Breastfeeding and Food Allergy

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Key Points

- Breast milk has important effects on the developing newborn and infant immune and gastrointestinal systems.
- The role of breast milk in the development of an infant's IgE response is uncertain but appears to be protective.
- Maternal dietary antigens can be found in breast milk, and the role of these antigens is the subject of ongoing research.

Introduction

Breast milk is the most natural source of nutrition for babies. It is recommended by the American Academy of Pediatrics (AAP), who in 2012 reaffirmed its recommendation of *exclusive breastfeeding for about 6 months, followed by continued breastfeeding as complementary foods are introduced, with continuation of breastfeeding for 1 year or longer as mutually desired by mother and infant* [1]. Breastfeeding rates are on the rise in the United States. In 2011, 79% of newborn infants started to breastfeed, 49% were breastfeeding at 6 months, and 27% at 12 months [2]. The incidence of food allergies is also on the rise: between 1997 and 2007, the incidence of food allergy increased by 18% in children under the age of 18 [3]. In 2018, approximately 8% of children had food allergies [4]. Moreover, 29% of patients with food allergies also reported other atopic conditions such as asthma and eczema compared to only 12% of children without food allergies [3]. The driving force – or forces – behind the increase in allergies is unknown and the subject of wide discussions and research.

The objective of this article is to review the composition of human breast milk and its role in food allergy. To do this, we will explore the nutrition and immunology of breast milk including the effects of a mother's diet and contemporary means of storage of breast milk. We will also review the current literature on breast milk and food allergy.

The Physiology of Breast Milk

Human breast milk is synthesized to match the developmentally appropriate nutritional needs of the baby. The processes and structures needed to create human milk begin when the woman herself is in her mother's womb. As reviewed by Creasy and Resnik [5], the milk streak is present at the fourth week of gestation, and the mammary gland is formed at the sixth week of gestation. Proliferation of milk ducts continues throughout embryogenesis, and breast buds are present at

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birth but, as maternal hormones diminish in the baby's circulation, the buds regress, growing proportionally to body growth until puberty.

Prepubertal changes in hormonal circulation induce the first phase of mammogenesis. Ductal growth is stimulated by estrogen production, which is generally unopposed in the first 1–2 years of menstrual cycles, creating type I lobules, which are alveolar buds clustered around a duct; upon cyclical changes in hormones, the types of lobules differentiate into type II lobules, which are more complex lobules that contain more alveoli [6]. This continues throughout puberty, completing mature breast development.

The second phase of mammogenesis occurs when a woman becomes pregnant so that breast milk may be produced by lactocytes, which utilize five transport mechanisms to create breast milk (see Table 12.1).

During the first half of pregnancy, lobules further differentiate into types III and IV, which have increased numbers of alveoli per lobule, thus establishing the milk-producing and milk-secreting framework [6]. During the second half of pregnancy, protein synthetic structures, such as the rough endoplasmic reticulum, mitochondria, and Golgi apparatus, begin to increase within the alveoli, and complex protein, milk fat, and lactose synthetic pathways are activated [6]. Regarding hormonal regulation, the initiation of human lactation involves (1) secretory differentiation in which mammary epithelial cells differentiate into lactocytes in the presence of progesterone, estrogen, and prolactin and (2) secretory activation, in which lactocytes secrete copious amounts of milk in the presence of prolactin, insulin, and cortisol when progesterone levels drop [8]. This ability to synthesize and secrete milk is termed lactogenesis. Lactogenesis I occurs about 12 weeks before parturition as acini produce colostrum while progesterone inhibits the production of milk. Lactogenesis II occurs around 2–3 days post delivery when the sudden drop in progesterone causes changes in the mammary epithelium, resulting in the beginning of mature-milk production. Lactogenesis III is the establishment of mature milk production occurring about 10 days after delivery and was formerly called galactopoiesis [9].

Table 12.1 Transport of milk components by the mammary gland [7]

Method of transport	Comments and components
Membrane route	Substances may traverse the apical cell membrane (and for those directly derived from blood, the basolateral membrane). Examples include Water Urea Glucose Sodium, potassium, and chloride ions
Golgi route	Secretory products are transported to, or sequestered by, the Golgi apparatus and secreted into the milk space by exocytosis. Examples include Casein Whey proteins Lactose Citrate Calcium
Milk fat route	Milk fat globules are extruded from the apex of the secretory cell surrounded by membrane (milk-fat-globule membrane). Examples are Milk fat Lipid-soluble hormones and drugs Growth factors (in milk-fat-globule membrane) Leptin
Transcytosis	Vesicular transport involves various organelles and, in some cases, also involving extrusion by Golgi route. Examples include Immunoglobulins (during colostrum formation) Transferrin Prolactin
Paracellular route	Direct passage from interstitial fluid to milk and this route reappears at the cessation of lactation

Adapted from Shennan and Peaker [7]

Nutrition of Expressed Breast Milk (EBM)

Regarded by the World Health Organization (WHO) and AAP as the optimum first food for infants, human milk is sufficient to meet the nutrition needs of the developing infant exclusively through the first 6 months of life and is the standard to which infant formulas are designed. The AAP recommends breastfeeding duration of 1 year minimum or as long as preferred by mother

and child, and WHO recommends breastfeeding continue through age two so that breast milk may continue to provide a substantial proportion of toddlers' nutrition needs [10, 11].

Though human milk is the standard for infant nutrition, its exact profile of nutritive substances is quite dynamic. On average, a deciliter of mature human milk provides 65–70 kilocalories, 0.9–1.2 grams of protein, 3.2–3.6 grams of lipid, and 6.7–7.8 grams of lactose [12]. In reality, the composition of human milk varies diurnally, within feedings, and individually from mother to mother; furthermore, compared to mature milk, the nutrient profiles of breast milk differ greatly among colostrum, transitional milk, and preterm milk (the milk of mothers who give birth prematurely) [11, 12].

Macronutrients

Protein

The total protein concentration of human milk is relatively lower compared to other mammalian milks, but the makeup is uniquely suited to provide both nutritive and non-nutritive benefits related to tolerance, development, and immune function. The relatively high proportion of whey compared to casein – the two main protein fractions – allows for greater solubility in gastric acid and faster gastric emptying compared to bovine proteins. Whey proteins of human milk include serum proteins (e.g., alpha-lactalbumin, lactoferrin), enzymes (e.g., lysozyme), and immunoglobulins (e.g., secretory IgA). Lactoferrin, lysozyme, and secretory IgA are resistant to proteolysis and impart initial immune defense in the gastrointestinal tract. Casein phosphopeptides, intermediates of casein digestion, maintain solubility of calcium, thereby aiding in absorption. Additionally, free amino acids taurine and glutamine may stimulate intestinal growth, and non-protein nitrogen from urea and nucleotides is used for the synthesis of nonessential amino acids, hormones, growth factors, and nucleic acids [11–13].

Lipid

Human milk is lipid rich. Half of the total energy in human milk is provided by its lipid fraction, and its globule structure, which contains bile salt–stimulating lipase, promotes efficient digestion. Lipid concentrations are lower at the start of feed (foremilk) and rich toward the end of a feed (hindmilk). Breast milk is high in cholesterol as well, which contributes to cell membrane construction of the rapidly growing infant [11–13].

Unlike its protein and carbohydrate constituents, the fatty acid profile of human milk is impacted directly by maternal diet, making it the most variable macronutrient. Despite this element of variability, breast milk remains higher in the polyunsaturated fatty acids arachidonic acid and docohexaenoic acid (DHA) compared to bovine milk. DHA is integral to visual and neurological function [11].

Carbohydrate

Lactose is the major carbohydrate source in breast milk, followed by oligosaccharides. Lactose facilitates calcium absorption and may contribute to the soft stools generally observed in breastfed infants. Oligosaccharides serve as prebiotics, aiding in the proliferation of beneficial *Bifidobacteria* and *Lactobaccilli* in the gut. Because they structurally resemble bacterial antigen receptors, they also impede bacteria from attaching to the gut mucosa [11–15].

Micronutrients

Vitamins

The vitamin content of breast milk is partly reflective of maternal diet and, in the case of fat-soluble vitamins, the overall fat content of the milk. An appropriately growing, healthy infant of a mother with a nutritionally adequate diet generally will meet his micronutrient requirements with the exceptions of vitamins K and D. Due to the low production of vitamin K by infant intestinal flora, infants are provided a single dose of vitamin K

at birth to prevent deficiency-associated hemorrhagic disease of the newborn. The vitamin D content of breast milk can be improved by maternal diet and sun exposure, but average levels are generally insufficient to meet the infant recommended daily allowances, necessitating routine supplementation [11–13].

Minerals

Mineral content of breast milk decreases gradually over the first 4 months of infant life, but this decline does not impact infant growth and may be kidney-protective [11]. Human milk is notable for having lower amounts of calcium and phosphorus than bovine milk, but these are more bioavailable as are magnesium, iron, and zinc. Nearly half the iron content of breast milk is absorbed compared to 10% in bovine milk and bovine milk-based infant formulas [11, 12]. Maternal diet does not greatly impact mineral content of breast milk [16].

Immunology of Breast Milk

Neonatal Immune System

To better understand incorrect immune development, such as in food allergy development, and how breast milk is immunologically beneficial, a basic comprehension of a baby's immune system is beneficial. The ultimate goal of a newborn baby's immune system is to possess both innate and adaptive systems of protection with complement bridging these two arms of immunity. The innate immune system identifies and combats immediate defense concerns while also signaling the development and recruitment of the adaptive immune system. Because both the innate and the adaptive immune systems take time to develop, babies benefit from exogenous sources of immune protection, specifically in the form of breast milk.

Although immunologically immature in neonates, the innate immune system – composed primarily of complement, NK cells, polymorphonucelar cells, monocytes, and macrophages – provides more immune-protection than does the less developed adaptive immune system, which is composed of T lymphocytes, B lymphocytes, and immunoglobulins [17]. The four major categories of immunity are impaired in babies: phagocytosis, cell-mediated immunity, humoral immunity, and complement activity (see Table 12.2) [18]. Collectively, the diffuse immaturity in these individual areas of immunity results in great susceptibility to infection, and the immunologic foundation developed during infancy in the presence of breast milk may contribute to tolerance more than currently recognized.

Table 12.2 Major categories of immunity in babies

Major mechanism of immune activity	Explanation of process in the neonate
Innate immunity (A) Phagocytosis: Ingestion and killing microbes [19]	Neutrophil chemotaxis is limited as is the presence of signaling molecules that participate in phagocytosis, such as immunoglobulins and complement [20]
(B) Cell-mediated immunity: Protection against intracellular pathogens provided by dendritic cells, NK T cells, and macrophages [21]	Neutrophils, monocytes, and antigen-presenting cells all hold both quantitative and qualitative defects [22]
(C) Complement activity (i) Activates the inflammatory response (ii) Opsonizes pathogens for phagocytosis and killing (ii) Lyses susceptible organisms [23]	Complement proteins are found in limited amounts in neonates and, thus, also convey less protection [24, 25]
Adaptive immunity (A) Humoral: Antibody-mediated protection against extracellular microbes and microbial toxins [26]	Neutrophils, monocytes, and antigen-presenting cells all hold both quantitative and qualitative defects [22]
(B) T cell-mediated (i) Tolerogeneic reactivity (ii) Reduced allo-antigen recognition (iii) Poor responses to foreign antigens	Peripheral Treg population is high initially to promote self-tolerance; however, foreign antigen activation of neonatal T cells results in a response skewed towards Th2 immunity [27]

Breast Milk Immunology

Breast milk is composed not only of macro- and micro-nutrients but also of living cells, antibodies, and other immunologically active agents, some of which fill immunological gaps of the immature immune system. Breast milk composition is dynamic, changing as the baby develops and even altering with clinical changes, such as in the face of infection [28]. While breast milk generally contains a repertoire of components, mothers produce milk with different defense functionality profiles [29].

Antimicrobial, anti-inflammatory, and immunomodulatory factors that are under-developed in the neonatal immune system are found in human breast milk, playing a substitute role for those immune agents until the baby has developed them [30]. Secretory IgA, lactoferrin, complement C3, and lysozyme are just a few of the antimicrobial factors found in EBM. Secretory IgA provides antimicrobial protection not by activating complement but by immune exclusion, which is the prevention of bacteria traversing the gut epithelium, and possibly immune inclusion, which is the maintenance of protective gut biofilms [31, 32].

Lactoferrin is an iron-binding glycoprotein secreted in breast milk. Highest total amounts are found in colostrum [33]. The amount decreases as milk matures; however, the percentage of total protein that is lactoferrin starts at 27% in colostrum, dips to 19% by day 28, then increases to 30% by day 84 [34], the timing of which correlates with the iron-deficiency anemia found in some exclusively breast-fed babies. High levels of lactoferrin, such as those found in colostrum, stimulate intestinal proliferation, whereas low levels of lactoferrin stimulate intestinal differentiation, both of which elucidate lactoferrin's critical role as a first line of defense against pathogens invading the GI tract [35, 36]. Lactoferrin also takes up iron, preventing it from being used by bacteria and fungi, which thereby diminishes pathogen proliferation [30].

Components of the complement system, such as complement C3, are present in human milk. Although small concentrations are present, such opsonins supplement the neonate's slowly developing complement system and aids in pathogen protection [20, 37].

Secretory IgA, lactoferrin, and complement C3 (as well as secretory component – IgA's chaperone from mammary gland into the gut) vary greatly amongst lactating mothers; however, the proteins decrease between weeks 2 and 5, seemingly decreasing as the baby's immune system is expanding [29]. Lysozyme is another important immunologic protein in breast milk. This enzyme disrupts glycosidic linkages of some bacteria, a process that is aided by lactoferrin's damaging of bacterial outer membranes, creating a synergistic bacterial killing process [38]. From 6 weeks to 6 months, levels of secretory IgA, lactoferrin, lysozyme, and total protein vary greatly while playing important roles in neonatal immunity [39]. Of note, lactoferrin and lysozyme play roles against inflammation as do PAF-acetylhydrolase and IL-10 [30].

Immunomodulatory factors are underdeveloped in the neonatal immune system, and the complete roster of factors present in breast milk continues to grow: humoral immunity is enhanced by IL-4 and IL-10; cellular immunity is enhanced by IL-12, TNF-alpha, and interferon-gamma; growth is enhanced by G-CSF; and chemokine activity is enhanced by RANTES [30], which plays a role in macrophage recruitment [40].

Cells found in EBM (expressed breast milk) include immune cells – leukocytes, such as granulocytes and mononuclear leukocytes (including lymphocytes, monocytes, and macrophages) – as well as mammary epithelial cells and stem cells [41]. While the roles of mammary epithelial cells and breast milk stem cells in the neonatal immune system are not fully understood, immune cells play a vital role in neonatal protection, increasing in maternal and in infant infections [42].

Bacteria are also present in human breast milk. While the sources of some of these microorganisms are thought to include maternal skin, infant mouth and skin, and the environment, maternal dendritic macrophages can transport bacteria from the maternal gut through the lymphatic system and into the mammary gland where the bacteria are

transferred into the breast milk [43]. This has been further shown when breastfeeding mothers consumed the probiotic *Lactobacillus* then the same strain of *Lactobacillus* was found in her feces and in her baby's feces [44]. This is similar to the development of secretory IgA, which is produced by the mother when her enteric mucosa recognizes antigen and stimulates B cell production of IgA; those B cells travel to the mammary glands where the IgA is glycosylated and secreted into the breast milk [45]. In addition, oligosaccharides are present in breast milk and serve an important role in the development of an infant's gut microbiota (discussed below) [46].

Effects of Storage on Breast Milk

Cultural trends affecting infant feeding and the recognition of breast milk's importance in the care of hospitalized infants have made feeding human milk apart from the breast increasingly a reality [47]. The AAP and the Academy of Breastfeeding Medicine have published guidelines for the storage of breast milk to ensure not only safe infant feeding but also that the integrity of breast milk's bactericidal and nutritional properties are preserved. Among these guidelines are parameters related to refrigeration, freezing and thawing, and storage containers.

Refrigeration

Fresh breast milk that is not used within 4–6 hours should be refrigerated for up to 5 days. During this time, nutrients may degrade at variable rates with vitamin C noted to degrade rapidly [12, 47]. The cream component of breast milk will separate during refrigeration but will blend easily with agitation upon thawing. This does not affect the fat composition.

Freezing and Thawing

Breast milk that will not be used within 72–120 hours of expression should be frozen. Freezing preserves its nutritional and immunologic properties for up to 3–4 months in a refrigerator freezer compartment or up to 6 months in a deep freezer. It is recommended that thawed milk should be used within 24 hours and not be refrozen. Heating breast milk will reduce the content and bioactivity of heat-labile vitamins and proteins [12, 47].

Containers

Glass and hard plastic containers with airtight seals are the ideal storage containers for breast milk. For short-term (<72 hours) storage, plastic bags designed for human milk storage are appropriate. Longer storage increases adherence of milk components to the plastic, thus impacting the nutritional quality of the milk [47].

Mom and Her Diet

The nutrient composition of breast milk remains relatively stable despite day-to-day fluctuations in maternal dietary intake and even during limited periods of dietary inadequacy. Chronic nutrient deprivation, however, can diminish the quality of human milk. Nutrients that are most vulnerable to maternal intake levels can vary [12].

Macronutrients

The macronutrient concentrations in breast milk are largely unaffected by maternal diet, though the types of fatty acids present mimic maternal intake. Protein levels are impacted more by infant age than maternal protein intake with colostrum and preterm milk being highest in protein compared to transitional and mature milk; however, women who consume high protein diets have been found to have higher concentrations of total nitrogen in their milk due to higher levels of urea and free amino acids. Carbohydrate concentration and type is not impacted by maternal diet [11, 12].

Micronutrients

Mature milk may be impacted by maternal diet depending on the nutrient. Vitamin concentrations decline when mothers are in deficiency states, and these concentrations respond to therapeutic supplementation. Upper thresholds for vitamin levels, particularly water-soluble vitamins, are regulated. In contrast to vitamins, minerals are not as susceptible to maternal intake. The exceptions are selenium and iodine, which correlate with maternal plasma levels [12].

Food Allergy and Breast Milk

Epidemiology and Developmental Pathophysiology of Food Allergies

Although the exact incidence of FA has yet to be established [48], a recent prospective, observational study found 9.9% of children developed food allergies by the age of 5 years old [49]. This finding in an inner-city, American cohort is similar to the >10% of 1-year-old children found to have food allergies in Melbourne, Australia [50]. What does appear certain is that the incidence of food allergy is increasing in westernized countries as well as countries in which food allergy was not previously considered to be a major issue, such as South Africa [51].

The pathophysiology of childhood food allergy is not understood and is likely a complex interaction of prenatal, neonatal, early childhood, and maternal immunity, specifically interacting with the environment. Sicherer and Sampson recently reviewed the possible mechanisms of the pathogenesis of food allergy, which include (1) gene-environment interaction, (2) the microbiome, (3) the route of sensitization (gut, skin, inhalation), (4) alteration of food preparation, such as heating/roasting, and (5) innate properties of the foods [52]. In fact, interactions of breastfeeding, genes, and the environment were highlighted in the study by Hong et al. in *JACI* in 2011 [53]. This study followed 970 children since birth and found that children who were ever breastfed were at higher risk of food sensitization. This risk was further increased in children with variations in IL-12 receptor, toll-like receptor 9, and thymic stromal lymphopoeitin genes.

Breast milk may also have a role in preventing certain infections, an additional factor that might influence development of food allergy. As proposed by Strachan in 1989, the hygiene hypothesis proposed that allergic disease is the result of increased cleanliness [54]. This has been further studied and currently includes that early-life exposure of microbial components induce Th1-type responses as opposed to Th2-type responses [55]. Such exposure involves immune mediators like toll-like receptors (TLRs). CD14 is a soluble component of TLR-4, which binds lipopolysaccharides of Gram-negative bacteria, thereby causing an immune response. While newborns initially have low levels of CD14, breast milk contains CD14 and is likely one of many breast milk constituents that influence allergy [56].

The gut microbiome, specifically the maternal gut microbiome, is an area of active research in food allergy and may have modifiable effects on breast milk that could be enhanced by probiotics and prebiotics. *Lactobacillus reuteri* was supplemented in breastfeeding mothers then found in the feces of 82% of those babies but only in 20% of the non-supplemented mothers' children's feces. *L. reuteri* was detected in more breast milk samples from the supplemented mothers compared to the non-supplemented mothers [44]. Human breast milk contains prebiotics in the form of oligosaccharides. These oligosaccharides are non-digestible to babies but are secreted in milk and feed the microbiota of the baby's gut, characteristics shared with prebiotics [46]. The oligosaccharides also serve to prevent pathogen invasion of the gut mucosa [44]. Taken together, these results demonstrate that bacteria in breast milk are modifiable and such changes do impact the constituents and relative populations of the infant microbiome. As additional data emerge, it will be important to understand whether such changes are as critical for regulating allergic responses to dietary antigens as some early data appear to suggest.

Breastfeeding's History with Food Allergy

Recently, breastfeeding has been added to the list of theories behind the increase is food allergies, a change from its previously protective reputation. The protective role was observed in a 1995 study published in *Lancet*, in which breastfeeding was associated with a decrease in food allergy [57]. In 2004, Muraro et al. completed a thorough review of literature and concluded the following: *In prospective observational studies, breastfeeding for at least 3–6 months and late introduction of solid foods (after 4–6 months) is associated with a decreased risk of cow's milk protein allergy/FA and atopic eczema up to 3 year and recurrent wheeze/asthma up to 6–17 year. As such, exclusively breastfeeding for the first 6 months of life as recommended by World Health Organization should be attempted in all infants and also recommended as an allergy-preventive measure* [58]. It was noted, however, that components of breast milk can both enhance and suppress the immune response and participate in antigen exclusion depending on the balance of such components [59]. Recent mouse models have supported the theory that breast milk reduces allergies. A 2011 study showed that the transfer of antigen and antibody in breast milk led to tolerance [60], the results of which were similar to a 2010 study in which oral tolerance was shown in pups of aerosol-sensitized mothers exposed to allergen [61]. Finally, a 2012 review in *Journal of Pediatric Gastroenterology and Nutrition* further supported breast milk as being protective against allergy [56].

In contrast to studies that suggest breast milk protects against atopy, some work does suggest that breast milk is not protective against food allergy and may actually play a role in both food sensitization and in allergy. A 2005 rostrum by Drs. Friedman and Zeiger indicated that it could not be definitively determined that breast milk prevented sensitization to allergens [62]. In keeping with the lack of a protective role, a follow-up study in *Lancet* showed that breastfeeding did not protect against atopy and may have increased the risk of atopy [63]. More recently, a study of inner-city children of atopic parents showed breastfeeding of any duration was significantly associated with food allergies [49].

Review of the Literature of Food Allergies and EBM

Understanding the relationship of food allergy and breast milk may create a new paradigm in allergy prevention research [64]. This area of allergy is already the focus of multiple studies including the content of allergen in breast milk and the immune factors in breast milk. Bernard et al. identified peanut antigen that had been transferred through breast milk of two non-atopic mothers and showed that IgE-mediated mast cell degranulation occurred in the presence of such antigen in mice, further arguing that such antigen can cause sensitization [65]. Macchiaverni et al. identified Der p 1 (a major allergen from house dust mite) in human breast milk and argued that it strongly promotes sensitization [66]. Palmer et al. found that the presence of egg ovalbumin in human milk was related to maternal egg intake but that excretion into breast milk varied amongst women and that some women did not secrete ovalbumin into their milk [67].

A mother's atopic status may impact her breast milk immunology. IL-4 has been shown to be higher in the breast milk of allergic mothers with similar trends in IL-5 and IL-13 compared to non-allergic mothers [68]. Atopic mothers have been found to have decreased levels of IgA in breast milk, but this was not associated with whether or not her child developed allergies [69]. Low levels of breast milk TGF-beta-2 have been associated with maternal allergy. In fact, TGF-beta in breast milk may play an important role in immune tolerance [70]. TGF-beta and IL-10 are tolerogenic cytokines found in breast milk [56]. In 2008, TGF-beta was shown to play a significant role in breast milk–induced tolerance, mediating CD4+ lymphocytes [71]. TGF-beta-1, along with IL-1beta, IL-6, and IL-10, was recently associated with tolerance to cow's milk [72]. Conversely, TGF-beta-1 has been shown not to be associated with atopy [73]. As previously

mentioned, low levels have been found in the milk of atopic mothers [74]; however, immune factors in breast milk that are related to milk allergy have been found to be independent of maternal atopy [72].

IgA is the major antibody found in breast milk and is inversely related to atopic dermatitis [73]. Atopic mothers have lower levels of IgA than non-atopic mothers, but these levels were not associated with food allergy in children [69]. Higher levels of IgA in breast milk were associated with positive skin prick testing at 6 months but not at 2 or 5 years of age [39]. Interestingly, and suggestive that some protein in breast milk may be associated with atopy in the first 2 years of life, the total protein in breast milk was higher in mothers with atopic babies compared to mothers with non-atopic babies [39].

While proteins are generally considered the immunologic compounds of breast milk, fatty acids may also play a role in food allergy. The rise in food allergy in westernized societies has been accompanied by increased consumption of saturated and omega-6 fats along with a concomitant decrease in omega-3 consumption, each of which may play a role in the development of allergy [75]. Thijs et al. recently explored this hypothesis in the context of fat content of human breast milk and found the sensitization at 1 year was inversely associated with breast milk concentrations of omega-3 fatty acids and rumenic fatty acids, which also had an impact on total IgE [76]. No differences in breast milk fatty acids or ratios were found between atopic and non-atopic mothers [76].

Current Recommendations on Breastfeeding and Food Allergy

In 2014, the AAP included in its 2014 *Pediatrics Supplement: Best Articles Relevant to Pediatric Allergy and Immunology* McGowan's systematic review of the literature regarding primary prevention of food allergy, which concluded *the only intervention for which there is evidence of preventing the development of food allergy is to avoid cow's milk during the first 4 months of life in children at high risk* [77]. Some commonly agreed upon recommendations are found in the 2010-published NIAID guidelines in food allergy by Boyce et al., which included (1) the recommendation against maternal diet restriction during pregnancy and lactation, (2) the recommendation supporting exclusive breast feeding until 4 to 6 months of age, and (3) the suggestion that high-risk infants consume hydrolyzed formula when exclusive breast feeding is unavailable (and "high-risk" was defined as babies with biological parents or siblings with existing or a history of food allergy, atopic dermatitis, allergic rhinitis, or asthma) [78]. A 2012 update of risk factors published in *JACI* further explores this topic [79]. A Cochrane review in 2014 also recommended against maternal dietary avoidance of antigens during pregnancy or lactation regarding decreasing atopy [80]. In 2014, the AAAAI published "Food allergy: A practice parameter update—2014" that included recommendations regarding the prevention of food allergy (see Table 12.3).

Indeed, recent studies have found that maternal exposure to food allergens decreases allergy in offspring in humans and in mice [82–85]. In fact, a prospective US study showed no benefit of maternal and early childhood avoidance of milk, egg, or peanut in preventing food allergies [86]. These

Table 12.3 AAAAI recommendations from food allergies practice parameter update 2014 [81]

AAAAI 2014 recommendations to prevent food allergies
1. Encourage *exclusive breastfeeding* for the first 4–6 months.
2. For infants with a *family history of atopy*, consider a partially or extensively hydrolyzed infant formula for possible prevention of atopic dermatitis and infant cow's milk allergy *if exclusive breastfeeding is not possible*.
3. Do not recommend allergen avoidance or avoidance of specific complementary foods at weaning because these approaches *have not proved effective* for primary prevention of atopic disease.
4. Do not routinely recommend supplementation of the maternal or infant diet with probiotics or prebiotics as a means to prevent food allergy because there is *insufficient evidence* to support a beneficial effect.

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studies and others provided experimental support for recent decisions to withdraw recommendations of allergen avoidance during pregnancy and breastfeeding and support potential beneficial effects of maternal allergen exposure to protect offspring from food allergy. Prior human studies examining the effect of maternal diets during pregnancy on peanut allergy have shown inconsistent results. However, a more recent study suggesting that early food introduction might decrease the risk of food allergy development underscored the potential benefit of food allergen transfer through breast milk as this may be the first food exposure for the infant [87]. Data from murine studies indicated a critical role of maternal immunoglobulin immune complexes in tolerance induction in offspring regardless of the sensitization status of mothers [27]. Interestingly, those findings could suggest a potential for immunoglobulin immune complexes as an immunotherapy to improve oral tolerance and possibly prevent food allergy in children [27].

Conclusion

Breast milk is a complex immunologic liquid. In addition to the nutritional growth it provides, it plays a dynamic role in the neonatal immune system, contributing to defense as well as apparent hyper-defense in the form of allergy. The literature continues to grow regarding breast milk and food allergy, and research to date indicates that this is just the beginning of understanding how breast milk impacts the development of food allergy.

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