



Allergic prevention through breastfeeding

Maurizio Mennini, Stefania Arasi, and Alessandro Giovanni Fiocchi

Purpose of review

To perform a nonsystematic review of the literature on the role of breastfeeding as primary prevention tool for allergic diseases.

Recent findings

Human milk contains vast amounts of biologically active components that have a significant impact on the development of the gut microbiota. Exclusively breastfed infants show a different microbiota, with a predominance of *Bifidobacterium* species in their intestines.

The mechanisms underlying the antiallergic effects of human milk are most probably complex, as human milk contains not only nutritional substances but also functional molecules including polysaccharides, cytokines, proteins, and other components which can produce an epigenetic modulation of the innate and adaptive immune responses of the infant in very early life.

Summary

Currently, there is not sufficient strong evidence to guarantee its effectiveness in allergy prevention and therefore the main international scientific societies still do not count it among the recognized primary prevention strategies of allergy.

Keywords

allergy, breastfeeding, prevention

INTRODUCTION

Allergic diseases are considered an emerging public health problem worldwide, mainly because of the increasing prevalence and the risk of severe and even life-threatening reactions with high impact on quality of life and social costs. Globally established scientific allergy societies are investing their efforts into the development of evidence based guidelines and of strategies to prevent allergy.

Our aim is to perform a nonsystematic review of the current evidence on the role of breastfeeding as a primary prevention tool for allergic diseases.

WHO IS AT RISK FOR THE DEVELOPMENT OF ALLERGY: WHO REALLY NEEDS PREVENTION?

There is no international consensus on the definition of what qualifies an infant being at high risk of developing allergy and the definition has been evolving.

Recent criteria defined an infant at high risk of developing peanut allergy since presence of severe eczema and/or egg allergy [1]. However, variability exists in interpreting what is considered 'severe' and the definition of egg allergy differs from that used in the LEAP study and defines this as a documented

history of reactivity upon egg ingestion and not just egg sensitization.

Previously, multiple international guidelines defined an infant at high risk of developing allergic disease as having 1 or more immediate family member(s) with an allergic condition [2,3]. However, a major problem with this definition is that it is widely inclusive.

Genetic susceptibility to food allergy has been supported to some degree by both genome-wide association studies [4,5] and population studies [6,7].

However, not all data have supported family history as significantly increasing the risk of allergic disease and parental report of allergy (which is often used for study inclusion) can be inaccurate [8]. Conversely, it should be noted that food allergy commonly develops even among children with no inherent risk factors.

Multifactorial and Systemic Diseases Research Area, Predictive and Preventive Medicine Research Unit, Division of Allergy Bambino Gesù Children's Hospital IRCCS, Rome, Italy

Correspondence to Alessandro Giovanni Fiocchi, MD, Ospedale Pediatrico Bambino Gesù – Piazza di Sant'Onofrio, 4, 00165 Rome, Italy. Tel: +390668592296; e-mail: agiovanni.fiocchi@opbg.net

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KEY POINTS

- Exclusive breastfeeding is recommended by both American Academy of Pediatrics (AAP) Committee on Nutrition for 4–6 months of life, as well as by the World Health Organization for the first 6 months of life.
- Human milk contains vast amounts of biologically active components that have a significant impact on the development of the gut microbiota and can produce epigenetic effect.
- There is not sufficient strong evidence to guarantee effectiveness of breastfeeding in allergy prevention and, therefore, the main international scientific societies still do not count it among the recognized primary prevention strategies of allergy.

To date, no evidence exists to suggest that the pathophysiologic mechanisms of sensitization would differ in general population infants, suggesting that any recommendations made for at-risk populations would likely be applicable in the general population as well.

SHORT-TERM AND POTENTIAL LONG-TERM ADVANTAGES OF BREASTFEEDING FOR INFANT HEALTH

Exclusive breastfeeding is recommended by both American Academy of Pediatrics (AAP) Committee on Nutrition for 4–6 months of life, as well as by the World Health Organization for the first 6 months of life [9,10].

Breastfeeding prolongs the interaction with the mother's immune system and may influence oral tolerance in childhood. Pivotal studies clearly confirm the relevant role of breastfeeding for short-term infant health (e.g., growth, protection against infections, immune function) as well as for potential long-term advantages (e.g., prevention of malignancies, neurocognitive development, and noncommunicable diseases) [2]. Nevertheless, the evidence for the role of Human Milk (HM) for the prevention of allergic diseases remains controversial. This is due to variable definitions of allergic outcomes and to the lack of randomized controlled trials with detailed information about the maternal diet in breastfeeding. Although many studies emphasize a protective effect, others arise the doubt on the potential role of HM in promoting allergies [11]. The balance between oral tolerance and skin IgE sensitization may affect food allergy risk among infants with eczema: additional evidence suggests that colostrum has a prophylactic role in maintaining oral

tolerance, but in case of severe cutaneous barrier dysfunction, the protective effect of prolonged breastfeeding is lost [12]. It has been speculated that early oral exposure to aeroallergens through HM intake could increase the risk of sensitization in offspring [13,14]. On the other side, exclusive breastfeeding seems to reduce the incidence of eczema in the first 2 years of life and the risk of asthma in the first 5 years [9], or even 10 years with weaker evidence [15].

Several reasonable explanations account for HM protective effects on allergy susceptibility in children: stimulation of immune development (direct interactions with infant immune cells), epigenetic actions (DNA methylation, and noncoding RNAs), and modulation of gut microbiota.

EFFECTS OF BREASTFEEDING ON MICROBIOTA

HM contains vast amounts of biologically active components that have a significant impact on the development of the gut microbiota [16].

Exclusively breastfed infants show a predominance of *Bifidobacterium* species in their intestines [17,18]. The microbiota of formula-fed infants is far more diverse, with a predominance of staphylococci, *Bacteroides*, clostridia, enterococci, enterobacteria, and generally lower numbers of *Bifidobacterium* and *Lactobacillus* species [19]. *Bifidobacterium* species can multiply in the intestines of breastfed infants due to the presence of unique human milk oligosaccharides (HMOs) [20]. HMOs are natural prebiotics that are resistant to digestive enzymes and when unchanged reach the large intestine, where they are a selective substrate for bifidobacteria [21]. Although HMOs are 'bifidogenic', it should be noted that only certain *Bifidobacterium* species, especially those present in the infant intestine (i.e., *Bifidobacterium breve*, *Bifidobacterium longum* subspecies *infantis*, and *Bifidobacterium bifidum*) have a high capacity for utilizing HMOs.

HMOs are not the only bioactive components that influence the formation of the intestinal microbiota [22]. Recent studies revealed that breast milk is not sterile and contains live probiotic *Lactobacillus* and *Bifidobacterium* species [23]. Apart from these two genera, *Streptococcus* and *Staphylococcus* are also present in HM. The most commonly isolated *Bifidobacterium* species is *B. breve* and those of the genus *Lactobacillus* are *Lactobacillus salivarius* and *Lactobacillus fermentum* [23,24].

Therefore, it can be stated that breast milk is a natural synbiotic, containing both probiotics and prebiotics [22].

The composition of breast milk microbiota, like that of the intestinal microbiota, depends on many factors: the composition of the mother's intestinal and skin microbiota, the state of her health, and exposure to medications, particularly antibiotics [25–30].

Despite the observed differences in the composition of breast milk, studies confirmed that breastfeeding protects the baby against the development of allergies. Exclusive breastfeeding for at least 3 months was shown to reduce the risk of developing atopic dermatitis (AD), even in genetically predisposed children [31].

An observational study in 3296 children (Canadian Healthy Infant Longitudinal Development Birth Cohort) showed that, in comparison to exclusive breastfeeding for the first 3 months of life, a different diet, such as formula-based feeding (OR = 2.14, 95% CI 1.37–3.35) or breastfeeding with formula supplementation (OR = 1.73, 95% CI 1.17–2.57) increased the risk of developing asthma by the age of 3 years by about twofold [14].

Chu *et al.* attempted to answer the question of whether exclusive breastfeeding may decrease the risk of allergy in children born by C-section [32]. Their study confirmed that C-sections without medical indication were significantly associated with elevated risk of asthma at 6 years of age (OR = 1.58, 95% CI 1.17–2.13). However, this risk was attenuated in children who were breastfed exclusively for the first six months of life (OR = 1.39, 95% CI 0.92–2.10). By contrast, the risk was more prominent in children with nonexclusive breastfeeding or formula feeding (OR = 1.91, 95% CI 1.22–2.99).

EPIGENETIC EFFECT OF BREASTFEEDING

Epigenetics etymologically means 'on top of' or 'in addition to genetics' to highlight the fact that it modulates gene expression without any change in the nucleotide sequence. Epigenetics contributes to cell differentiation during the first 1000 days of life—a period that includes forty weeks of pregnancy plus the first two years of life. DNA methylation switches genes off in order to differentiate more than 250 cell types that characterize tissues and organs in our body. Cells acquire an epigenetic memory of the neonatal exposome, which is maintained throughout life.

Therefore, if the environmental cues are unhealthy (e.g., poor methyl group donor diet, endocrine disruption, stress, etc.), unwanted changes in the epigenome can occur, and alterations of gene expression could be observed later in life (e.g., adolescence or adulthood) increasing the risk for multifactorial environmentally driven diseases [33,34].

Several epigenome wide-association studies on allergies have been performed. These studies have shown that allergic disease is accompanied by changing DNA methylation patterns in Th2, Th1, Th17, Th9, and Treg subsets in affected tissues. The epigenetic mechanism behind T cell subset differentiation is strongly affected by essential micronutrients (e.g., folate, vitamins B2, B6, and B12, methionine, choline, and betaine) [35], bioactive food components (tea polyphenols, genistein from soybean, isothiocyanates from plant foods, curcumin, and curcumin-derived synthetic analogs) [36] total diet (fiber, protein, fat, and hormones) [37], ethanol, and carbohydrates [38].

Epigenetic modulation of the FOXP3 gene by farm milk was demonstrated in an animal model. In this study, exposure to raw, unprocessed, cow's milk for 8 days, increased histone acetylation of FOXP3 in splenocyte-derived CD4+ T cells compared to processed milk exposure [39]. In the same study, mice were subjected to an ovalbumin-induced food allergy model after milk exposure and, interestingly, histone acetylation of Th2 genes was lower in raw milk-pretreated mice compared to processed milk-pretreated mice. These mice also showed a reduction in food allergic symptoms. As for farm exposure, exposure to raw milk in the first year of life was also associated with changes in gene expression of the innate immune receptors [40].

Moreover, it was demonstrated that a polymorphism in the CD14 gene influenced the protective effect of raw cow milk consumption on allergic diseases [41]. DNA demethylation and increased FOXP3+ in the regulatory T cell numbers in the peripheral blood mononuclear cells of 4.5-year-old children were also shown in farm children [42].

These regulatory T cell numbers were negatively associated with doctor-diagnosed asthma. It remains to be seen if these changes also precede the onset of allergic disease and can be predictive for allergy development.

The mechanisms underlying the antiallergic effects of HM are most probably complex, as HM contains not only nutritional substances but also functional molecules including polysaccharides, cytokines, proteins, and other components forming a real biological system that can modulate and shape the innate and adaptive immune responses of the infant in very early life [43,44].

If and how those components affect the epigenetic status of the growing child and what consequences this has for allergy development need to be addressed in future studies. Considering the observations made about farm milk, as well as indications that breastfeeding may be capable of changing DNA methylation patterns in the offspring such studies are justified [45].

EUROPEAN ACADEMY OF ALLERGY AND IMMUNOLOGY: SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

During the last year, the European Academy of Allergy and Immunology (EAACI) realized an up-to-date systematic review of ways to prevent immediate-onset/IgE-mediated food allergy [46^{***}].

The GRADE approach was used. Eleven databases were searched from 1946 to October 2019 for randomized controlled trials (and large prospective cohort studies in the case of breastfeeding). The studies included heterogeneous interventions, populations, and outcomes and so were summarized narratively.

According to the analyzed evidence, breastfeeding seems to have many benefits for infants and mothers, but it may not reduce the risk of food allergy [47].

Five large prospective birth cohorts examined the link between breastfeeding and food allergy in general risk infants, [48–52] and two studies focused on infants at increased risk (cow's milk protein allergy RR ranged between 0.38 and 2.08, low certainty). Most studies did not include robust diagnostic criteria [53,54].

This review was conducted by a task force of many clinicians, public representatives, and researchers. This approach allowed studies to be considered on clinical and methodological grounds, with robust checks by multiple experts. This also had challenges because it required consensus about study interpretation and bias from people with diverse perspectives.

This review provides an up-to-date summary of robust research, but it has several limitations. The available evidence is heterogeneous and mostly at high risk of bias. Several studies did not use appropriate criteria to diagnosis food allergy. Studies were often small and so may not have been powered to detect significant differences between groups. Meta-analysis was not deemed appropriate because the interventions and population risk profiles varied greatly. Very few studies reported in detail on safety outcomes or explored costs. The official EAACI guidelines providing recommendations are awaited in the next future; the public revision of the draft has been run July 2020.

GUIDANCE FROM AMERICAN ACADEMY OF ALLERGY, ASTHMA & IMMUNOLOGY, ADVERSE REACTIONS TO FOODS COMMITTEE OF THE AMERICAN ACADEMY OF ALLERGY AND CANADIAN SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY: A CONSENSUS APPROACH

Guidance from the American Academy of Allergy, Asthma, and Immunology; American College of

Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology: a consensus approach.

The 2019 AAP Clinical Report suggests that no conclusions can be made about the role of breastfeeding in preventing or delaying any specific food allergy [9].

A recent consensus, strengthened by the inclusion of the 3 primary national allergy organizations in North America (the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAI) and the Canadian Society for Allergy and Clinical Immunology (CSACI)) tried to affront this dilemma. The consensus showed that RCTs to explore preventive effects of HM versus alternative options regarding the development of food allergy are difficult to conduct, and likely unethical, which hampers the ability to provide high-certainty to address this question. In the same consensus, it is well stated that also the role of concurrent breastfeeding whereas introducing complementary food in the development of food allergy is unclear. Authors conclude that, because the World Health Organization and AAP both recommend, when possible, to preferentially breastfeed an at risk or not-at-risk baby as first feeding option, the recommendation to preferentially breastfeed an infant would likely not be enhanced by any specific food allergy prevention outcome [55^{***}].

CONCLUSION

In conclusion, it is possible to state that there is strong evidence in favor of breastfeeding for the prevention of numerous pathological conditions in the short and long term.

Indeed, the role of HM seems essential in the constitution of a healthy immune system and a functional intestinal microbiota.

However, currently there is not sufficiently strong evidence to guarantee its effectiveness in the allergy prevention; therefore, the main international scientific societies still do not count it specifically among the recognized primary prevention strategies of allergy both in the general population and in infants considered at higher risk to develop allergic disease. However, it remains a general consensus in promoting breastfeeding for several general health reasons.

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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