cited so far and the classic Jarrett one (the repeated little doses of allergens are more sensitizing than larger ones for the predisposed individual) [84]. In addition, 93% [85], 68% [86], or 64% [80] of breast-fed infants were exposed to less or more inadvertent supplements in the neonatal nursery. The babies presented CMA proved by challenge on an average after 7 weeks of life [80], or immediate symptoms at the first introduction of CM, at the age of 1-8 months (median 4.0) [85]. We emphasize that when the "pirate bottle" has administered HFs: the neonates presented with anaphylactic reactions when they were fed such formulas on weaning from BM [86,87]. The infants kept an immunologic memory of the type of supplement received at that time. Since several years in the Maternities of Northern countries [59,88] and in a London hospital [33], these CM feedings are no more permitted.

A typical case is reported by Lifschitz et al. [89], an anaphylactic shock due to CM protein hypersensitivity in a newborn who was mistakenly fed BM that had been expressed before CM products were eliminated from his mother's diet is correctly shown in the title, however in the abbreviated title and in the discussion is referred to as "anaphylactic shock in a breast-fed infant" [89].

The anaphylactic reactions triggered in young infants by the first CM administration show that apparently it is not easy to protect neonates at risk of atopy. Such reactions could be explained by transfer of maternal antigens directed versus the antigen-binding site of anti-idiotypic antibodies: if anti-idiotype antibodies against poliovirus antigens can be transferred from the mother to the offspring, similarly anti-idiotype antibodies to food antigens (e.g. lactoprotein), having the capacity of recognizing an idiotope within the paratope, could replace the antigen, mimicking its functional properties, and be transferred from the mother via the placenta to the fetus, acting like antigens during the neonatal period or subsequently [90].Therefore IgE-mediated sensitization through BM is rather rare: 0.042% [91] or 0.28% [30].

Immunology of breast milk: Nutrition and defense

It is increasingly manifest that BM contains a wealth of immune factors, which are designed to nourish and protect the vulnerable newborns during the critical postpartum period. Thanks to the mammary gland, a true immune organ [16,66], BM represents an excellent protection against the dangers of a deficient intestinal defence system, based on unique immunological, anti-infective, anti-inflammatory and immunomodulating factors functionally interacting among themselves (Table 6) [92-105]:

- Provides, together with colostrum, in addition to T and B lymphocytes and Ig, IFN, complement components and other bioactive molecules protecting against bacterial and viral infections [106], is rich of vital cells (up to 106/ml), thus insuring a continuing supply of

Components	Properties
sIgA 240 µg/mg/day until 3rd day, ~20 µg/mg/day from 15 days to 6 months	Does not activate complement, suppresses PMN chemotaxis, blocks adhesion of microbial pathogens, prevents infections, limits the allergenic penetration
IgM about 100 mg/day	Activates complement, forms antibodies against bacteria and virus, retains opsonic activity after traversing the intestinal canal
IgG about 70 mg/day	Activates complement, has heat-stable opsonic activity, blocks toxins and virus
IgG subclasses	Anti-infective activity
IgD	Forms antibodies against bacteria
α-2-glycoprotein associated with pregnancy	Inhibits the lymphocytes, lymphocyte blastogenesis, ADCC, and immunoglobulin productions
Antioxidants: ascorbic acid, cysteine, ß-carotene, α tocopherol	Contrast superoxide production
Arylsulphatase	Degrades leukotrienes
Catalase	Degrades H_2O_2
Cytokines [95,97,103,105]: IFN-γ (0,5 UI/ml)	Increases chemotaxis and opsonization, enhances Th1 and antagonizes Th2 cells
IFN-γ (0,5 UI/ml)	Increases chemotaxis and opsonization, enhances Th1 and antagonizes Th2 cells
IL_1 (1 ng/ml)	Activates T lymphocytes
IL_6 (50 pg/ml)	Enhances IgA production and favors oral tolerance
IL_{10} (3.000 pg/ml)	Carries on anti-inflammatory activity in the infants' gut, has effects opposed to those of IFN-γ on Th1 e Th2 cells
M-CSF, GM-CSF	Induces macrophage differentiation
TGF-ß (1.000 ng/ml)	Enhances isotype switching to B_{IgA+} cells and favors oral tolerance
TNF-α (500 pg/ml)	Induces proliferation of epithelial cells from G-CSF; activates macrophage motility and SC production
Glycoproteins, glycolipids	Antiviral activity, offer protection against bacterial colonization
fibronectins	membrane protein, mediates cell interactions and adhesion plasma protein with opsonic functions
Histaminase	Catabolize histamine
Inhibitors of proteases	Reduce inflammation
α-1-antichimotripsina	Degrades the enzymes active in the inflammatory reactions
α-1-antitripsina	
Inhibitors of viruses	
Lactoferrin	Inhibits complement and inflammation, is bacteriostatic and iron-binding factor
Lipids	Inhibits superoxide production, disrupt enveloped virus
Lysozyme	Inhibits PMN chemotaxis and free radicals formation, antibacterial activity
Macrophagesc	Have sIgA, produce lysozyme and PGE_2 which reduces intestinal permeability
Modulators of growth	
EGF	Enhances maturation of epithelial cells: levels in "mature" BM 20-111 ng/ml, versus pasteurized CM 155 ng/ml (101)
NGF	neuropeptides: GIP, bombesin, cholecystokinin, gastrin, etc
taurine	
Oligosaccharides	Receptors for certain microbes, block their attachment to mucosal sites
Prostaglandins	Inhibit degranulation of neutrophils, activation of lymphocytes, are cytoprotec¬tive, promote intestinal and cellular integrity, release brush border enzymes
Protein binding B_{12}	Antibacterial activity, is bacteriostatic
Receptor analogues	Anti-infective activity, protection of mucosal barrier
Evaluation of BM immune activity	
Poor or absent cellular reactivity	
Absence of basophils, mast-cells, eosinophils, platelets	
T lymphocytes respond weakly to allogenic cells	
Poor activity of NK cells and of ADCC	
Slow motility of neutrophils	
Active cellular reactivity	
Macrophages: contain IgA, produce IFN and lysozyme, modulate phagocytosis, epithelial growth, immunoregulation	
Neutrophils: contain IgA, regulate chemotaxis, phagocytosis	
B lymphocytes: Ig synthesis	
T lymphocytes: cellular immunity, produce IFN, modulate cytotoxicity, immunoregulation	
* Features denoting that BM lymphocytes are activated [99]	
T cells: IFN-γ, CD45RO, CD25, HLA-DR ↑	
macrophages: motility ↑ CD11b ↑ CD62L ↓	
neutrophils: chemotactic response ↓ CD11b ↑ CD62L ↓	
* Number of lymphocytes and other cells/mm^3 (mean ± SD) (94,98,100)	

Total lymphocytes=1.196.7± 358.7	
B lymphocytes=376.2 ± 138.1	
T lymphocytes=222.3 ± 251, CD4 = 504.2 ± 155.3, CD8 = 318.4 ± 98.6; CD4/CD8 = 1.6 ± 0.15	
Macrophages=2.325.5 ± 660.5	
Neutrophils=948.9 ± 368.3	
* Determinants (% of positive cells ± SD) (93, 96)	
CD3 (T lymphocytes)	25.6 ± 14.9
TcR αß	24.5 ± 15.6
TcR γδ	4.0 ± 3.6
CD4	13.6 ± 8.7
CD8	12.2 ± 7.0
CD14 (macrophages)	64.0 ± 18.2
CD19 (B lymphocytes)	10.2 ± 5.3
CD103	4.7 ± 1.6
IL_2R	10.5 ± 4.6
ADCC = antibody dependent cell mediated cytotoxicity, EGF = epidermal growth factor, GIP = gastric inhibitory peptide, NGF = nerve growth factor, TGF-ß = transforming growth factor-ß, TNF = tumor necrosis factor Data from references 92-105	

Table 6: Breast milk components with immunological, anti-infective, anti-inflammatory and immunomodulating activities.

factors with a high immune role in the defense of the vulnerable infant. IgA and sIgA antibodies inhibit or prevent the penetration of harmful luminal antigens [107]. IgA and sIgA have the potential for lessening or abrogating possible hypersensitivity reactions [92,93,102], with levels equal also to 0.5-1 g/die or 0.2-0.3g/kg of sIgA [107], in addition to anti-infective factors to protect infants against pathogens during the critical period [108], such as anti-VRS sIgA [109]. BM stimulates IgA and sIgA secretion, thus actively facilitating the maturation of the neonatal immune system, unlike bottle-fed neonates [110]. It appears that sIgA are significantly more elevated in the saliva of breast-fed babies [111], whereas the production is developmentally delayed in the recipient baby: for example 4 weeks-12 months are needed for sIgA maturation, 1-2 years for lysozyme and about 2 years for memory (CD45RO) cells [2,112].

• Idiotype/anti-idiotype antibodies may have lasting effects on the offspring immune system, activating both B- and T-cell clones, and thus priming protective immune responses [113] also inducing tolerance versus environmental antigens, such as food antigens [113,114]. Such antibodies generate in 4-month old breastfed infants serum and secretory responses to vaccines (tetanus and diphtheria toxoids) statistically more significant than in formula-fed babies [115], and can also explain the occasional cord blood (CB) findings of IgE antibodies to several antigens [116,117]. This finding would also agree with the enhanced antibody responses to oral poliovirus vaccine in babies breastfed for 6 months compared to babied fed a conventional formula supplemented with nucleotides; moreover the titresanti-Haemophilusinfluenzae type b are higher if breastfeeding is longer than 6 months [118].

• EFA, polyunsaturated (PUFA), long chain (LCP) C20 and C22: arachidonic (AA, 20:4w6), docosahexaenoic (22:6w3), dihomo-g-linolenic (DGLA 20:3w6) necessary also for intellectual development [119], notably the ratio 18:2w6 /18:3w3 allowing the incorporation of 22:6w3 into the neonatal neural tissue and the retina [120]. CB studies suggest a preferential and selectivematerno-fetal transfer of LCP [121], therefore the breastfed premature infants receive a higher LCP supply [122]and in general a threefold higher dietary LCP phospholipide concentration than LCP-enriched formulas, apparently because the infants transform dietary LCP into structural lipids sparing them from oxidation [121]. On the other hand, the EFA abnormality found in umbilical CB in newborns 'at risk' of atopic disease was shown to correlate with IgE levels, suggesting that the EFA abnormality may be of fundamental importance in the development of the atopic state [123]. Several studies yielded controversial results about the presence of an EFA deficit in BM of atopic mothers, and suggested that an EFA supplementation could be useful for preventing atopy in genetically at risk infants [124-129]. But the small cohort size [125,126]can introduce a possible type II error in the data. But atopic mothers provide with BM normal amounts of w-6-fatty acids; such data were supported by extensive statistical analyses [129]. In addition, w-6-fatty acids were of no value in children with atopic bronchial asthma [130,131], nor in AD being no differences between treated and control children [132]. The EFA levels (Table 7) [133,134], higher in both control babies and in those fed supplemented formulas [135], regularly absorbed [136], are to be found in BM for at least 8 weeks with a ratio w6:w3=5:1 [137]: the w6 level is twofold higher than that of w3 in brain and 1.3-fold higher in retina [120]. Although the EFA levels are variable, taking into consideration the marked differences in methods and dietary composition of the population studied [133], most EFA levels are comparatively similar in several European studies [133,138] (Table 7).

• Nucleotides, monomeric units of polymeric DNA and RNA, present in BM (% of nitric products) five times more than in CM

EFA	Mean of 14 studies done in Europe (N. 329)	EFA	Mean of 10 studies done in Africa (No. 259)
ω–ϕ PUFA		ω–ϕ PUFA	
C18:2ω-6	11.0 (6.9-16.4)	C18:2ω-6	12.7 (5.7-17.2)
C18:3ω-6	0.54 (0.16-0.9)	C18:3ω-6	0.2 (0.1-0.3)
C20:2ω-6	0.35 (0.2-0.5)	C20:2ω-6	0.41 (0.3-0.83)
C20:3ω-6	0.32 (0.2-0.7)	C20:3ω-6	0,4 (0.2-0.5)
C20:4ω-6	0.55 (0.2-1.2)	C20:4ω-6	0.66 (0.3-1.0)
C22:4ω-6	0.08 (0.0-0.1)	C22:4ω-6	0.08 (0.0-0.1)
C22:5ω-6	0.15 (0.1-0.3)	C22:5ω-6	0.15 (0.1-0.3)
ω–3 PUFA		ω–3 PUFA	
C18:3ω-3	0.87 (0.7-1.4)	C18:3ω-3	0.86 (0.1-<2.0)
C20:3ω-3	0.06	C20:3ω-3	0.14
C20:5ω-3	0.23 (0.04-0.6)	C20:5ω-3	0.22 (0.1-0.48)
C22:5ω-3	0.2 (0.1-0.52)	C22:5ω-3	0.19 (0.1-0.39)
C22:6ω-3	0.29 (0.1-0.59)	C22:6ω-3	0.38 (0.1-0.9)
Modified from reference 120		Modified from reference 290	

Table 7: BM values of essential fatty acids (EFA) polyunsaturated (PUFA) in 14 European and 10 African studies; mean and highest and lowest values.

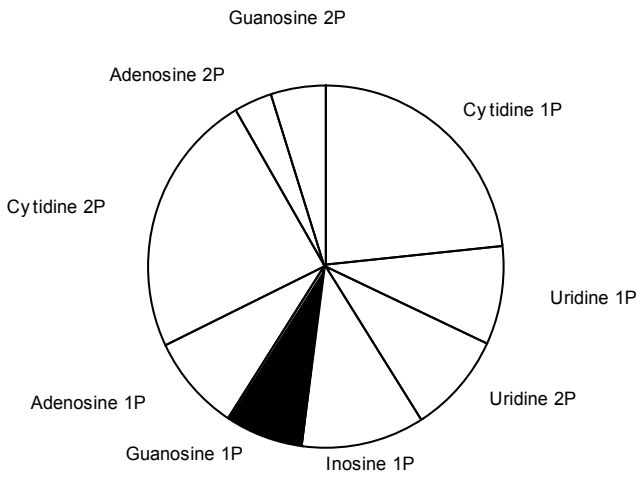

Figure 1: Nucleotide content of breast milk from data of reference 101 Mean of 2,4,8 e 12 weeks of breastfeeding, values are expressed in µmol/l1P, 2P = mono-, di-phosphate.

Type of BM	uridine	cytidine	guanosine	adenosine	TPAN
Colostrum Mean + (range)	26 (21-30)	71 (33-84)	21 (15-26)	21 (13-26)	139 (82-164)
Transitional BM Mean + (range)	32 (23-37)	86 (76-100)	30 (19-43)	29 (17-42)	177 (144-210)
Early mature BM Mean + (range)	48 (30-67)	102 (79-146)	45 (23-91)	46 (21-97)	240 (172-402)
Mature BM Mean + (range)	47 (36-58)	96 (73-124)	28 (22-40)	31 (24-49)	202 (156-259)
General mean ± SD	38 ± 13	88 ± 24	31 ± 18	32 ± 20	189 ± 70
Range	21-67	33-146	19-92	13-97	82-402
Notes: colostrum, 1st-2nd day; transitional BM, 3rd-10th day; early mature BM, 1 month after delivery; mature BM, 3 months after delivery, Modified from reference 140					

Table 8: Nucleotides as such and total potentially available nucleoside (TPAN) (µmol/l) in a pool of 100 samples of breast milk (BM) distinct by stage of lactation.

[139], are essential in energy metabolism, enzymatic reactions, and during rapid growth, have been reported to be especially important for the growth and maturation of the developing gut, in addition to enhancing immune system potentialities in neonates [140]. The human body synthesizes nucleotides to cover its metabolic needs, and is also dependent on external supplies, such as dietary nucleotides; BM levels are shown in Figure 1 [141], in Table 8 [140]and in comparison with supplemented formulas (Table 9) [142]. BM is provided with the complete enzyme sequence to convert purine nucleotides to uric acid [142]. Nucleotides influence several indices of neonatal immune function [143]. They are essential nutrients for normal development, maturation and repair of the gastrointestinal tract, since rapidly growing tissues such as the intestinal epithelium and lymphoid cells have limited de novo synthetic capacity and require exogenous sources of purine and pyrimidine bases [144]. Dietary purines are not significantly incorporated into hepatic nucleic acids, but pyrimidines are: both are taken up by gut cells, which convert to uric acid the excess purines [144]. Carver [143]has documented that breastfed infants have higher NK cell and IL2 production compared with a group of healthy babies fed a CM formula supplemented with nucleotides (41.7 ± 4.7 versus 32.2 ± 3.4), and levels significantly higher than infants fed a standard non-nucleotide-supplemented formula; at 4 months only breastfed babies maintained the statistical differences versus the standard CM-fed group [143]. High levels of NK cells and IL2 may represent a defense against pathogenic invasion [143]. Principally in preterm infants [145], dietary nucleotides may influence the conversion into LCPs of linoleic (w-6 series) and a-linolenic (w-3 series) acids.

• Several factors insure a nonspecific protection against potential pathogens, including the enteric colonization with nonpathogenic bacteria, lectins, additional carbohydrates different from lactose providing a protective effect for the developing mucosa, lipids with antibacterial, antiviral and antiprotozoan activity, and growth factors stimulating gut closure etc[146].

• Leukocytes (Table 6) consist of (%): neutrophils 55-60, macrophages 35-40, lymphocytes 5.80% of which are T lymphocytes [147], including memory T cells [148]; the total lymphocytes, B and T cells, CD4 and CD8 lymphocytes, macrophages and neutrophils are present in preterm babies in a significantly greater number [149]. Moreover are present more T cells than those found in peripheral blood, such as TcRgd, CD8 and CD103 and an increased proportion of activated cells, which impart to BM cells a "mucosal" phenotype [150]. What is more, healthy breastfed infants have significantly fewer CD4 T cells, and a greater number of CD8 T cells, so that the CD4/CD8 ratio is lower than in age-matched bottle-fed babies, whereas in peripheral blood the ratio is 2:1, in addition to a greater number of NK cells [151]. It was suggested that maternal T cells carry on a prominent activity, promoting the secretion of maternal IgA [152].

• Macrophages are functionally active by means of M-CSF (macrophage colony-stimulating factor) present with levels 10-100 times above the levels found in human blood [153], mean 30 times [150], ready to bridge the early neonatal "deficits" since they are provided with receptors for sIgA and may be activated via these receptors [154]. BM macrophages are able to increase sIgA levels up to 5-10% of BM content [104], yet intracellular sIgA, a valid means to progressively transport the antibodies directly into critical areas [154], in addition to phagocyting the immune complexes formed by sIgA to exclude potential pathogens invading BM. Macrophage concentration is greatest at the 6th day but

Compound	Breast milk	Not supplemented formula	Supplemented formula
Nucleic acid	23 ± 19 (8,6-71)	<2	<2
Nucleic acid*	68 ± 55 (25-209)	<6	<6
5'-CMP	66 ± 19 (41-106)	-	60
5'-UMP	11 ± 5.3 (4.8-21)	-	22
5'-GMP	1.5 ± 1.6 (0-5.9)	-	8.4
5'-IMP	-	-	9.8
5'-AMP	5.7 ± 4.9 (1.7-19)	-	14
Cytidine	5.4 ± 1.6 (3.6-9.8)	6.2	8.5
Uridine	4.9 ± 1.3 (2.8-7.8)	10	9.7
Guanosine	-	1.4	1.2
Inosine	-	1.5	1.5
Adenosine	-	-	-
Guanine	0.76 ± 1.3 (0-3.3)	-	-
Hypoxanthine	-	-	-
Xanthine	-	-	-
uric acid	69 ± 12 (47-86)	35	33
orotic acid	-	240	188
All values are expressed in µmol/l, the first value of nucleic acid is expressed in mg/l, * nucleic acid expressed as nucleotide equivalent, - not measurable Modified from reference 142			

Table 9: Levels (mean ± standard error of the mean and limits) of nucleic acids and their metabolites found in breast milk at 3-24 weeks of breastfeeding, and in formulas supplemented or not of ribonucleotides.

can persist and act up to the 6th month [93], they can also be primed to release large amounts of O2 metabolites and could thus contribute to the protection of newborns against invading microorganisms [155]. In keeping with these findings the ability of immunocompetent cells to survive sticking to the intestinal mucosal sites [149]and to secrete their soluble products, is also a means to potentiate the local immune responses of neonatal gut as well as their systemic ones;

• In addition to the ILs listed in Table 6, almost all generated by macrophages, there are several others including IL1a, IL2-5, IL8 [156] and IL2 produced by T cells [148]. Such ILs are therefore able to meet all requirements of breastfed neonates, moreover the leukocytes if properly stimulated produce TNF-a [157] and mononucleates GM-CSF likewise [156]. In particular IL10, present in placental lysates of 2nd and 3rd trimesters and in amniotic fluid [158], could represent a bridge among the anti-inflammatory and immunomodulating factors forming the defense system of BM [159], also because it is necessary for the synthesis of IgA antibodies [160]. The undetectable expression of IL10 in preterm babies [161], confirmed by the decreased secretion by neonatal monocytes and T cells [162], is in relationship with severe respiratory manifestations and can predispose to chronic lung inflammation in preterm neonates [161].

• Regarding the chemokines IL8 and RANTES, it is intriguing the hypothesis that they facilitate the transfer of maternal cells into BM, their adhesion to intestinal walls and their migration into infantile immune tissues, leading in prospective to the modulation of neonatal immunity [105].

• Some oligosaccharides (Table 7) contribute to augment the defense potential of babies against infectious agents, acting as receptors for E. coli and Vibrio cholerae, preventing their adhesion to the intestinal mucosa, so decreasing the inflammatory reactions at the mucosal level.

Immunology of colostrum

Centuries were necessary in order that the alimentary value was acknowledged, the immunologic one was still denied in 1939 [163]. Contains:

• IgA, IgM, IgG; as a compensation of poor quantity of IgG (3% of maternal IgGs), colostrum and BM contain significant concentration of subclasses, » 50% of maternal titres [157]; Table 10 shows also the salivary values [164].

	IgG_1	IgG_2	IgG_3	IgG_4	IgG totali
Colostro	0.0372 (46.6)	0.0349 (43.9)	<0.0034 (<4.0)	0.0049 (6.2)	0.0804
Siero	6.209 (64.0)	2.585 (28.5)	0.577 (6.0)	0.194 (2,1)	9.986
Rapporto C/S (%)	0.6	1.1	<0.4	1.4	0.8
LM	0.0251 (46.9)	0.0196 (43.1)	<0.0016 (<3.7)	0.0042 (5.7)	0.0469
Siero	7.546 (63.0)	3.204 (29.0)	0.786 (7.0)	0.201 (2.0)	12.480
Rapporto LM/S (%)	0.3	0.6	<0.2	0.9	0.4
Saliva	0.0097 (27.9)	0.0187 (53.7)	<0.0016 (<4.6)	0.0013 (3.7)	-
Siero	8.246 (60.7)	4.504 (33.2)	0.473(3.5)	0.161 (0.8)	-
Rapporto Saliva/S (%)	0.1	0.4	<0.3	0.8	-
C = colostro, LM = latte materno, S = siero; Modified from reference 164					

Table 10: Levels (geometric mean, g / l) of the subclasses IgG in colostrum, milk maternoe saliva (average levels, g/l) (with relative percentage of each IgG) in comparison with the percentage values with the serum (S) corresponding.

*Lymphocytes (about 10-15% of total cells) x ml (x 10^4)			
CD3	74.7 ± 2.5		
CD4	50.6 ± 2.3		
CD8	24.0 ± 1.7		
(mean ± ESM) T4/T8 cell ratio higher than that of circulation			
(mean and range)	colostrum	autologous blood	
CD3+	69 (55-81)	75 (65-84)	
CD3+/CD45RA+	12 (4-31)	49 (28-69)	
CD3+/CD45RO+	78 (56-98)	54 (40-85)	
* Immunoglobulins (Igs)			
IgA (mg/dl) days 1-2:	619.0 ± 110.6	days 3-4	239.3 ± 55.8
IgG (mg/dl) days 1-2:	31.4 ± 12.3	days 3-4	14.1 ± 5.0
IgM (mg/dl) days 1-2:	38.3 ± 7.8	days 3-4	5.3 ± 1.6
IgG subclasses (about 50% of maternal levels, see Table 6)			
sIgA with levels higher than BM levels			
* IFN-γ (U/ml)	colostrum	autologous blood	
anti-CD3	39.5 ± 9.6	33.8 ± 10.7	
anti-CD2	20.6 ± 6.5	22.3 ± 6.2	
* macrophages 30-47% of total cells (levels higher than BM levels)			
* antioxidants (may serve to block neutrophil-generated toxic oxygen metabolites)			
* EGF			
pre-colostrum	130-180 ng/ml		
colostrum	35-438 ng/ml		
* enzymes and proteins (levels higher than BM levels)			
* lactate-dehydrogenase			
* trace elements (levels higher than BM levels)			
Human colostrum activities:			
* hastens the development of an intact mucosal barrier			
* enhances brush-border enzyme production (lactase, sucrase, and alkaline phosphatase)			
* cytotoxic activity			
ADCC			
lectine-dependent			
NK cells			
* decrease of antigen penetration in neonates			
* presence of IgE suppressor factors			
No. of lymphocytes and other cells/mm^3 (mean ± SD)			
Total lymphocytes	1.532 ± 520.2		
B lymphocytes	414.2 ± 218.2, T = 1.095 ± 347.6, T4 = 662.2 ± 218.4, T8 = 425.5 ± 143,9; T4/T8 = 1,6 ± 0.35		
Macrophages	2.860 ± 860.3		
Neutrophils	1.2019 ± 479		
ADCC = antibody dependent cell mediated cytotoxicity, EGF = epidermal growth factor, SD = standard deviation, SEM = standard error of the mean Data of Igs from ref. 164, 166, of T cells 149, 165, of CD45RA+, CD45RO+, CD3+ and IFN-γ from ref. 93, of EGF from ref. 104, of other cells from ref. 149, IgE suppressor factor from ref. 167			

Table 11: Immunologic factors in human colostrum.

• sIgA, macrophages and EGF with titres higher than the BM ones (Table 11) [93,101,149,164-167]. IgA antibodies (5-10 g/l) are transferred to newborns during the first 3 days after delivery: IgA can represent up to 80% of total content of proteins [104,105], while CD154 could increase their levels influencing the B-cell isotype switching [168].

• Nucleotide levels not much lower than those of transitional BM (Table 12);

Xenobiotic	Milk/plasma rate
Caffeine	0.8
Chloramphenicol	0.5-0.6
Ethanol	0.9-0.95
Iodum^{131}	65
Nicotine	0.17
Streptomycin	0.5-1.0
Theobromine	0.7
Theophylline	0.7
Tetracycline	0.62-0.81
Note: the high Iodum^{131} value in milk/plasma rate means that Iodum, due to its specific properties tends to accumulate into breast milk	

Table 12: Maternal milk/plasma rate of certain xenobiotics.

• Factors binding IgE and specifically suppressing IgE synthesis by B cells of atopicindividuals [169].

• Factors eliciting a non-specific protective function at the level of mucosal barrier because the existent antibodies, not being absorbed, stick to the intestinal wall, carrying on a function of passive defense [170].

• In addition an amount of EFA equal to the recommended ones [171]

• Titres of CD45RO+ and T-CD3+ cells mostly expressing CD103 and of IFN-g which assume a highly positive significance in the context of the above alluded to inadequacy of such neonatal cells [172] moreover there is a double volume of TcRgd cells compared with that in the peripheral blood [173].

• Substances able to accelerate the development of an intact mucosal barrier, enhance the production of brush-border enzymes (lactase, sucrase, alkaline phosphatase), and decrease food antigen penetration through an anti-inflammatory activity within the intestinal mucosa [174].

• Antioxidant substances which could be feasible to inactivate O_2 toxic metabolites deriving from the neutrophil excessive secretion [175].

• Colostral B cells respond with Ig secretion to the antigen stimulation [176]; similar growth has been observed in culture, therefore such results have given credit to the theory that B cells partially maintain their functional activities after having colonized the colostrum/BM [176]. This hypothesis was not confirmed since the IgE concentrations, similar in atopic and not atopic mothers, are so low that they have no significant effect on IgE regulation in the neonatal age [177].

As far as we have as yet discussed it seems antiscientific and antimedical depriving the neonate of colostrum and early milk in the very first days of extrauterine life adds to the risk that potential pathogens from other foods and fluids may cause infections [178].

All evidence as yet gathered tends to prove that maternal breast is an immune organ belonging to MALT [102]: BM not only has components protecting the vulnerable infant against the first infective and inflammatory episodes, but is also the vehicle for the transfer of immune regulation from the mother to her offspring, thus contributing to the maturation of the immune system of the newborn infant [179]. Several immunomodulating factors present in BM that may actively modulate the immunologic growth of the baby, many of which are produced and are common to other mucosal sites, often share synergical features, provide a protective activity without inducing inflammation, moreover their production decreases with reference to the duration of breastfeeding and synchronously with the increased secretion of those factors from the neonate [179]. In addition EGF has been shown to play a role in reducing macromolecular absorption and to promote the functional maturation of the epithelial cells of the gut barrier (Tables 6 and 11): indeed the proliferation of the intestinal epithelium is more rapid in breastfed animals compared to the artificially fed ones [101]. However pasteurized CM contains EGF values almost similar, which likely do not resist to subsequent manipulations [180].

sIgA is the major antibody of BM [92,93,102]: primed IgA-B cells home to the mammary gland through the enteromammary axis and are transferred to the suckling newborn, where they act against noxious intraluminal antigens and also respiratory microorganisms [92,93,102]. In the neonatal gut were detected specific sites where maternal sIgA antibodies bind the glycocalyx of epithelial cells more firmly than the endogenous ones [170]. Furthermore, maternal IgA antibodies have been shown to block effectively the antigen entrance into BM [181]. Clearly, maternal MALT is in turn "educated" and, again through the enteromammary pathway, contributes to the de novo synthesis of sIgA; next as previously alluded to, the studies on anti-idiotypic antibodies show that they are favored in infants by maternal antibodies [90,182]. Even human milk macrophages play a role in the local protection of the infantile gut [154]. Beginning from the first week of breastfeeding, the baby receives spermine and spermidine, with a virtual protective effect on food allergy. Consequently it appears to be pivotal the immune defense insured to the offspring firstly by colostrum and then by BM, in a particularly critical period concerning a possible sensitization [179], in which the maturation of the gastrointestinal barrier and the antibody secretion still are inadequate [158]. In conclusion, breastfeeding can prevent atopy development in genetically at risk newborns/infants and promote la maturation of the gastrointestinal tract with several mechanisms [2], however there are conditions potentially associated with immature mucosal barrier, for instance the elimination of gut flora following an antibiotic treatment. It is not out of place to state that the most common immunodeficiency may be that of the young infant deprived of BM with the ensuing paucity of sIgA and other immune and defense factors [178]. This is demonstrated by the study of 24 variables, as presumed causes of neonatal septicemia: only the protection insured by BM versus CM or formula reached the statistical significativity ($p<0.001$) [178].

As regards possible effects of malnutrition on breastfeeding, neither the nutritional status, nor the ethnic origin influence the immunological components; instead Rotavirus infections may cause a significant rise in intestinal permeability to antigenic macromolecules (ßLG), in particular if associated with malnutrition, so that CM introduction can trigger an inflammatory reaction if the local microflora is reduced or absent [89].

Conclusion

The development of sensitization to food antigens depends on genetic factors, however the phenotypic expression of the disease is modulated by the age of the baby or child and by the different diets administered early in life. Early exposure to food allergens in infancy is associated with an increased risk of sensitization, favoring the start of the atopic march. Exclusive, prolonged breast feeding and delayed weaning should be encouraged in babies of atopic families. Elimination of the most common offending foods from the maternal diet should be considered during the period of lactation (Tables 1 and 2) [34,92]. There is no agreement on the most suitable formula if the mother

cannot breastfeed. SPFs have been employed for many years and their safety and nutritional adequacy has been definitely documented. In the last few years HFs have been suggested by several studies. However, at present, there are no data on the safety and nutritional adequacy on vulnerable babies exclusively fed these products since birth and for many months. Finally, due to the significant amount of immune reactive epitopes and intact CM proteins, HFs may be immunogenic in a predisposed host and should therefore not be given as a BM substitute [146]. Further studies are necessary in order to rule out this likelihood before widely using these products in atopic prone babies. Only BM can prevent the atopic march, as confirmed by recent studies. This is best demonstrated by the high proportion of atopic children breastfed from their mothers in this study=89.6%.

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Citation: Cantani A (2014) Immunological Properties of Breast Milk: A Prospective Study in 589 Children. Interdiscip J Microinflammation 1: 127. doi:10.4172/ijm.1000127