Immunity and the infant GI-tract

Rees L, RD (SA)

Correspondence: leannerees@telkomsa.net

Introduction

The intestine is the largest organ in the immune system of the body, and as such is the location for the majority of lymphocytes and other immune effector cells. The intestine is exposed to vast quantities of dietary and microbial foreign bodies (pathogens), which, in some instances, are potentially lethal. The development of normal immune function of the intestine is therefore vital for survival, and is dependent on appropriate antigen exposure and processing, and an intact intestinal barrier. In early life, maternal colostrums and milk can significantly augment resistance to enteric infections. The mechanisms of enhancing disease resistance are thought to be passive, involving a direct support of anti-microbial factors, and active, by promoting the development of specific immune functions. A tolerance response to dietary and non-invasive antigens is generally induced in the gut. However, it must also be able to mount an adequate immune response to ensure clearance of foreign antigens. Regulation of tolerance and active immune responses are critical to health, and failure to regulate these responses can lead to recurrent infections, inflammatory diseases and allergies. The education of the immune system in early life is thought to be critical in minimising the occurrence of these immune-based disorders.[1]

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Intestinal flora

Immediately after birth the intestines of infants are totally sterile and do not contain any bacteria, not even 'good' bacteria. During the natural birth process, the infant receives some beneficial bacteria from the mother. This gift of organisms immediately starts to multiply in the tiny gastro-intestinal (GI) tract of the infant and boosts its immunity. *Bifidobacteria infantis* is the dominant bacteria in the infant's digestive tract. These bacteria decrease the growth of so-called rota-viruses which cause diarrhoea and thrush, thus protecting the newborn infant against common infections. The bifidobacteria also help to prevent lactose intolerance and increase the absorption of minerals and B vitamins, and boost the infant's immature immune system. Breastfeeding is an excellent way of increasing the number of bifidobacteria in the infant's GI tract.[2, 3]

Infant formula has also been supplemented with these beneficial bacteria in the form of bifidobacterium and lactobacilli called probiotics to enhance this response in non-breastfed infants. These probiotics or cultures of beneficial bacteria compete with harmful bacteria in the GI tract for food and prevent the transport of pathogens into the body. Probiotics also increase the uptake of important minerals from the GI tract, thus preventing deficiencies which can also lower immunity.[2] As humans get older, they develop a deficiency of beneficial bacteria and therefore become more vulnerable to infections.

LCPUFAs

Human breast milk is also rich in long-chain polyunsaturated fatty acids (LCPUFA), which have immunomodulatory actions. Probiotics and LCPUFAs together modulate T-helper 1 and 2 responses, show antibiotic-like actions, and alleviate changes related to allergic inflammation. LCPUFAs promote the adhesion of probiotics to mucosal surfaces, which augment the health-promoting effects of probiotics. In view of the similarity in their actions and because LCPUFAs promote the actions of probiotics, a combination of LCPUFAs and probiotics offers significant protection. It is likely that breastfeeding and probiotics are two naturally occurring, appropriate events in early human life that have significant health benefits.[4] In a study by Duchen *et al,* mothers whose children were found to be allergic were shown to have lower levels of long chain polyunsaturated fatty acids in their breast milk compared to the milk of non allergic children. It has been recommended that infant formula for term infants should contain at least 0.2% of total polyunsaturated fatty acids as docosahexaenoic acid (DHA) and 0.35% as arachidonic acid (AA). The highly unsaturated nature of DHA, with 6 double bonds, makes it particularly susceptible to lipid peroxidation. Because the generation of damaging free radicals is associated with extensive lipid peroxidation, there is some concern regarding the safe use of long chain polyunsaturated fatty acids in infant

formula.[5,6] However, the benefits may outweigh these safety concerns.

Cytokines and lymphocytes

Cytokines and lymphocytes present in breast milk can influence the development of the immune system. This suggests an immunoregulatory role for breast milk that is absent in infants consuming formula. A study by Hawkes *et al* was conducted to investigate the potential difference in lymphocyte subsets between breast-fed and formula-fed infants at 6 months of age. The frequency of natural killer (NK) cells (CD_3-/CD_{16}+ +CD_{56}+) was greater in breast-fed infants (9,2%) than in formula-fed infants (6,6%, $p<0.001$), while the CD4 to CD8 ratio was 2.8 in breast-fed infants compared with 3.4 in formula-fed infants ($P<0.001$). Therefore breast-fed infants (<250ml formula/ breast milk per week) had a greater proportion of NK cells and a lower CD_4 to CD_8 ratio than formula-fed infants at 6 months of age.[7]

Nucleotides

The immunoprotective benefits of human milk, the biology of human milk nucleotides and the immunological and gastrointestinal effects of dietary nucleotides have also been investigated. Several animal studies by Yu,[8,9] animal studies have shown that dietary nucleotides enhance a number of immune responses, and the growth, differentiation and repair of the gut. Several clinical studies have reported beneficial effects of nucleotide supplementation on gut micro flora, diarrhoea and immune function, and another study has reported better catch-up growth in term infants with severe intra uterine growth retardation.[8]

Human milk has a higher concentration of nucleotides than bovine milk which is the source of most infant formulas. As the composition of breast milk is taken as the "gold standard", an increasing number of infant formulas are supplemented with nucleotides. Although dietary nucleotides have been suggested to have beneficial gastrointestinal and immunological effects, nucleotide-supplemented formula feeding has not been shown to confer the same benefits as breast feeding. Randomised controlled trials have yet to prove that healthy term infants fed nucleotide-supplemented formulas have accelerated physical growth and neurological development, and better growth and development of the gastrointestinal tract. Furthermore, it should still be proven that they result in improved digestive and absorptive functions, enhanced development of their immune system with subsequent increased resistance to infection and lower bacterial and viral infection rates during infancy, and a more favourable intestinal micro flora associated with a lower rate of infectious diarrhoea. However, a randomised controlled trial by Yu has reported that term infants with severe intrauterine growth retardation have better catch-up growth with nucleotide supplementation. The hypothesis that nucleotides are semi-essential nutrients needs to be further studied, in particular in the presence of prematurity, foetal growth retardation, intestinal injury and limited nutrient intake. As no deleterious effects have been reported with the use of nucleotide-supplemented formulas, the first of which was introduced over 30 years ago, such products are considered safe when nucleotides are supplemented to an amount equivalent to the free nucleotide concentration of human milk.[9]

Conclusion

Nutrition is essential to the health and development of infants and children. Breastfeeding is superior to infant formula feeding because in addition to breast milk's nutritional advantages, it protects against infections through specific and non-specific immune factors and has long-term consequences for metabolism and disease later in life. Human milk enhances the immature immunologic system of the neonate and strengthens host defence mechanisms against infective and other foreign antigens. Mechanisms to explain active stimulation of the infant's immune system by breastfeeding are through bioactive factors in human milk. Following breastfeeding termination there may be prolonged protection against infections due to influences on the infant immune system mediated via human milk.[10] Evidence exists to indicate that probiotics, long chain polyunsaturated fatty acids and nucleotides have a critical role to play in the development of the immune system and its response and therefore manufacturers attempt to imitate breast milk by supplementing these nutrients to ensure that non-breast-fed infants experience these benefits.

References

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