

Breast-feeding and protection against infection

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Microbial exposure and the immune system of the newborn

The newborn starts to be colonized in the upper respiratory tract and gastrointestinal tract, as well on the skin, directly from birth onwards. Delivery next to the anus exposes the newborn to the mother's intestinal microflora, in which harmless anaerobes are predominant, but where aerobic and facultative anaerobes are also prevalent. Some of the latter may contain species that are potentially pathogenic. Before the strict anaerobes have totally taken over, reaching levels over 99%, there is an early period where they have not yet reached numbers high enough to compete successfully with the aerobes and facultative anaerobes for space and nutrients and bring their numbers down. The potential pathogens may then reach levels at which they can initiate infections. Thereafter, the infant is also at a special risk of infections because of its somewhat limited host defences. This is strikingly illustrated by the high early infant mortality caused by infections, as seen in poor regions across the world (1, 2).

The infant has a complete immune system at delivery, but it is very small. It will start to expand as soon as it meets all the microbes on the mucosal membranes, especially in the gut. The neonate remains deficient in several defensive functions during the first weeks and months of life (3). This includes, in particular, various aspects of phagocytes and their functions, but also reduced antigen presentation, a slow start to the production of secretory immunoglobulin A (SIgA), which normally protects mucosal membranes where most infections start, and a somewhat reduced capacity of cell-mediated immunity.

Some of the protective components in human milk

The defence provided by breast-feeding compensates for these various early deficiencies in the host

defences of the neonate (3). Human milk contains several major protein components, which are obviously aimed at defence rather than nutrition, although the protein content of human milk is low compared with that of bovine species, for example. The SIgA antibodies are present in about 1 g l^{-1} of mature milk. They are produced in the mother's mammary glands by lymphocytes, which have migrated there from her gut. This is called the enteromammary link. As a consequence, the milk SIgA antibodies are directed against the mother's intestinal microflora, making bacterial colonization with the mother's gut flora at delivery and thereafter harmless, even if it contains pathogens (4). The primary function of this kind of antibody is to bind microbes already on the mucosal membranes, preventing them from attaching to the mucosal epithelium and then invading the underlying tissues. Therefore, they prevent tissue defence from being activated, which otherwise would start protection built on induction of inflammation. This is due to activated neutrophils and macrophages producing numerous cytokines. They induce symptoms such as fever, tiredness and loss of appetite due to cytokines elevating leptin levels. Instead, the SIgA-mediated defence prevents both symptoms and energy loss, suggesting that it is an ideal defence for a young, growing individual.

Lactoferrin is another major milk protein ($1\text{--}3 \text{ g l}^{-1}$) that is able to kill certain bacteria, viruses and *Candida*. At the same time it enters the nuclei of leucocytes, where it binds to the transcription factor nuclear factor- κ B (NF- κ B), blocking the capacity of leucocytes to produce the proinflammatory cytokines (5). In experimental animals, lactoferrin and some of its fragments, given orally, resulted in decreased inflammatory colitis. There was also protection against urinary tract infections, because lactoferrin and fragments are taken up in the gut and appear in the urine (6, 7).

α -Lactalbumin, also a major milk protein, has recently been shown to have the capacity to take a shape that makes it capable of killing numerous human tumour cell lines, and also skin papilloma in a clinical study (8, 9).

Human milk contains a major fraction of oligosaccharides and glycoconjugates. Such structures can prevent mucosal infections through microbes binding to these soluble structures instead of similar molecular structures on the surface of mucosal cells in the gut, as well as in the respiratory and urinary tracts (10, 11).

Recent work shows that the antisecretory factor (AF) can be induced in milk by the mother eating a specially prepared cereal, or by exposure to enterotoxin-producing *Vibrio cholerae* or *Escherichia coli*. The AF was found to prevent mastitis, which is a very common and painful condition in lactating mothers (12). A randomized placebo-controlled trial in Pakistan found that AF together with oral rehydration led to recovery from acute or prolonged diarrhoea in 83–90% of 6–24-month-old children, within 3 days (13).

Human milk also contains numerous hormones, cytokines, chemokines, growth factors, and so on, some or many of which seem to allow the mother to influence many functions in the breast-fed offspring, both directly and in some instances with seemingly long-term effects (3).

Breast-feeding and protection against certain infections

Breast-feeding, especially the early onset of exclusive breast-feeding, has been shown strikingly to reduce infant mortality in poor areas in the world (3). The strong contraceptive effect of breast-feeding adds much to this effect, as illustrated by the fact that spacing of less than 2 years between births increased the risk of dying before the age of 5 years by 50% (14).

Protection against neonatal septicaemia, meningitis and necrotizing enterocolitis has been demonstrated, along with some effect against sudden death in infancy (3). Breast-feeding reduces the prevalence of diarrhoea and pneumonia, which partly explains how breast-feeding can reduce infant mortality. In most regions these two forms of infection are the most common causes of morbidity and death. Significant protection against these infections is also seen in better-off countries (3). Protection is provided against diarrhoeal agents

such as *Campylobacter*, *Shigella*, enterotoxin-producing *E. coli*, *V. cholerae* and *Giardia lamblia*, with milk SIgA shown to be a sufficient, but not the only explanation for milk-mediated protection. The antiadherence effect of the milk oligosaccharides is likely to play a role in both the respiratory and gastrointestinal tracts. Recently, it was found that high levels in the milk of fucosylated oligosaccharides related to milk-mediated protection against diarrhoeal infections with *Campylobacter* and calicivirus (15).

Breast-feeding may, via its SIgA antibodies, prevent *Haemophilus influenzae* colonizing the nose and mouth (16), thus reducing the risk of infections. Such an effect was not observed for pneumococci (17). Accordingly, breast-feeding provides some protection against acute and recurrent otitis media (3). There are reports claiming that breast-feeding may reduce the risk of infections in the upper and lower respiratory tracts. Recent studies also show that breast-feeding reduces the risk of urinary tract infection (18).

Breast-feeding can have long-term effects, possibly due to some of the many signals from the mother to her infant via the milk affecting the immune system of the infant. Thus, there is evidence that for one to several years after the termination of breast-feeding enhanced protection may remain against certain infections such as otitis media, respiratory infections with or without wheezing, urinary tract infections and invasive infections with *H. influenzae* type b (3).

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