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ABSTRACT

Metabolic modulation of immunity by immunonutrients holds much future promise of improved clinical outcome in neonates. This review provides considerable evidence for the potential role of various immunonutrients in neonates. Some infant formulas are already supplemented with several of the immunonutrients. The efficacy and how we can optimally use these immunonutrients require study as their role is still not completely clear. Studies are needed to elucidate how these agents interact with genes. Studying microbial-intestinal relationship will provide us with insights and maybe fresh directions for the use of immunonutrients in not only preventing disease but also improving health and outcomes in our neonates. It would also substantiate the long standing belief that what we eat and what our mothers ate can deliver several benefits much beyond basic nutrition.

Key Words: Arginine, Glutamine, Human milk, Immunonutrients, Lactoferrin, Neonatal gastrointestinal handicaps, Nucleotides, Prebiotics, Probiotics, Polyunsaturated fatty acids.

INTRODUCTION

Nutrients that affect the immune system are termed as Immunonutrients. The knowledge of the immunoboosting capacity of ingested foods existed since the 1800s. However, it is only in the last 50 years that a scientific relation between nutrition and immune function started emerging. It is recognized today that nutrient metabolism and immunity are both essential to sustain and to preserve life and during evolution both of them co-developed organ systems and signaling pathways. Human epidemiological data indicate that prenatal and early postnatal nutrition modulates the developing immune system. In this sense, the fact that early life events, including gestational development can have significant long-term effects is the basis of early programming of the immune system. Hence, it is not only the neonatal diet but also what the mother ate which can influence the immune system.

Besides being the gateway for nutrient intake, gut is the largest immune organ, containing over 65% of all the immune cells in the body and over 90% of all immunoglobulin-producing cells. Thus, a significant part of an

animal's immune system can interact with what they eat. The gut-associated lymphoid tissue (GALT) is unique in its ability to be exposed to a diverse array of antigens from foods and from numerous commensal microorganisms and yet remains quiescent until it encounters a pathogen. GALT, therefore, offers unique opportunity for immunomodulation via diets. The intestinal barrier consists of epithelial, immunologic, luminal, and mucosal factors that control antigen entry and the generation of immunologic phenomena in the gut.[1-2]

Nutrients that have been shown to have a considerable influence on immune function (delayed hypersensitivity, lymphocyte sub-population counts, immunological tests, etc.) are called "immunonutrients" or "immunity regulators".[10] Dietary components with immunomodulatory potential include vitamins, minerals, polyphenols and dietary polyunsaturated fatty acids. Dietary components with the ability of modulating the gut microflora are fiber, prebiotics and probiotics. This chapter shall review some of the common immunonutrients which could be useful in the practice of neonatology.

ETIOPATHOGENESIS OF DISEASE IN NEONATES

Evidence is accumulating that the defense mechanisms in the newborn that normally maintain a healthy balance in the intestine (both immune and nonimmune) may be inadequate or at least not functioning at optimum levels. Neonates, particularly the premature ones, may be at an increased risk for luminal proliferation of and mucosal invasion by microbial pathogens and intact dietary antigens.

Several factors lead to a hostile GI environment that predisposes the newborn infant, specifically the sick hospitalized one, to disease (Table 2.1) These include the introduction of feeding tubes into the stomach or more distal intestine, the routine use of broad-spectrum antibiotics that select for resistant pathogens that thrive in the unusual microbial environment of the neonatal intensive care unit (NICU), intrinsic immaturities of the infant GI tract, physical and chemical factors, the lack of adequate nutrition and the

Table 2.1 Factors influencing neonatal nutrition accretion

S. No	*Factor*
1.	Immature gut motility
2.	Suboptimal gastric acid secretions
3.	Low pancreaticobiliary secretions
4.	Developing lymphoid tissue
5.	Reduced mucin secretion
6.	Immature gut barrier
7.	Ischemic reperfusion injury
8.	Enhanced proinflammatory response
9.	Tube feeds
10.	Histamine blockers usage
11.	Broad spectrum antibiotics usage

immune system with an emphasis on the innate immunity of the intestinal mucosa.

There are specific attributes with respect to the neonatal gastrointestinal tract especially in the preterm infants. The motility is immature because coordinated motor complexes that are important for digestion and absorption are not mature until 34 to 35 weeks' gestational age. Immature motility promotes bacterial overgrowth and, thus, reduces absorption of key dietary nutrients. Gastric acid secretion increases in preterm infants during the first weeks after birth. Normal gastric acid and pancreaticobiliary secretions decrease the amount of viable microorganisms and intact dietary protein antigens that reach the small intestine. Pancreatic insufficiency in the preterm infant can last throughout the first year of life. Low gastric acid and pancreaticobiliary secretions, coupled with the common use of histamine-blockers to prevent gastric ulcers, allow a greater bacterial load to reach the distal intestine, thus predisposing the infant to sepsis and necrotizing enterocolitis (NEC). Peyer patches are aggregations of lymphoid tissue located in the lamina propria and submucosa of the GI tract. They first appear at about 19 weeks of gestation, spread throughout the jejunum and ileum from 24 to 40 weeks' gestation, and remain prominent in the terminal ileum in the adult. In a critically ill neonate, the intestinal barrier to pathogens becomes compromised because of stress, lack of enteral feedings, and ischemic-reperfusion injury. A damaged or immature gut barrier may lead to increased intestinal permeability and aberrant antigen transfer and immune response, thus explaining vulnerability to infection, inflammation, and hypersensitivity at an early age.[1,3-5] In patients dying of sepsis there is an imbalance in pro- and anti-inflammatory cytokine production. There is a failure of antioxidant defenses in addition to high levels of nuclear factor- kB (NF-kB). This proinflammatory cytokine response is part of an uncontrolled systemic inflammatory response syndrome (SIRS), which plays an integral role in premature labor, chronic lung disease, cerebral palsy, necrotizing enterocolitis (NEC), and sepsis.[6-7] Because the gut is a primary origin of SIRS, it is intuitive to consider that nutritional agents might stabilize the intestinal mucosal barrier, alter the balance of pro- and anti-inflammatory cytokines, and prevent excessive activation of NF-kB.

IMMUNONUTRIENTS

Milk

The best example of immunonutrition in neonates is human milk which protects the intestinal tract from infection and damage induced by dietary antigens. It also contains protective agents, including immunoglobulins, lactoferrin, lysozyme, glycoconjugates, oligosaccharides, and various cell types. Biologically-active antibodies appear in human milk as the result of maternal exposure to antigens and confer protection to the infant.[8-9] It is particularly relevant as maternal perineal bacterial flora commonly colonize

the infant at birth and thus generate a shared microbiome specific to the maternal-infant dyad.

Although a commonly held belief is that the intestinal tract of the fetus is sterile, recent studies suggest that many preterm infants are exposed to microbes found in the amniotic fluid, even without a history of rupture of membranes or culture-positive chorioamnionitis. One of the first comprehensive nonculture-based studies of intestinal microbes in 14 healthy term infants, using a ribosomal DNA microarray-based approach, showed that the composition and temporal patterns of the microbial communities varied widely. Antibodies in human milk reflect the antigenic repertoire of the mother's intestine and respiratory tract. If the mother and infant are colonized by the same bacteria, the mother can produce specific antibodies that can protect the infant through her milk.

Milk bioactives from bovine colostrum have been shown to have immune-enhancing effects in both humans and animals, making bovine colostrum an interesting immunomodulating ingredient. Colostrum contains IgS, cytokines, lactoferrin, and lactoperoxidase, each of which can positively influence the immune system. Colostrum supplemented diets have been shown to enhance immune status in animals as evidenced by increased response to vaccination and increased GALT activity measured by IgA production.

Glutamine

Glutamine, the most abundant amino acid in the human body, plays a central role in inter-organ carbon and nitrogen transfer. Glutamine is generally considered as a "non-essential amino acid" because it can be synthesized in the body. However, glutamine stores may become depleted, during catabolic insults such as injury, infection or chronic glucocorticoid treatment. Currently, glutamine is considered a "conditionally essential amino acid" in the critically ill with a number of potential functions (Table 2.2). Glutamine is thought to be an important fuel for rapidly dividing cells such as enterocytes and immune cells. The amide nitrogen of glutamine is thought to be critical in the biosynthesis of nucleotides and hexosamines. Glutamine and nucleotides appear to act synergistically in intestinal epithelial proliferation and differentiation. Hexosamines are very important in maintaining gut

Table 2.2 Glutamine: Immunonutrient properties

S. No	*Function*
1.	Metabolic fuel for rapidly dividing cells
2.	AIDS synthesis of nucleotides and hexosamines
3.	Precursor of glutathione
4.	Improves gut integrity
5.	AIDS protein synthesis, preserves and maintains aminoacid pool
6.	Acts synergistically with nucleotides in enterocyte proliferation and differentiation
7.	Modulates the pro-inflammatory response

barrier functions via surface mucin and glycoprotein forming intercellular tight junctions. The antioxidant glutathione is also formed from glutamine.[7,11]

Over the past few decades, glutamine has been shown to be beneficial in the prevention of infectious morbidity and mortality in the seriously ill patients. In various studies, glutamine administration reduced Gram-negative bacteremia in severely burned patients, sepsis in polytrauma patients and bone-marrow transplant recipients.[12-14] A study of very low birth weight infants receiving enteral glutamine supplementation during their 1st month of life demonstrated that the glutamine-supplemented group developed less culture proven sepsis and analysis of T-cells found a blunting of HLA-DR+ and CD16+ T-lymphocytes in glutamine-supplemented infants compared with controls, which was consistent with decreased stimulation of the immune response secondary to decreased translocation of bacteria or their antigens across mucosal surfaces. Glutamine has been found to modulate the pro-inflammatory response in different animal and human studies with significantly decreased production of pro-inflammatory cytokines (IL-6 and IL-8) by the intestinal mucosa which support the hypothesis that some of glutamine's beneficial effects may be a result of improved gut integrity or immune function. Glutamine could thus be used to regulate the inflammatory response in situations when a major clinical stress is anticipated or in the therapy of inflammatory disease. The sudden cessation of glutamine supply from the mother to premature infants, who are highly stressed and undergoing rapid growth, may be detrimental. There is no glutamine in their total parenteral nutrition (TPN) and they are frequently not enterally fed for weeks. Premature and sick infants seem to depend on an adequate supply of glutamine and its metabolites for growth and normal physiologic development such as increased intestinal mucosal integrity and immune function. Premature neonates who subsequently develop NEC have been found to have lower plasma glutamine and arginine concentrations.[2] Thus, it appears that glutamine has a strong potential as an immunonutrient.[15-18]

Arginine

Arginine is an essential amino acid in the fetus and neonate, and is a conditionally essential nutrient for adults. As a precursor for the synthesis of nitric oxide (NO), creatine, polyamines, urea, ornithine, proline, glutamate, and other molecules with biologic importance, and as a stimulant to the production of growth hormone, L-arginine is an important component of nutrition and metabolism.[19-20] Major immunonutrient properties of arginine are listed in Table 2.3. Adequate concentration of arginine may be necessary not only for tissue growth but also for normal physiological function. It has been shown that premature infants who subsequently developed NEC had a significant lower plasma concentration of arginine than did infants who did not develop NEC. Reduced arginine concentrations may be due to an increased metabolic demand for arginine or limited endogenous synthesis. In

Table 2.3 Arginine: Immunonutrient properties

S. No	*Function*
1.	Precursor of nitric oxide synthesis
2.	AIDS synthesis of aminoacids, polyamines and glutamates
3.	Decreases hyperammonemia
4.	AIDS creatine, urea, ornithine and proline synthesis
5.	Protects gut integrity in inflammation
6.	AIDS tissue growth
7.	Stimulates production of growth hormone

the presence of inflammation or injury, nitric oxide (NO) is a critical mediator for the regulation of blood flow in the intestine. The studies also found that hypoargininemia is associated with increased severity of respiratory distress syndrome and decreased systemic oxygenation in preterm infants supported by TPN solutions.[8,21-22]

Nucleotides

Nucleotides, nucleosides and nucleobases belong to the non-protein-nitrogen fraction of milk. Nucleotides are provided by either endogenous biochemical sources: de Novo synthesis and/or salvage pathway, and by dietary supply. They provide purines and pyrimidines for nucleic acid synthesis. Nucleotide supplementation in infant formula leads to improved growth and reduced susceptibility to infection. Many studies have suggested that nucleotides again may be "conditionally essential nutrients" for the gastrointestinal tract under the conditions of stress when the indigenous synthesis of nucleotides cannot keep up with the increased demand.[23-24] Studies of nucleotide supplementation support the strong interaction between glutamine and nucleotides in the intestinal epithelium. Nucleosides and nucleotides are not only active as metabolites but are also involved as bioactive substances in the regulation of body functions. Supplemental nucleotides have been shown to be helpful in enhancing antibody responses, helping in the repair of damaged gut mucosa, contributing to iron absorption in the gut and influencing long-chain polyunsaturated fatty acid (PUFA) synthesis in early life. A study of full-term healthy infants showed that infant formula fortified with nucleotides enhanced infant immunity. Due to the bio- and trophochemical properties of dietary nucleosides/nucleotides, the European Commission allows the supplementation of infant and follow-up formula.[25-26]

Probiotics and Prebiotics

Probiotics are defined as live microbial food supplements that beneficially affect the host animal by improving its intestinal microbial balance. The classification of a strain as probiotic requires that its beneficial physiologic effects be proven, that the strain be of human origin, be safe for human use, be stable in acid and bile, and that it adheres to the intestinal mucosa. The most frequently used probiotics fulfilling these criteria are Lactobacillus

Table 2.4 Probiotics and prebiotics:Immunonutrient properties

S. No	*Function*
1.	Limits infection by competitive inhibition of bacterial colonization
2.	Produces antibiotic molecules *in vivo*
3.	Metabolizes nutrients into volatile fatty acids
4.	Prevents bacterial translocation in the gut
5.	Enhances secretory antibody response
6.	Balances T-helper cell response

and Bifidobacterium.[1] These can be found in yogurt and other fermented milk products. Probiotics work through a variety of mechanisms to produce several positive clinical effects (Table 2.4). These "good" micro-organisms can produce antibiotic molecules that directly impede proliferation of pathologic organisms. They can competitively prevent pathologic bacterial colonization by competing for the same glycoconjugate on the epithelial surface, and they can metabolize nutrients into volatile fatty acids and chemically modified bile acids that creates a local environment that is unfavorable for the growth of many enteric pathogens. Their attachment to the intestinal epithelium can strengthen the host's mucosal defenses through enhancement of secretory antibody responses, through a tightening of the mucosal physical barrier to microorganism translocation, and by a balance in T-helper cell response.[24-25] A better understanding of probiotic-epithelial interactions can be used to devise new strategies to prevent and treat bacterial infections of the gut. Breastfed infants with bifidobacterial flora show a greater resistance to various infectious diseases than do bottle-fed infants. Studies showing administration of *Bifidobacterium bifidum* to bottle-fed infants resulted in an increase in fecal counts of bifidobacteria and a decrease in fecal pH, factors which protect preterm infants and other newborns from intestinal disease.[27] Probiotics have now been proven to reduce NEC in preterm meonates.[28]

Prebiotics are non-digestible food ingredients that affect the host by selectively targeting the growth and/or activity of one or a limited number of bacteria in the colon and thus have the potential to improve host health. Examples of prebiotics include inulin, fructo-oligosaccharides, galacto-oligosaccharides, and lactulose. These occur naturally in many foods but can also be incorporated into beverages, confectionery and dairy products. Prebiotics are simple, naturally occurring or synthetic sugars that are used by certain colonic bacteria, especially bifidobacteria, as a carbon source for growth and metabolism. Inulin, a naturally occurring sugar, is considered to be a part of dietary fiber. Inulin has one molecule of glucose and 60 molecules of fructose and is thus considered to be an "extended-sucrose" molecule. Dietary fructo-oligosaccharides or inulin increased fecal bifidobacterial counts almost 10-fold, whereas those of bacteroids, coliforms, and cocci decreased[29] in a study.

A new term that has entered the literature is "synbiotic", which is the mixture of prebiotics and probiotics that beneficially affect the host by improving the survival and multiplication of live microbial dietary

supplements in the gastrointestinal tract.[24] Because probiotics need to be administered frequently to obtain maximal effect, the combined use of pre and probiotics could offer advantages over the administration of probiotics alone.

Omega-3 Polyunsaturated Fatty Acids (PUFAs)

Dietary fatty acids such as linoleic acid (LA) and a-linolenic acid (ALA) of the n-6 and n-3 series of PUFA, respectively, are considered "essential" because they must be derived from the diet. Once ingested, the essential fatty acids are converted to longer chain, more highly unsaturated fatty acids, including arachidonic acid (AA) from LA and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from ALA. Modulation of immune and inflammatory responses has been reported with increased intakes of PUFA of the n-3 series (Fig. 2.1). The outcome is dependent on the type of PUFA, the target tissue, as well as the immune status of the host before exposure. Specific cellular mechanisms for these events may include modulation of transcription factor expression, e.g. NF-kB, alteration of signal transduction protein (protein kinase C) activity, inhibition of cellular transport proteins (Mg2+-ATPase), inhibition of apoptosis, stimulation of the antioxidant system and modulation of cytokine and prostaglandin metabolite receptor activation.[4,30] Intake of long-chain PUFAs may be related to structural and functional development of sensory, perceptual, cognitive and motor neural systems. DHA is selectively incorporated, retained, and highly concentrated in the phospholipid bilayer of biologically active brain and retinal neural membranes. PUFA supplementation of neonatal formula has been studied extensively for the outcomes of central nervous system development and visual acuity.[31]

Lactoferrin

Lactoferrin (LF), an iron-binding protein, is the most abundant whey protein in human milk. As implied by its name, LF was first isolated from milk. Subsequently, it was found to be present in most exocrine fluids such as saliva, bile, pancreatic fluid, and tears. Plasma also contains LF. Human

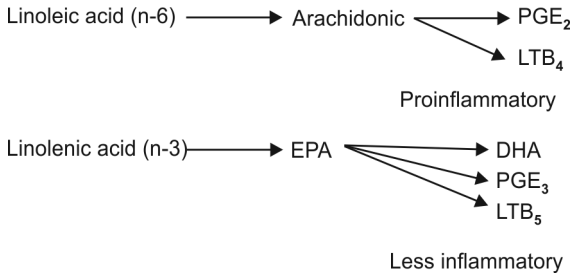

Fig. 2.1 Inflammation and PUFA

LF consists of 691 amino acids. Iron-depleted LF with less than 5% iron saturation is called apolactoferrin, whereas iron-saturated LF is referred to as hololactoferrin. In breast milk, the LF is predominantly apolactoferrin. The affinity of LF for ferric iron is about 260 times that of blood serum transferrin. The binding capacity is dependent on the presence of small amounts of bicarbonate.[32-33] LF can also bind other metal ions such as copper, manganese, and aluminum. LF has been reported to have bacteriostatic, bactericidal, antifungal and antiviral effects. Because iron is an essential growth factor for most microorganisms, the low degree of iron saturation of LF in human milk and high affinity for iron suggests that LF is a bacteriostatic agent that inhibits the growth of bacteria. In one study, oral therapy with recombinant human lactoferrin (rh-LF) + $FeSO_4$ did not alter the protective effect of rh-LF in neonatal rats model infected with *E. coli*. Thus, the putative binding of iron by LF as a mechanism for bacteriostasis is not clear.[34] The cationic N-terminus of LF is a bactericidal domain distinct from the iron-binding region, that causes bacterial membrane permeability changes, releases lipopolysaccharide from cell walls of Gram-negative bacteria, and thus renders the bacteria more susceptible to killing by phagocytes.[32] LF has been shown to have antioxidant effects by controlling iron or copper catalyzed reactions, which generate hydroxyl free radical from peroxides.[33] LF was identified as a possible growth factor. Chronic oral consumption of human LF promotes the growth and maturation of the intestinal mucosa. LF also exerts immunomodulatory functions, helps to block excessive immune responses and may stimulate the activity and development of the infant's own immune system.[9] LF is not likely to be the sole responsible agent for the alteration of gut flora in breast-fed infants. A recent study showed neonatal rats pretreated orally with rh-LF had less bacteremia and lower disease severity scores after intestinal infection with *E. coli*.[34] In vitro studies have confirmed that rh-LF interacts with the infecting bacterium and rat macrophages. Rat macrophages were activated, as measured by increased levels of NO and tumor necrosis factor-α, when stimulated with increasing concentration of rh-LF. A combination of rh-LF and lysozyme was microbicidal. These in vitro studies suggest that rh-LF may act with other "natural peptide antibiotics" or may prime macrophages to kill *E. coli in vivo*.

CURRENT DILEMMAS AND FUTURE PERSPECTIVES

Metabolic modulation of immunity by pharmaconutrients appears to be an exciting arena. Anecdotal reports have suggested that these agents individually and in combination reduce infection rate, length of hospital stay and gut barrier immune function. As a combination of immunonutrients have been often used, it is difficult to conclude which is the most beneficial one.[35] Besides the combination of immunonutrients may have synergistic effects on the physiological and immunological function of individual pharmaconutrients. Interconversion and interaction of nutrients are issues

Table 2.5 Current evidence on utility of immunonutrients in neonates[28,35-37]

Immunonutrient	*Sepsis*	*NEC*
Enteral glutamine	Not clear	Maybe useful
Parenteral glutamine	Not clear	Not clear
Parenteral arginine	Not clear	Not clear
Oral arginine	Not clear	Maybe useful
S. boulardii + Polyamines	Not clear	Not clear
Oral lactoferrin	Beneficial	Not clear
Oral lactoferrin + lactobacillus GG	Beneficial	Beneficial
Lactobacillus, Bifidobacterium, Sacharomyces	Not clear	Beneficial
LCPUFA	Not clear	Not clear

that need to be addressed. Some of the studies which have evaluated the effects of immunonutrients on outcomes in sick newborns are shown in Table 2.5. Based on these, no conclusive recommendations could be made on the usefulness of individual immunonutrients in NEC and sepsis.[28,36-38]

Grey areas that need to be focused on should be the optimum dose of specific nutrients alone and in combination, delivery route, duration and timing of administration. The studies on disease specific action mechanism of various nutrients would be helpful. Scientific expansion of global methodological approaches are beginning to influence research in immunonutrition and may prove to be useful tools in establishing mechanisms of action. As nutrients are consumed as food, we must recognize the importance of absorption, bioavailability, etc. Moreover, the impact of genetic variability (nutrigenetics) and variation in the microbiome are still emerging and may in the future become increasingly important in the appropriate selection of subjects for experimental and clinical studies. Use of 'genomics' techniques may help clear the grey areas in the field of immunonutrition.

KEY LEARNING POINTS

- Dietary components with immunomodulatory potential include vitamins, minerals, polyphenols and dietary polyunsaturated fatty acids. Dietary components with the ability of modulating the gut microflora are fiber, prebiotics and probiotics.
- Human milk protects the intestinal tract from infection and damage induced by dietary antigens. It also contains several protective agents, including immunoglobulins, lactoferrin, lysozyme, glycoconjugates, oligosaccharides, and various cell types. Biologically-active antibodies appear in human milk as the result of maternal exposure to antigens and confer protection to the infant.
- Metabolism of nutrients such as glutamine, arginine, omega 3 fatty acids, nucleotides, and probiotics have been shown to have a considerable influence on immune function with their varied effect on the common signaling pathways.

Contd...

Contd...

- Currently, probiotics seem to have a role in the reduction of incidence of NEC and there is promising role of lactoferrin in prevention of sepsis. Other immunonutrients need more evidence for clinical use despite novel theoretical advantages.
- More studies are needed before extrapolating current evidence into universal practice.

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He has represented India at several international conferences, workshops, symposia, seminars, etc. worldwide as plenary speaker, guest speaker, chairperson, panelist, etc. and has bagged several national and international awards, and visiting Fellowships/Professorships abroad.

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