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Approaches to Enhance Immunity in Newborn Infants: Review Article

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ABSTRACT

Background: The neonatal immune system is not completely developed until six months old. Newborns have elevated concentrations of maternal antibodies in the circulation. Newborns who are breastfed receive antibodies from breast milk. Probiotic species are "live organisms, which when supplied in sufficient amounts produce health benefits in the host", so they might protect high risk infants via increasing the barrier to translocation of pathogens and bacterial products across mucosa.

Objective: The aim of the current work was to discuss factors, which influence the immunity in newborn infant exposed to infection and the current search for factors enhancing immunity in these babies.

Methods: The following keywords were entered into on PubMed, Google Scholar, and Egyptian Knowledge Bank: Breast feeding, Complement system, Colostrum and Probiotics. Just the most recent or comprehensive study between March 2005 and July 2022, was included after the authors thoroughly examined references from the pertinent literature, including all the recognised studies and reviews. Papers written in a language other than English were disregarded since no sources for interpretation were discovered. Dissertations, conversations, conference abstract papers, and anything other than the primary scientific investigations had been disqualified.

Conclusion: Early breastfeeding initiation within 30 minutes after birth promotes health, prevents diseases and decreases healthcare and costs. Babies must have exclusive breastfeeding in the initial six months after birth, which significantly decreased infant mortalities in developing countries. Probiotics decrease the incidence of necrotizing enterocolitis (NEC) in preterm and very low birth weight infant (VLBW) babies. Vaginal delivery strengthens both maternal and neonatal defense against infections.

Keywords: Breast feeding, Complement system, Colostrum, Probiotics.

INTRODUCTION

The neonatal immunity is not completely developed until six months-old. Pregnant females pass immunoglobulins, through the placenta, to their fetuses. Such immunoglobulin antibodies have a crucial role in neonatal immunity through identification and binding to bacteria, viruses, or fungi. These antibodies induce immune cells to destroy harmful substances [1]. After labor, newborns have elevated circulatory concentrations of mother's antibodies. Newborns who are breastfed receive antibodies in the milk. Breast milk contains all 5 antibody types, which are immunoglobulins A (IgA), D (IgD), E (IgE), G (IgG) and M (IgM). This helps to prevent the baby from developing diseases [2].

Some neonates are at high risk when viewed from the immune system status such as preterm and low birth weight. These babies need extra concern for improving their immune status. And whether measures to enhance and protect them from infection are of paramount importance [3].

Breast feeding, plays an important role in enhancing immunity in newborn infant. It has the benefit of less necrotizing enterocolitis in preterm infant, greater immune health, fewer incidence of infections, less tendency to develop allergic diseases, higher intelligence, protection from sexually transmitted diseases and other long-term health benefits [4]. Colostrum is the first breast milk and it has additional stimulatory properties [5].

Neonatal Immune System: The key function of immune system is to protect against pathogens [5].

I. Innate Immune System:

The elements of this system include anatomic barriers, secretory molecules as well as cellular components.

❖ **Anatomic barriers to infection:**

The skin of preterms, particularly extremely preterms, is not mature and inefficient as epidermal barrier. Although maturation is accelerated after labor up to the 2nd post-natal week, the skin of VLBW neonates is more susceptible to rupture, facilitating microorganism penetration. The key component of such compartment is the secretory immunoglobulin A (SIgA). Many studies revealed lower SIgA concentrations in preterms at the age of 3 - 8 post-natal months [6].

❖ **Chemical factors:**

The complement system is the main humoral non-specific defense mechanism. On activation, many substances are produced (C3a, C3b, C5a and others), which secrete proinflammatory mediators, induce chemotaxis and phagocytosis. When complement activation is completed, it induces pathogen lysis via the components of membrane attack complex (C5b-C9). Complement elements are present in the embryo early during pregnancy, however their concentrations remain low up to the third trimester. These elements do pass through the placenta, however the embryo and newborn can form them and such capacity is increased with gestational age [7].

❖ **Cellular barriers to infection:**

Neutrophils, monocytes as well as macrophages can phagocytose and kill pathogens

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intracellularly through the action of many substances, such as superoxide anions, hydroxyl radical, NO, cationic protein, hypochlorous acid as well as lysozymes. Macrophages and dendritic cells (DCs) are the major antigen-presenting cells which trigger T cells proliferation via secreting cytokines [8].

II. Adaptive (specific) immunity:

❖ **T-lymphocytes:**

Neonatal T lymphocytes immunoproliferation in both preterm and term infants, is significantly lower as compared to children and adult [9].

❖ **B-cells**

The key function of B lymphocytes is to produce immunoglobulins, which constitute the humoral immunity. From precursor cells, plasma cells are the most differentiated cells that produce antibodies. The immaturity of T and B cells and of antigen presenting cells are responsible for significant deficiency of antibodies production in the neonate [9].

III. Passively acquired immunity:

❖ **Immunoglobulin G:**

It protects against bacteria and viruses, it crosses the placenta and enter fetal bloodstream by 30 weeks' pregnancy and continues till the 40th week. Preterms do not have such protective barrier and are at increased risk for infection [9].

❖ **Immunoglobulin A:**

It is the commonest Ig in the gastrointestinal tract, respiratory system, colostrum, and breast milk. It does not cross placenta, and its intrauterine production is insignificant [10].

❖ **Immunoglobulin M:**

It does not cross the placenta and its deficiency enhances the newborn's susceptibility to gram-negative infection. Its levels can be detected by 30 week's pregnancy with greater levels are detected when intrauterine infection does exist [10].

Breastfeeding:

It is the feeding of infants with milk directly from the breast through lactation rather than bottles or other containers. It promotes health, prevents diseases, and decreases health-care and feeding costs. Experts agree that it is of benefit, however might disagree regarding the length, which has the most benefit, and regarding the risks of artificial formula [11].

Exclusive Breastfeeding:

Exclusive breastfeeding is to consume human milk with no supplementation of any type of food apart from vitamins, minerals, and drugs. International guidelines recommend exclusive breastfeeding over the initial 6 months of life, which significantly decreased infant mortalities in developing countries [12].

Colostrum:

This is the pre-milk fluid produced in the mammary gland just prior to labor. Though it is technically not milk at all, colostrum is usually called "first milk" because it is obtained in the first milking following labor. Colostrum is yellow to orange in color and typically quite thick and sticky**.** Colostrum has a laxative effect, facilitating passage of first faeces (meconium). This clears excessive bilirubin at birth and prevents jaundice. It is highly rich in proteins, vitamin A, and sodium chloride, however contains lesser quantities of carbohydrates, fats, and potassium compared with normal milk**.** Colostrum contains main components of the adaptive immunity including IgA, IgG, and IgM and key components of innate immunity including lactoferrin, lysozymes, lactoperoxidases, complement, proline-rich polypeptides and cytokines like interleukins, tumor necrosis factor (TNF), chemokines and others [13]**.**

The ten Steps for effective breastfeeding [14]:

1. Have a written breastfeeding policy for all health-care personnel.
2. Training of health-care personnel on skills required for implementation to policy.
3. Inform all pregnant females concerning the benefits and how to manage breastfeeding.
4. Help mother start breastfeeding in 30 min after labor.
5. Teach mother how to breastfeed and maintain lactation even if she is separated from the infant.
6. Give neonate no foods or drinks other than milk except if medically indicated.
7. Practice rooming in, permit mother and newborn to remain together 24 h daily.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers to breastfed newborn.
10. Foster the establishment of breastfeeding support group and refer mother to them.

Protecting components in breastmilk:

I. Antibodies (immunoglobulins):

Antibodies are of 5 major forms, which are IgG, IgA, IgM, IgD and IgE. IgA is the major immunoglobulin known to be present abundantly in breastmilk, thus allowing the mother to pass some form of passive protection to her infant. In the milk of the mother with healthy baby, IgA levels was highest in the colostrum and decreased as the milk transits to mature milk [15].

The secretory IgA protects intestinal mucosa against pathogens during infections. It prevents bacterial adherence to mucous, interferes with their motility, and neutralizes toxic products. Other mechanisms include eradication of antigens and viruses by transcytosis**.** SIgA actions against infections, predominantly diarrhea and colitis are important for the immunologic protection of infants, particularly preterm infants [16]**.**

II. Immunological factors:

a) Lactoferrin:

Lactoferrin enhances both innate and adaptive immunity, in innate immunity it increases neutrophil and macrophage activity, direct antimicrobial and antiviral by depriving microorganisms from iron and prevent oxidative stress. In adaptive immunity Increases

dendritic cell activity resulting in T-cells proliferation, enhances and modulates T-cells activation and activity and Moderates cytokines secretion helping prevent a "cytokine storm", which is due to immune overstimulation [17].

b) Lactoperoxidase:

It does not have antibacterial activity. But, along with H_2O_2 and thiocyanate, lactoperoxidase forms a powerful antibacterial system, known as lactoperoxidase system that inhibits bacteria, fungi, viruses and mycoplasma together with some types of mammalian tumour cells [18].

c) Oligosaccharides:

Human milk oligosaccharides are anti-adhesive antimicrobial agents, which act as soluble decoy receptors, interfere with pathogen adherence to mucosa surface and reduce the risk of viral, bacterial as well as protozoal infections. Furthermore, oligosaccharides moderate epithelial and immune cells responses, reduce mucosal leukocytes infiltration, reduce necrotizing enterocolitis risk, and provide newborns with sialic acid necessary for cerebral development and cognitive function [19].

d) Bifidus Factor:

It's an oligosaccharide that stimulates Lactobacillus bifidus growth. The increased lactose level, reduced protein level, reduced bulk and reduced buffering capacity of human milk also enhances L. bifidus growth, producing an acidic environment that decreases viability of several pathogens [20].

e) Growth factors:

Human milk comprises numerous growth factors, which might participate in several biologic functions for newborns. It is supposed that such factors have growth-promoting and protective effects. These factors include [21]:

- ✓ Growth hormone and growth hormone releasing factor.
- ✓ Epidermal growth factor and insulin-like growth factor-I.
- ✓ Transforming growth factors α and ß.
- ✓ Epidermal growth factor.
- ✓ Hepatocyte growth factor.
- ✓ Platelet-derived growth factor.
- ✓ Vascular endothelial growth factor.

f) Milk Lipids:

They protect against infections through various mechanisms. Firstly, membrane glycoprotein acts as bacterial and viral ligands that interfere with bacterial adherence to gut mucosa. Second, the digestive products of triglycerides, free fatty acids, as well as monoglycerides have lytic actions against viral, protozoal, and bacterial species. Lastly, milk contain omega-3 in significant quantities, which act as precursors of biologic mediators (such as eicosanoids: prostaglandins, thromboxanes, and leukotrienes) and structural components of membrane systems in all tissues [22].

III. Cellular Components:

Breast milk comprises macrophages, T and B cells, neutrophils, as well as epithelial cells. The average total cell count in colostrum is significantly greater as compared to in full-term colostrum. Macrophages provide the first line defense against bacteria and may be responsible for long-term immune alterations due to their endocrine functions [23].

Health effects of breast feeding:

1. Fewer Infections:

Breast feeding appeared to lower incidence of upper respiratory tract infections in preterm infants up to seven months after release from hospital and reduces the risk of acquiring urinary tract infection in infants up to 7 months of age with protection is strongest immediately at birth [24].

2. Lessening tendency to develop allergic diseases (atopy):

A study found that children who are at risk for developing allergic diseases (defined as at least one parent or sibling having atopy), atopic syndrome can be prevented or delayed through exclusive breastfeeding for four months, which may not be present after four months of age [25].

3. Lessening risk of diabetes:

Infants exclusively breastfed have less chance of developing diabetes mellitus type I than peers with a shorter duration of breastfeeding and an earlier exposure to cow milk & solid foods [26].

4. Enhancement of vaccine response:

The antibody levels of immunized infants were significantly higher in the breastfed than the formula fed group. These findings are strong evidence that breastfeeding enhances the active humeral immune response in the first year of life. Breastfed infants thus showed better serum and secretory responses to per oral and parenteral vaccines than the formula fed, whether with a conventional or low-protein content [27].

5. Protection from cardiovascular diseases:

Breast-feeding may decrease the risk of cardiovascular disease in later life, as indicated by lower cholesterol and C-reactive protein levels in adult women who had been breastfed as infants [28].

6. Protection from celiac disease:

A study about the association between breastfeeding and celiac disease (CD) concluded that breast feeding while introducing gluten to the diet reduced the risk of CD [28].

Mode of Delivery and Immunity:

Labor possibly induces the production of important modulators of immune responses, both in mothers and their newborn infants, strengthening maternal and neonatal defense against prenatal infections [29].

The new finding is the elevation, of all three cytokines, IL-1β, IL-6 and TNF-α, gradual or rapid, and their soluble receptors in all neonatal samples. This can be explained by elevation of maternal IL-1β and IL-6

values, which seems to reflect a systemic reaction from the pregnant female to the fetus and may be related to cytokines increase. Another likely clarification may be the physical effort of labor, as prolonged exercise is accompanied by enhanced IL-6 synthesis. IFN-γ values were greater among females with vaginal delivery compared to Caesarean section. A likely clarification is the increased lipopolysaccharides absorption in mother's gut during labor, resulting in an enhanced production of many cytokines [30].

The levels of sTNFRI and sTNFRII in maternal circulation are elevated dramatically during delivery indicating an enhanced synthesis of TNF-α and its effect in labor. Since TNF-α soluble receptors has longer half-life compared to TNF-α, it was proposed that both receptors indicate cytokines induction, and biomarkers of the induction of immunological response, for a long period following TNF-α normalization [31].

Probiotics and Immunity:

Probiotics are "live organisms that when provided in sufficient quantities produce health benefits in the host" (FAO/WHO 2002). For appropriate health benefits, 5 billion colony forming units ($5x10^9$ CFU/d) are recommended for a minimum of five days. The ideal probiotics must remain viable in the intestine and must attach to its epithelium to produce health benefits. The significance of viability in studies, with viable bacteria having higher immunologic effects compared to non-viable and killed bacteria being accompanied by side effects. In addition, probiotics should resist gastric acid digestion and bile salts to reach the intestinal level intact. Species from other bacteria like Streptococcus, Bacillus, and Enterococcus are utilized as probiotic species, however there are concerns about their safety as they contain several pathogenic organisms, mostly Enterococcus. Non-bacterial organisms like yeasts from the genus Saccharomyces can be also utilized as probiotic agent [32, 33].

Mechanism of Action of Probiotics:

Probiotics protect high risk newborns through increasing the barrier to translocation of bacteria and their products across mucosa, modifying response to bacterial products and facilitating enteral nutrition that inhibits the growth of bacteria like Kleibsiella pneumonia, E.coli and Candida albicans. Intestinal microbiota has a significant role in activating normal immune development, mainly the gut-associated lymphoid tissue. The existence of intestinal microbiota is essential for several functions, such as antibodies synthesis, development of oral tolerance against food antigens, and the development of germinal centers in lymphoid follicles [34].

Probiotics influence intestinal microbiota in diseases. For instance, in disease state accompanied by enhanced mucosal permeability, it was found that Lactobacillus administration decreased mucosal permeability. Probiotic species form bacteriocins, H_2O_2 and biosurfactants, to help their survival in the GIT and can suppress the attachment of more pathogenic microorganisms to mucosa (Table 1). Several probiotics increase mucin formation by intestinal epithelium in vitro and some also stimulate the synthesis of defensin-ß2, which is antimicrobial peptide. Probiotics should colonize the GIT to produce health effects and it is known that some probiotics colonize the GIT for >14 days following administration. These seem to be significant mechanisms through which probiotics prevent the attachment of bacteria to mucosa. Furthermore, such antagonism seems to have more effectiveness when probiotics themselves attach to the mucosa [35].

Table (1): Immune functions of probiotics [35]

Function	Description	Finding
Phagocytosis	The phagocytic cells (neutrophils and monocytes) engulf foreign bodies and debris; this results in presentation of antigens on phagocyte surface and facilitation a cell-mediated immune response.	L.rhamnosus and L. coryniformis enhanced, other probiotics showed mixed results.
Natural Killer (NK) Cells Activity	NK cells kill infected cells or tumour cells via apoptosis or necrosis.	L.rhamnosus and L. lactis enhanced NK activity.
Cytokine Production by T cells	Cytokines, like interferons, TNF and interleukins, modulate the function of different cell types.	Probiotics seem to exert insignificant effects on most of cytokines
Antibody production after vaccination	Antibodies identify and neutralize foreign substances (such as bacterial and viral species).	Antibody responses are enhanced by probiotic species in some, but not all studies.

CONCLUSIONS

Early initiation of breastfeeding within 30 minutes of life promotes health, prevents disease and decreases health-care and feeding costs. All newborns should have exclusive breastfeeding for the initial 6 months after birth, which significantly decreased neonatal mortalities in developing countries. Exclusive breastfeeding & probiotics significantly decrease the incidence of NEC in preterm and VLBW newborns. Vaginal delivery should be encouraged as it strengthens both maternal and neonatal defense against infections.

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