

The immunological role of breast feeding

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**L. Å. Hanson¹, S.-A. Silfverdal²,
L. Strömbäck¹, V. Erling¹, S. Zaman³,
P. Olcén², E. Telemo¹**

¹Department of Clinical Immunology, Göteborg University, Göteborg, Sweden, ²Departments of Paediatrics, Microbiology and Immunology, Örebro Medical Centre Hospital, Örebro, Sweden and ³Department of Social and Preventive Pediatrics, King Edward Medical College, Lahore, Pakistan

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L. Å. Hanson, Department of Clinical Immunology, Guldhedsgatan, 10 SE-41346, Göteborg, Sweden

Introduction

The immune system of the newborn is very small. The major stimulus of its growth is the infant's intestinal microbial flora, which normally is picked up from the mother at delivery. Hygienic measures now prevent that and the gut flora of the young infant today is very different from previously.

The transplacental IgG antibodies from the mother contribute to the infant's defence but at the expense of induction of inflammation, tissue damage, clinical symptoms caused by release of pro-inflammatory cytokines and a high energy cost.

Breast feeding provides large amounts of secretory IgA antibodies against the microbes in the mother's milieu. This is due to the enteromammary link resulting in IgA-producing lymphocytes after antigen-exposure migrating from the Peyer's patches in the mother's gut to the lactating mammary glands.

These antibodies protect mucosal membranes without inflammation, tissue damage and high energy consumption. The milk also contains several other protective factors and the defence against otitis media, respiratory tract infections, diarrhoea, urinary tract infections, *Haemophilus influenzae* type B infections, neonatal septicaemia, wheezing bronchitis and necrotising enterocolitis are most significant. Recent data indicate that there is an enhanced protection also for some

years after termination of lactation. This may be due to active stimulation of the infant's immune system by transfer of anti-idiotypic antibodies, lymphocytes and certain cytokines via the milk.

Breast feeding prevents coeliac disease in childhood. Single studies suggest similar effects for some autoimmune and inflammatory bowel diseases, but this needs to be confirmed. Recent studies provide evidence for protective effects against allergic diseases. Others have not confirmed that for atopic asthma.

Host defence of the neonate

The newborn has a small immune system, possibly amounting to just one or a few percent of that of an adult (1). The major cause of its rapid expansion after birth is the exposure to the microbes colonising the intestine. Normally these have come from the mother soiling the baby with her stool at delivery. After the introduction of efficient hygienic measures at delivery this is efficiently prevented and now the infant is colonised with bacteria of other origin (2). Thus, toxin-producing *Staphylococcus aureus* now appear early in the stool and are actually present in a majority of infants at the age of 2–6 months (3). Gram-negatives appear much later than previously. Gram-negatives are known to be required in the gut for oral tolerance to develop adequately.

It takes time for the specific immune system to expand and provide efficient host defence just as it does to become protected after an infection or a vaccination. It is likely that the innate immune mechanisms can be important until that time, but little is yet known about those mechanisms in infancy.

Thus it can be realised that the contributions by the mother to the infant's host defence are important. There seems to be a new situation in those infants who nowadays attract an intestinal microbial flora of a different origin than that originally obtained from the mother's gut flora.

The maternal IgG antibodies actively transported via the placenta to the fetus are important in this respect. It should be noted, however, that they come to use only when an infection has reached the tissues. When the IgG antibodies react they will activate complement, bring in granulocytes and induce production of cytokines such as IL-1 β , TNF and IL-6. All this results in inflammation, tissue damage and high energy consumption. The latter, together with the increase in leptin caused by the listed cytokines, induces a loss of appetite. This may result in impaired growth and even under-nutrition in infants with repeated infections.

Another most efficient mode of maternal support of the infant's host defence is provided via the milk.

Mother's milk and host defence

Human milk contains a number of components supporting the infant's host defence, both passively and actively. The predominant protein in colostrum and a major one in mature milk is the secretory IgA (SIgA). The SIgA milk antibodies are produced in the lactating mammary glands by committed lymphocytes migrating there via the enteromammary route after antigens exposure in the Peyer's patches in the mother's gut. Therefore they are directed against microbes and foods, which are or have been present in the mother's gut. Also memory lymphocytes migrate into the mammary glands so the mother has a very broad range of specificities of her milk antibodies, actually against all the microbes which have exposed her Peyer's patches throughout life. Such antibodies have been shown to provide significant protection against numerous microbes such as *Shigella*, *V. cholerae*, *Giardia lamblia*, *Campylobacter* and ETEC (4–8).

Lactoferrin is the major protein in mature milk. It has a number of effects, such as killing bacteria, viruses, fungi and tumour cells, activation of the immune system and blockage of

production of the cytokines IL-1 β , TNF and IL-6 (9–11). However, there are no critical studies attempting to define the clinical effectiveness of these functions of milk lactoferrin. In an animal model lactoferrin or peptides thereof given perorally can prevent or dampen experimental urinary tract infections in mice and colitis in rats (12).

The large oligosaccharide fraction in the milk contains several structures, which function as receptor analogues for microbes. Thus they can prevent binding of microorganisms to mucous membranes, blocking infections (13). Again, the clinical role of this mechanism has not been evaluated.

We have demonstrated recently that human milk may contain the peptide anti-secretory factor (AF) (14). Such peptides can be induced by certain foods such as heat-treated oat or by exposure to bacterial enterotoxins. The AF can prevent mastitis in sows and diarrhoea in calves and piglets. It is likely that AF in human milk may have a similar role, but this is only now being studied.

There are numerous other potentially protective factors in milk, such as the 90K, Mac-2 binding glycoprotein, which may prevent upper respiratory tract infections (15, 16). Lactadherin is a mucin-related glycoprotein which may be protective against rotavirus (17, 18).

The milk also contains a substantial fraction of nucleotides. It is likely that they are important as building blocks for the DNA required for the rapid early expansion of the lymphoid system as well as the early rapid growth of the gut of the young infant.

Numerous careful studies have now confirmed that breast feeding protects against several diseases such as otitis media, respiratory tract infections, diarrhoea, invasive *H. influenzae* type B (Hib) infections, neonatal septicaemia, necrotising enterocolitis and wheezing in non-atopic children (19). These effects are seen in developed as well as developing countries. In poor countries the milk mediated protection is often dramatic. Thus the odds ratio comparing the occurrence of neonatal septicaemia in partially, compared to non-breast-fed infants in Pakistan, is as much as 18 and the risk of dying of diarrhoea is 25 times comparing non-breast-fed with exclusively breast-fed infants (20, 21).

Breast feeding also provides long-term protection against infections

Several studies have shown that after breast feeding for 3–4 months or more there is enhanced

protection against otitis media for some 3 years, against diarrhoea for at least 4 years, for respiratory tract infections and wheezing for 6–7 years (22). For every week of additional breast feeding there seems to be further enhancement of the protection against Hib (23, 24). An enhanced protection was still seen for this infection at 10, but not 15 years after termination of breast feeding.

An exception to such long-term effects appears in our studies in Pakistan. In detailed analyses of a large study it seemed that the enhanced protection against diarrhoea by breast feeding vanished a few weeks after the termination of lactation (25). This may be due to the much higher infectious doses occurring in this poor country.

Breast feeding also seems to enhance serum and mucosal antibody responses to several vaccines, such as diphtheria, tetanus, live poliovirus vaccine, BCG and Hib vaccines (26). In some studies, such effects have not been obtained. In a recent work we have noted that priming of the immune response in neonatal mice also have effects on the immune response in the next generation (27). Thus it may be that we cannot interpret immune responses in infants, unless the response of the mother and grandmother also is taken into account.

The likely mechanisms behind these long-term protective effects may be stimulation of the infant's immune system by anti-idiotypic antibodies (28) and lymphocytes in the milk, as well as milk cytokines. Thus human milk contains anti-idiotypic antibodies and in experimental models in mice such antibodies given via the milk could enhance the antibody response to a bacterial as well as a viral antigen (29, 30).

A transfer of milk lymphocytes with their uptake into the offspring's gut mucosa and mesentery lymph nodes has been noted in several experimental studies (31–35). It has also been demonstrated that such milk lymphocytes from a vaccinated sheep could prime lambs after intestinal transfer, resulting in an enhanced immune response after vaccination of the lambs using tetanus toxoid (36).

As a remarkable result of this transfer of milk cells it has been noted that breast-fed infants become tolerant to the maternal HLA (37). Thus renal transplants from mothers to offsprings do significantly better if the offsprings have been breast-fed (38, 39).

In a recent study of children >18 months old when attracting invasive Hib infections we noted that those who had been exclusively breast fed for >13 weeks (mean 19 weeks) produced signifi-

cantly more IgG2 anti-Hib than those exclusively breast fed for <13 weeks (mean 5 weeks) (40). Since IgG2 antibody production is dependent upon IFN- γ , it may be that the relatively high content of IFN- γ in milk might have played a role.

Recent studies have indicated that breast feeding increases the size of the thymus (41, 42). The possible implications of this are not known. It has also been demonstrated that breast feeding may prevent obesity in schoolchildren (43). This interesting observation based on a large study suggests that breast feeding, possibly via effects on metabolism via certain cytokines, may have much wider effects than previously recognised. This has been discussed in a recent publication (44).

Long-term effects of breast feeding on immunological diseases

If breast feeding by stimulation of the infant's immune system makes it function better by providing enhanced protection, one may question whether the risk of malfunction of the infant's immune system resulting in immunological disease is decreased due to better control. Recent data confirm that breast feeding decreases the risk of developing coeliac disease in childhood (45). Single studies also suggest preventive effects on Crohn's disease and ulcerous colitis (46, 47). Similar single observations also exist for multiple sclerosis and rheumatoid arthritis (48, 49). Further evaluation will have to await additional critical studies.

When it comes to allergy the situation is quite complex, with some conflicting data and much debate (26, 50). Recently Wright et al. showed, in a very interesting study, protection against asthma by breast feeding in non-atopic children only (51). Furthermore, they noted that some mothers with the most severe asthma might increase the risk of the child to attract asthma with a longer duration of breast feeding. If this observation holds it could be thought of as an effect of transfer of milk lymphocytes.

However, in a follow up for 17 years of 150 children, Saarinen and Kajosaari (52) showed that the only factor significantly affecting the appearance of food allergy during years 1–3 and after that inhalant allergies (with only few cases of asthma) was breast feeding. It should be added that the study took into account relevant confounders, but strangely that information was not included in the paper by the journal (Saarinen, personal communication). A large and carefully controlled study in Australia by Oddy et al.

recently gave evidence for protection by breast feeding against asthma (53). This was confirmed by an additional study by the same author (54).

In a recent experiment in rats we tried to study whether or not breast feeding could influence immune reactivity to a food protein in the offsprings. In a cage with ovalbumin (OA) in the food breast feeding reduced delayed-type hypersensitivity (DTH) to the OA in the offspring compared to those in a cage without OA. However, when mother rats from a cage with OA were transferred to offspring in a cage without DTH reactivity to OA, they also showed reduced DTH reactivity to OA. Further studies are needed to clarify whether such tolerance via breast feeding could be of clinical relevance.

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