The Importance of Human Milk for Immunity in Preterm Infants

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KEYWORDS

• Leukocytes • Inflammation • Maturation • Peptides • Gangliosides
• Immunoglobulins • Long-chain polyunsaturated fatty acids

KEY POINTS

- Preterm infants have a lower number of immune cells, lower functional capacity, and dysregulated inflammatory response compared with term infants.
- Human milk provides a variety of immune protective and immune maturation factors that are predicted to be important for immune development in the preterm infant.
- The most studied immune components in human milk include antimicrobial proteins, maternal leukocytes, immunoglobulins, cytokines and chemokines, oligosaccharides, gangliosides, nucleotides, and long-chain polyunsaturated fatty acids.
- Provision of these components in human milk, donor milk, or formula may provide immunologic benefits to the preterm infant.

INTRODUCTION

The immune system of preterm infants is immature, placing them at increased risk for serious immune-related complications. Human milk contains immunologic components that have the potential to provide immune benefits to the preterm infants.

IMMUNE SYSTEM DEVELOPMENT AND THE PRETERM INFANT

The infant, particularly the preterm infant, is born with an immune system that is distinct from an adult's. Maturation occurs in the early postnatal period and is influenced by the infant's diet (breast milk and foods) and environment (pathogens,

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allergens, microflora) (reviewed in Ref.[1]). The acquired/adaptive immune system, consisting of T and B lymphocytes, recognizes foreign pathogens and antigens after presentation by antigen-presenting cells (APCs). However, because of low antigen exposure in utero, the infant acquired immune system is naïve at birth, lacking the immunologic memory and functionality of the adult (reviewed in Ref.[2]). Because of this, the innate immune system (which includes mast cells, neutrophils, natural killer [NK] cells, monocytes/macrophages, dendritic cells [DCs], basophils, and eosinophils) serves as the primary immune defense for the infant. Although the infant relies on their innate immune system, it is reported to produce fewer cytokines than the adult, in response to various challenges.[3]

OVERVIEW OF THE IMMUNE IMMATURITY OF THE PRETERM INFANT

Preterm infants have increased risk of infections compared with term infants, partly attributed to immune immaturity. Further, preterm infants are reported to have poorer immunosurveillance and a hyperregulated or dysregulated inflammatory response compared with term infants.

The major differences are as follows:

1. Lower concentration of circulating T cells, a higher proportion of naïve T cells, and a smaller bone marrow neutrophil storage pool.
2. Lower functional capacity of most immune cells (macrophages, neutrophils, DCs, NK cells, T and B cells).
3. Lower production of immunoactive proteins (complement and cytokines, immunoglobulin) when challenged.

Details of the differences and perturbations that characterize the preterm immune system have been comprehensively reviewed by others[4–10] and are summarized in **Table 1**.

CLINICAL BENEFITS OF HUMAN MILK TO THE IMMUNE HEALTH OF PRETERM INFANTS

Provision of human milk, has been demonstrated to reduce the risk of many immune-related conditions in preterm infants.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is the most frequent and serious cause of gastrointestinal-related morbidity and mortality in preterm infants (reviewed in Ref.[11]). The inability to appropriately defend against microbes, and regulate inflammation and wound healing, contribute to the high systemic concentrations of inflammatory mediators (interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor [TNF]-α) characteristic of NEC (reviewed in Ref.[11]). Studies have demonstrated that preterm infants, including very preterm infants (<32 weeks), fed mother's milk[12,13] or donor milk[14] have lower incidence of NEC than those not exposed to human milk (Cochrane review by Quigley and colleagues[14]). This suggests that components in milk modulate this condition, possibly through their immune properties.

Allergies and Other Atopic Diseases

Allergies and other atopic diseases (asthma, allergic rhinitis, and atopic dermatitis) are more commonly observed in a preterm infant and believed to result from a failure to develop tolerance to an antigen.[15,16] Tolerance is a state of local and systemic immune unresponsiveness to antigens that occurs early in life.[17] At birth, the immune system is characterized by a predominant type 2 T-helper (Th2) cytokine response