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Innate and Adaptive Immune Components in Human Breast Milk and Their Role in Early-Life Immunity

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ABSTRACT

Human breast milk is a uniquely complex biological fluid renowned for delivering essential nutrients to newborns. Beyond its nutritional value, it also contains important immunological components that play a fundamental role in infant health and development. This review explores the immunological characteristics of breast milk, highlighting its diverse array of immune cells and bioactive molecules, including secretory IgA, cytokines, and chemokines. These components actively contribute to the maturation of the infant's immune system, strengthen defenses against infections, and facilitate the development of a balanced gut microbiome. This discussion also explores how the immune components in breast milk function to benefit infants, examining their protective mechanisms and developmental impacts. Additionally, it addresses how storage conditions—such as freezing, refrigeration, or pasteurization—may alter the integrity and effectiveness of these vital immune factors. Furthermore, the influence of external environmental factors, including maternal diet, stress, and exposure to pollutants, is considered for their potential effects on the immunological quality of breast milk. For this literature review, relevant studies were systematically searched across multiple academic databases, including PubMed, ScienceDirect, Google Scholar, ResearchGate, and Elsevier. The search was limited to publications from the past ten years. Emerging research underscores the adaptive nature of breast milk and its profound impact on early-life immunity, offering valuable insights for optimizing infant feeding practices and potential clinical applications.

1. Introduction

Human breast milk (HBM) represents the ideal nutritional source for infants, providing essential physiological and immune-supporting benefits. As the globally recognized gold standard for infant feeding, HBM receives strong endorsement from leading health organizations like World Health Organization (WHO) advises mothers to begin breastfeeding during the first hour after delivery, practice exclusive breastfeeding for the initial six months of life, and sustain breastfeeding for two years or more while gradually introducing nutritious complementary food.[1] Scientific evidence confirms that exclusive breastfeeding offers significant protection against numerous neonatal health conditions, ranging from cardiorespiratory and metabolic disorders to autoimmune diseases, neurodevelopmental issues, and infectious complications. The maternal benefits are equally compelling, including faster postpartum recovery through enhanced uterine involution, lower risks of postpartum depression, and reduced long-term susceptibility to cardiovascular disease, type 2 diabetes, and breast cancer.[2–4]

HBM's unique value extends beyond basic nutrition through its rich array of bioactive immune components. These include diverse cellular elements like macrophages, neutrophils, and lymphocytes (both T and B cells), along with soluble immune mediators such as cytokines, chemokines, immunoglobulins (particularly secretory IgA), and antimicrobial proteins (including lactoferrin and lysozyme).[1,5] The presence of prebiotic oligosaccharides further enhances HBM's benefits by nurturing beneficial gut microbiota.[6] Population studies consistently demonstrate superior health outcomes in breastfed infants compared to formula-fed counterparts, emphasizing HBM's irreplaceable role in immune development and disease prevention.[2] This review explores the comprehensive

immunological characteristics of HBM and their critical importance for infant health outcomes.

2. Methods

This paper presents a narrative review of peer-reviewed literature, synthesizing current research on the immunological properties of human breast milk. A systematic search was conducted across multiple academic databases, including PubMed, ScienceDirect, Google Scholar, ResearchGate, Elsevier, and Web of Science, to identify relevant studies. Rigorous selection criteria were applied to ensure the inclusion of high-quality, pertinent literature. Eligible articles were required to be published in accredited scientific journals with peer-review processes and to focus specifically on innate and adaptive immune components in human breast milk, as well as their role in early-life immunity published between 2014 and 2024. Studies encompassing clinical research, systematic review, and meta-analysis were considered. The search strategy employed Boolean operators, such as the PubMed query: *("Breast Milk" OR "Human Milk" OR "Lactation") AND ("Innate Immunity" OR "Adaptive Immunity" OR "Immune Cells" OR "Immune Factors" OR "Cytokines" OR "Chemokines") AND ("Early-Life Immunity" OR "Neonatal Immunity" OR "Infant Immunity" NOT "Animal Studies" OR "Bovine Milk" OR "Formula Milk").* Exclusion criteria comprised animal studies, incomplete or paywalled publications and case reports. This methodological framework was designed to provide a comprehensive analysis of contemporary scientific understanding regarding the immunomodulatory effects of human breast milk in neonatal and infant health.

3. Types and Composition of Breast Milk

Human breast milk undergoes distinct compositional changes throughout lactation, progressing through three well-defined stages: colostrum, transitional milk, and mature milk. Colostrum, the initial milk produced during late pregnancy and continuing for the first 1-5 days postpartum, is characterized by its yellowish-creamy appearance and viscous consistency.[7–9] This immunologically rich secretion contains high concentrations of protective factors including secretory IgA (sIgA), lactoferrin, leukocytes, and growth factors like epidermal growth factor, while demonstrating relatively lower lactose content that reflects its primary immunological and trophic functions rather than nutritional role. The electrolyte profile of colostrum shows elevated sodium, chloride, and magnesium levels with comparatively reduced potassium and calcium concentrations.[10] The transition to mature milk production is marked by physiological changes in the mammary epithelium, including closure of tight junctions leading to decreased sodium-to-potassium ratios and increased lactose concentrations, typically occurring around day 4 postpartum. Transitional milk, produced from approximately after days 5 to 14 postpartum, contains higher fat content, increased lactose, greater concentrations of water-soluble vitamins, and higher caloric value compared to colostrum. The mature milk as a final stage is produced after 14 days postpartum, consists of about 90% water and 10% macronutrients including carbohydrates, proteins, and fats for growth and energy needs. Mature milk further differentiates into foremilk, released at the beginning of a feed with higher water, vitamin, and protein content, and hindmilk, released later in the feeding with substantially higher fat content crucial for infant weight gain.[7–9] While dramatic compositional changes occur during the first month, subsequent variations in mature milk composition during continued breastfeeding are relatively minor.[10]

Human milk's complex nutritional composition arises through three principal pathways. First, nutrients are obtained from the mother's current dietary consumption. Second, they're mobilized from the mother's existing nutrient reserves. Third, specialized mammary gland cells actively synthesize certain components. These interconnected biological processes work synergistically to produce milk's optimal nutrient blend. While breast milk generally maintains good nutritional quality, maternal diet significantly influences certain vitamins and fatty acid profiles.[10] Macronutrient composition shows inter-individual variation but remains relatively consistent across populations, with mature term milk typically containing 0.9-1.2 g/dL protein, 3.2-3.6 g/dL fat, and 6.7-7.8 g/dL lactose, providing 65-70 kcal/dL. Preterm milk differs by containing higher protein and fat concentrations. Multiple maternal factors influencing milk composition at 4 months postpartum, including weight-for-height ratio, protein intake, parity, menstrual cycle return, and breastfeeding frequency, with an inverse relationship observed between milk production volume and fat/protein concentrations but positive correlation with lactose content.[10] The protein fraction consists of whey and casein components, with predominant proteins including casein, lysozyme, α-lactalbumin, lactoferrin, secretory IgA, and serum albumin, showing higher concentrations in preterm milk and gradual decline during the first 4-6 weeks postpartum regardless of gestational age. The lipid component demonstrates the greatest variability among macronutrients, characterized by high palmitic and oleic acid content and showing two- to three-fold higher concentrations in hindmilk versus foremilk, with fatty acid profiles particularly responsive to maternal dietary intake of long-chain polyunsaturated fatty acids. Lactose represents the most stable macronutrient, though higher concentrations correlate with increased milk production, while human milk oligosaccharides constitute approximately 1 g/dL with concentrations influenced by lactation stage and maternal genetics.[10]

Breast milk provides essential micronutrients such as vitamins A, B1, B2, B6, B12, D, and iodine. Since maternal diets may not always be sufficient, continuing multivitamin intake while breastfeeding is advised. Vitamin D levels in breast milk are typically low, particularly when mothers have limited sun exposure, leading to recommendations for vitamin D supplements in breastfed infants.[10] Beyond its nutritional benefits, breast milk also contains immune-supporting elements, microbiota, hormones, growth factors, stem cells, nucleotides, and microRNAs (miRNA) (Figure 1).[9] The breast milk microbiota plays a critical role in promoting the maturation of the infant's immune system, as comprehensively outlined in Table 1.[11]

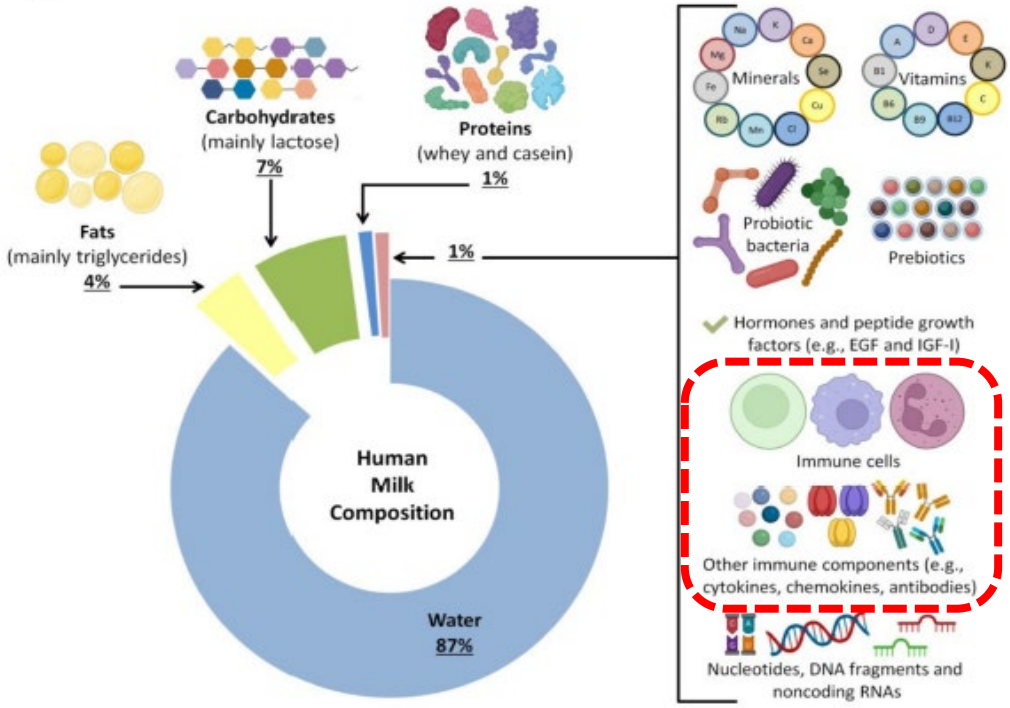

Figure 1. Breast milk composition[9]

Table 1. Probiotic bacteria in healthy woman breast milk[11]

Group	Species
Bifidobacterium	*B. longum*
	B breve
	B lactis
	B. adolescentis
Lactobacillus	*L. salivarius CECT5713*
	L. gasseri CECT5714
	L. plantarum
	L. fermentum CECT5716
	L. rhamnosus
	L. reuteri
	L. acidophilus

4. Immunological Profile of Breast Milk

At birth, a newborn's immune system is underdeveloped compared to an adult's, making them more vulnerable to infections. Breastfeeding helps bridge this gap by teaching the infant's immune system to distinguish between harmful pathogens and harmless substances, promoting both defense and tolerance. Breast milk plays a crucial role in strengthening and training the infant's immunity, offering optimal protection. It contains various immune cells, including monocytes/macrophages, neutrophils, natural killer (NK) cells, T lymphocytes, and B lymphocytes.[12] These cells actively support the baby's immune defense by producing bioactive compounds such as lactoferrin, lysozyme, oligosaccharides, and cytokines. Additionally, B cells contribute by generating immunoglobulins like secretory IgA, IgG, and IgM.[10,12]

Beyond immediate immune support, breast milk influences the long-term development of the infant's immune system and gut microbiota.[13] One proposed

mechanism, maternal micro-chimerism (MMC), suggests that maternal cells from breast milk transfer to the infant's intestinal lining and other immune tissues before gut closure occurs. This process enhances the maturation of both mucosal and systemic immunity, ensuring a more robust immune response in the newborn.[14]

Innate Immune Cells In Breast Milk

a. Macrophages

Macrophages are most abundant immune cells in human breast milk, about 50% of leukocytes and key players in the innate immune system, identifying harmful microbes or infected cells and initiating immune responses by releasing inflammatory signals and activating adaptive immunity.[12,15] In breast milk, these macrophages develop from blood monocytes that migrate through the breast epithelium. Upon encountering breast milk components, they undergo phagocytosis, transforming into specialized breast milk macrophages (BrMM) with distinct capabilities—including the potential to mature into dendritic cells that enhance infant T-cell function.[10,15] As professional antigen-presenting cells, BrMM are crucial for adaptive immune activation. They constitute up to 80% of immune cells in colostrum and transitional milk, highlighting their role in safeguarding infants. These macrophages are classified into inflammatory (CD16−) and non-inflammatory (CD16+) subtypes, while most originate from the bloodstream, gut, and nasopharyngeal lymphoid tissues, some reside locally in breast tissue.[9,16]

BrMM are particularly abundant in breast milk due to their strong phagocytic activity and their ability to produce granulocyte-macrophage colony-stimulating factor (GM-CSF) when exposed to milk components. When stimulated by interleukin-4 (IL-4), they can further differentiate into CD1+ dendritic cells, which effectively activate T cells.[17] Breast milk macrophages may help protect infants against respiratory infections by maintaining an anti-inflammatory state, reducing mucosal inflammation.[12] Thus, they contribute significantly to gut immunity and the overall development of the infant's immune system—without triggering excessive inflammation.[16,18]

b. Neutrophils

Neutrophils represent a major proportion of breast milk leukocytes, accounting for 12-27% of these immune cells on average.[13] As essential components of the immune system, neutrophils combat infections through multiple mechanisms including pathogen engulfment, neutralization, and destruction. They play crucial roles in both acute inflammatory responses and chronic inflammatory processes, while also influencing adaptive immunity.[19] Newborns exhibit notable deficiencies in neutrophil function compared to adults. Neonatal neutrophils are not only fewer in quantity but also demonstrate impaired bactericidal capacity due to their inability to form neutrophil extracellular traps (NETs). Additionally, reduced expression of adhesion molecules (CD62L/L-Selectin and MAC-1/Integrin) compromises their endothelial binding capability. These functional limitations are further characterized by diminished TLR2 and TLR4 receptor expression, impaired phagocytic activity, and reduced intracellular pathogen degradation capacity.[20] Breast milk neutrophils help compensate for these neonatal deficiencies by demonstrating the enhanced activity and mobility, superior interactive capabilities, and active participation in infant immune responses.[16]

Table 2. Immune cells in human breast milk

Component	Key Findings	Role in Infant Health	References
Macrophages	Most abundant (50% of leukocytes); produce lactoferrin, lysozyme.	Phagocytosis of pathogens; anti-inflammatory effects.	Zheng et al. (2020)[12]
T Cells	~10–20% of milk leukocytes; memory T cells (CD4+) dominate.	Transfer of maternal immunity; infant immune education.	Trend et al. (2015)[13]
B Cells	IgA-producing plasma cells detected in milk.	Source of sIgA for mucosal protection.	Demers-Mathieu et al. (2018)[28]
Neutrophils	Median about 12-27%. Elevated in colostrum; decrease in mature milk.	First-line defense against bacterial infections.	Trend et al. (2015)[13]
NK Cells	2% of mature milk leukocytes	High cytotoxicity in preterm breast milk, early immune protection crucial for newborns, antiviral (CMV) and antibacterial effects, and may protect against NEC and late-onset sepsis	Caba-Flores et al. (2024)[26] Pighi et al. (2024)[27]

Notably, neutrophil concentration in breast milk shows dynamic changes during lactation, with their proportion among leukocytes increasing significantly from colostrum to mature milk.[16] This temporal pattern suggests their important role in protecting infants. Research indicates that maternal conditions like asthma can influence breast milk neutrophil characteristics, potentially affecting infant immune development. For instance, milk from asthmatic mothers shows elevated neutrophil levels and activation states, which may modify infant immune responses.[21]

c. Natural Killer (NK) Cells

Natural killer (NK) cells serve as crucial components of the innate immune system, migrating from lymphatic and circulatory systems to the mammary glands.[16,22] These multifunctional immune cells provide dual protection by defending both the infant's digestive tract and the mammary tissue against infections. NK cell activity is regulated by various interleukins (IL-1, IL-10, IL-12, IL-15, and IL-18) and chemokines including CCL2/MCP-1, CCL3/MIP-1α, CCL4/MIP-1β, CCL5/RANTES, CCL10/IP-10, CCL19/MIP-3β, CCL21/SLC, and CX3CL1/fractalkine. Their recruitment to breast milk is facilitated by an array of chemotactic molecules such as CXCL8/IL-8, CXCL10/IP-10, CXCL11, CXCL12, CX3CL1/fractalkine, CCL3/MIP-1α, CCL4/MIP-1β, CCL5/RANTES, CCL19/MIP-3β, and CCL21/SLC.[23]

As active immune mediators, NK cells produce significant quantities of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), along with other immune modulators like GM-CSF, CCL2/MCP-1, CXCL8/IL-8, CXCL10/IP-10, XCL1/lymphotactin, IL-5, IL-10, IL-13, CCL1, and CCL22. Early activation triggers the release of CCL3/MIP-1α, CCL4/MIP-1β, and CCL5/RANTES, enabling NK cells to combat infections both directly and indirectly through cytokine-mediated activation of other immune components, thereby enhancing neonatal immunity.[16,23]

The concentration of NK cells in breast milk shows progressive increases during lactation, comprising approximately 0.5% of colostrum leukocytes, 1.3% of transitional milk cells, and 2% of mature milk cells.[24] Another study shows that cytotoxic T cell and NK cells in colostrum are more abundant than mature milk, and in mature milk there is a significant different comparison in moderate preterm mothers.[13] This proportion is notably reduced in milk from very preterm mothers and in formula-fed infants.[13,16] A study demonstrates that breast milk-associated *Lactobacillus* can stimulate Th1 cytokine production and activate NK cells along with other immune elements. NK cells in preterm breast milk are dominated by cytotoxic cells.[25,26] While NK cells have been detected in breast milk during *Cytomegalovirus* (CMV) reactivation, suggesting their role in antiviral defense, further investigation is needed to fully understand their participation in antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) mechanisms for pathogen clearance in infants.[27]

Adaptive Immune Cells In Breast Milk

a. T Lymphocytes

T lymphocyte is about 10–20% of milk leukocytes.[13] Lymphocytes, crucial components of adaptive immunity, constitute 5-10% of all leukocytes in breast milk, with T lymphocytes making up over 80% of this population compared to just 4-6% for B lymphocytes.[16] Within breast milk, CD4+ T lymphocytes exist in an activated state, displaying markers such as CD40L, sCD30, IL-2 receptor, HLA-DR+, hMLA-1, and LAP-1, along with the memory marker CD45RO. Interestingly, 26-76% of these CD4+ T cells co-express CCR5 and CXCR4, the primary HIV co-receptors, yet remain preserved in HIV-infected mothers' breast milk despite their mucosal origin marked by CD103 expression. This preservation contrasts with other mucosal sites where HIV typically depletes such cells. Even HIV-positive women on effective antiretroviral therapy maintaining undetectable viral loads often fail to achieve peripheral CD4+ T-cell recovery, suggesting that breast milk's CD45RO+ memory T-cells may possess HIV-resistant properties that protect mammary tissue from viral replication.[16,29,30]

The breast milk environment contains proportionally more CD8+ T-cells than CD4+ T-cells, which migrate from maternal mucosal immune sites. These cytotoxic T lymphocytes demonstrate heightened production of IFN-γ and granzymes during viral infections like CMV, *Human Immunodeficiency Virus* (HIV), influenza, or *Epstein Barr* virus (EBV), with their numbers correlating directly with breast milk viral loads.[16] This relationship implies that local viral replication triggers antigen-specific CD8+ T-cell recruitment to the mammary gland for viral containment, potentially limiting transmission.[31] Notably, breast milk-derived cytotoxic T cells exhibit superior cytolytic and inflammatory mediator production compared to infant-produced T cells.[16] Such mechanisms contribute to breast milk's role in establishing neonatal immunological tolerance to maternal and environmental antigens, potentially preventing immune-related disorders later in life.[32] Supporting this, breastfed infants demonstrate thymus sizes twice those of formula-fed counterparts during the first postnatal weeks, indicating breast milk's influence on early T cells development including T cells expansion during three first postnatal weeks.[33]

Additionally, regulatory T cells (Tregs) in colostrum appear at higher frequencies than in peripheral blood, particularly after vaginal deliveries, and display elevated expression of immunomodulatory molecules like CD25, CD152,

CD279, and TGF-β. These colostrum-derived Tregs exhibit enhanced tolerogenic capacity, mediating maternal immunomodulation and facilitating micro-chimerism.[34] Their presence benefits newborns by reducing intestinal inflammation and potentially lowering risks for allergies, asthma, obesity, and type 1 diabetes throughout infancy and beyond. The collective action of these lymphocyte populations underscores breast milk's multifaceted role in shaping infant immunity through both active protection and tolerance induction.[35]

b. B Lymphocytes

Breast milk's immunological significance lies particularly in its rich content of diverse immunoglobulins (Ig), which are antibodies produced by plasma cells derived from mature B lymphocytes.[13] Following activation, these B cells transform into either memory B cells or Ig-secreting cells that subsequently migrate through various lymphoid tissues - including peripheral lymph nodes, spleen, tonsils and ultimately reach mucosal effector sites such as the lactating mammary glands.[16] This targeted migration to mammary tissue is facilitated by the mucosal chemokine CCL28, which becomes upregulated during lactation and specifically interacts with CCR10 receptors expressed on IgA-secreting cells (IgA-SCs). This selective mechanism explains why IgA-SCs predominantly accumulate in mammary glands, resulting in sIgA constituting over 90% of breast milk immunoglobulins, unlike IgG or IgM.[16,28]

An additional protective mechanism, known as the entero-mammary pathway, enables maternal-infant immunological communication. This process suggests that pathogens from the infant's oral cavity can travel retrogradely through the nipple to stimulate specific antibody production in the maternal breast. When the maternal immune system detects these pathogens, it generates targeted antibodies that are then delivered back to the infant through breast milk.[16,36] Both maternal and infant infections trigger rapid leukocyte activation in breast milk, demonstrating this dynamic immunological exchange. For newborns, whose adaptive immunity is still developing the capacity to recognize and combat pathogens, maternal antibodies serve as crucial immunological support - initially transferred in utero and later through breastfeeding.[22]

Notably, breast milk IgA possesses distinct antimicrobial properties, with concentrations being particularly elevated in milk from mothers of very preterm infants compared to term deliveries. sIgA functions by binding pathogens and forming antigen complexes that are subsequently captured by intestinal dendritic cells. These specialized immune cells then process and present the antigens, contributing to the infant's developing immune competence. This sophisticated immunoglobulin transfer system underscores breast milk's vital role in providing both immediate protection and immunological education to the developing infant.[16]

c. Cytokines and Chemokines In Breast Milk

Breast milk is rich in various cytokines and chemokines that play crucial roles in infant immunity and development. These signaling molecules, primarily produced by the mammary gland, include interleukins (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13), tumor necrosis factors (TNFα, TGFβ), interferon-gamma (IFN-γ), granulocyte colony-stimulating factor (G-CSF), and several chemokines (MCP-1/CCL2, MIP-1α/CCL3, MIP-3α/CCL20, MIP-1β/CCL4, RANTES/CCL5).[37,38] Cytokines function as multifunctional peptides acting locally, while chemokines specifically direct cell migration. Remarkably, these molecules can cross the infant's intestinal barrier intact, protected by breast milk protease inhibitors like alpha 1-antichymotrypsin and alpha 1-antitrypsin, and further aided by the newborn's immature digestive system during the first three months of life.[11,16,38]

These bioactive compounds exert diverse immunological effects, with some promoting inflammation to combat infections while others suppress inflammation. Their influence extends beyond immunity, as certain cytokines can cross the blood-brain barrier and participate in neural development, memory formation, and neurogenesis. The cytokine profile in breast milk dynamically responds to the infant's health status - for instance, infections can shift milk macrophages toward an anti-inflammatory phenotype. Specific cytokines like TGF-β, IL-6, and IL-10 are particularly important for gut immune development, promoting IgA production and naive immune system maturation. Activated TGF-β helps regulate inflammation, supports tissue repair, and may prevent allergic diseases, while G-CSF contributes to intestinal development and sepsis management.[16,38]

The composition of these immunomodulatory factors varies significantly based on maternal factors including geographic origin, migration history, and parity. Research demonstrates that a mother's country of birth can influence her breast milk cytokine profile, highlighting how these bioactive components reflect both the maternal environment and the infant's developmental needs. This sophisticated system ensures optimal immune programming and neurodevelopment while adapting to both maternal and infant conditions.[16]

5. Impact of Storage on Immunological Components of Human Breast Milk

The use of expressed breast milk (EBM) has grown significantly as an alternative to direct breastfeeding in modern infant feeding practices. Typically, mothers store this expressed milk in freezers before thawing it for later use. Current CDC recommendations establish clear storage guidelines: human milk maintains safety when kept at room temperature (25°C/77°F) for four

hours, refrigerated (4°C/39°F) for four days, or frozen (-18°C/0°F or colder) for six to twelve months.[39,40] For thawing, frozen milk can either sit at room temperature for one to two hours or refrigerate for twenty-four hours. Scientific evidence confirms that crucial immune factors in colostrum - particularly cytokines, immunoglobulin A (IgA), and growth factors - maintain their stability during six months of frozen storage at -20°C/-4°F. Nevertheless, research by Putri and colleagues reveals that temperature variations during storage substantially impact milk's leukocyte concentrations. Although extended freezing (approximately nine months) can modify some characteristics such as pH balance and free fatty acid levels, the majority of nutritional components and immune-protective proteins stay intact when following proper storage protocols. These include positioning milk containers at the freezer's rear (avoiding self-defrosting walls) and maintaining airtight seals to block potential contamination.[41,42]

The development of flash heating methods aimed to provide accessible pasteurization for resource-limited settings, particularly to reduce HIV transmission. Various pasteurization techniques have been evaluated for their ability to balance pathogen elimination with preservation of milk's bioactive components. However, all heat treatments inevitably degrade some nutritional and immunological properties of breast milk, with proteins being particularly vulnerable. Studies show significant reductions in sIgA, cytokines, and TGF-β following pasteurization, with the extent of damage varying by method - boiling being the most destructive to milk's bioactive components. This creates an important trade-off between safety and nutritional or immunological quality that must be carefully considered when processing breast milk.[41]

6. Conclusion

Human breast milk (HBM) serves as the primary source of nutrition that fulfills both the dietary and physiological requirements of newborns, widely regarded as the optimal nutritional standard for infants. Beyond its essential nutrients, HBM contains a complex biological composition including microbiota, hormones, growth factors, stem cells, nucleotides, microRNAs, and numerous immunologically active compounds. These components collectively provide protection against pathogens while supporting the development of the infant's immune system, building upon maternal immunity transferred both prenatally through the placenta and postnatally through breastfeeding. The immunological properties of HBM, comprising innate and adaptive immune cells along with cytokines and chemokines, are remarkably preserved during digestion. This preservation is facilitated by natural protease inhibitors in milk such as alpha 1-antichymotrypsin and alpha 1-antitrypsin, allowing these bioactive factors to maintain their functional integrity when reaching the infant's gastrointestinal tract.

Human breast milk (HBM) exhibits a remarkably adaptable immunological profile that dynamically adjusts to infant-specific conditions such as prematurity or illness. This adaptive capability enables HBM to provide essential immune protection while simultaneously supporting immune system maturation and the development of immunological tolerance. Beyond its immunomodulatory functions, these bioactive components play a significant role in promoting the growth and development of various organ systems. Current practices in expressed milk storage and handling, however, may potentially compromise these critical immunological factors, emphasizing the need for optimized protocols to preserve HBM's bioactive integrity and maximize its health benefits for infants. The synergistic relationship between nutritional and immunological components in HBM highlights its irreplaceable role in infant development and underscores the importance of maintaining its biological potency through proper handling procedures.

This review identifies several important knowledge gaps: (1) insufficient longitudinal studies examining potential links between HBM's immunological composition and long-term autoimmune disorders; (2) limited understanding of the precise mechanisms by which milk-derived immune factors shape infant immune tolerance; and (3) inadequate data regarding the duration of passive immunity provided by HBM components, particularly in vulnerable preterm infants. Addressing these research gaps could significantly enhance our understanding of HBM's long-term immunological impacts and improve clinical practices for infant nutrition.

7. Author Contribution

F.C.I. and H.S. carried out the topics. H.S. wrote the manuscript with support from F.C.I.

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