# Supplementation of the Breastfed Baby
# "Just One Bottle Won't Hurt"---or Will It?

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**January 2014**

## Background

- The gastrointestinal (GI) tract of a normal fetus is colonized in utero with bacteria from the maternal digestive tract (Jimenez et al, 2008)
- Maternal immune factors, health, and lifestyle contribute to the diversity and type of pioneering bacteria that first reach the fetal gut (Gosalbes et al, 2013)
- the type of delivery has an effect on the development of the intestinal microbiota
    - vaginally born infants are colonized with their mother's bacteria
    - cesarean born infants' initial exposure is more likely to environmental microbes from the air, other infants, and the medical and nursing staff which serve as vectors for transfer.
    - infants deprived of contact with the maternal vaginal microbiota experience a deficiency of strict anaerobes such as *E. coli, Bacteroides*, and *Bifidobacteria* and a higher presence of facultative anaerobes such as *Clostridium* species, compared with vaginally born infants (Adlerberth & Wold, 2009)
    - the primary gut flora in infants born by cesarean delivery may be disturbed for up to 6 months after birth (Gronlund et al, 1999)
- babies at highest risk of colonization by undesirable microbes or when transfer from maternal sources cannot occur are cesarean-delivered babies, preterm infants, full term infants requiring intensive care, or infants separated from their mother
    - infants requiring intensive care acquire intestinal organisms slowly and the establishment of bifidobacterial flora is retarded
    - a delayed bacterial colonization of the gut with a limited number of bacterial species tends to be virulent
    - control and manipulation of the neonatal gut with human milk can be used as a strategy to prevent and treat intestinal diseases (Dai & Walker, 1999)
- major ecological disturbances are observed in newborn infants treated with antimicrobial agents
    - one way of minimizing ecological disturbances in the NICU is to provide these babies with fresh breast milk (Zetterstrom et al, 1994)
- breastfed and formula-fed infants have different gut flora
    - breastfed babies have a lower gut pH (acidic environment) of approximately 5.1-5.4 throughout the first six weeks that is dominated by bifidobacteria with reduced pathogenic (disease-causing) microbes such as *E coli, bacteroides, clostridia, and streptococci*
    - flora with a diet-dependent pattern is present from the 4$^{th}$ day of life with breast milk-fed guts showing a 47% bifidobacterium and formula-fed guts showing 15%. Enterococci prevail in formula-fed infants (Rubaltelli et al, 1998)
    - babies fed formula have a high gut pH of approximately 5.9-7.3 with a variety of putrefactive bacterial species
    - in infants fed breast milk and formula supplements the mean pH is approximately 5.7-6.0 during the first four weeks, falling to 5.45 by the sixth week
    - when formula supplements are given to breastfed babies during the first seven days of life, the production of a strongly acidic environment is delayed and its full potential may never be reached
    - breastfed infants who receive supplements develop gut flora and behavior like formula-fed infants
    - the dominance of bifidobacteria during exclusive breastfeeding decreases when infant formula is added to the diet (Favier et al, 2002)
- bifidobacterial numbers are higher in infancy and *Staphylococcus aureus* is lower in infancy for 7 year old normal weight children compared with children who become overweight. This implies that high numbers of bifidobacteria and low numbers of *S. aureus* during infancy as seen in breastfed infants may confer a degree of protection against overweight and obesity. Because adiposity is characterized by low-grade inflammation, the provision of breastmilk with its modulation of inflammatory pathways contributes to the protection of infants from the development of overweight and obesity (Kalliomaki et al,

2008)

- infant formula has a different effect on the architecture, hydrolysis, and absorption functions in the intestine compared with breastmilk.
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- The neonatal GI tract undergoes rapid growth and maturational change following birth
    - Infants have a functionally immature and immunonaive gut at birth
    - Tight junctions of the GI epithelial cells take many weeks to mature and close the gut to whole proteins and pathogens
    - Intestinal permeability decreases faster in breastfed babies than in formula-fed infants (Catassi, et al, 1995)
    - Any delay, change, or insult to the gut that changes this process predisposes the infant to infection, inflammatory states, and allergic sensitization (Maheshwari & Zemlin, 2009).
    - sIgA from colostrum and breast milk coats the gut, passively providing immunity during the time of reduced neonatal gut immune function
    - mothers' sIgA is antigen specific. The antibodies are targeted against pathogens in the baby's immediate surroundings
    - the mother synthesizes antibodies when she ingests, inhales, or otherwise comes in contact with a disease-causing microbe
    - these antibodies ignore useful bacteria normally found in the gut and ward off disease without causing inflammation

- infant formula should not be given to a breastfed baby before gut closure occurs
    - once dietary supplementation begins, the bacterial profile of breastfed infants resembles that of formula-fed infants in which bifidobacteria are no longer dominant and the development of obligate anaerobic bacterial populations occurs (Mackie, Sghir, Gaskins, 1999)
    - relatively small amounts of formula supplementation of breastfed infants (one supplement per 24 hours) will result in shifts from a breastfed to a formula-fed gut flora pattern (Bullen, Tearle, Stewart, 1977)
    - the introduction of solid food to the breastfed infant causes a major perturbation in the gut ecosystem, with a rapid rise in the number of enterobacteria and enterococci, followed by a progressive colonization by bacteroides, clostridia, and anaerobic streptococci (Stark & Lee, 1982)
    - with the introduction of supplementary formula, the gut flora in a breastfed baby becomes almost indistinguishable from normal adult flora within 24 hours (Gerstley, Howell, Nagel, 1932)
    - if breast milk were again given exclusively, it would take 2-4 weeks for the intestinal environment to return again to a state favoring the gram-positive flora (Brown & Bosworth, 1922; Gerstley, Howell, Nagel, 1932)
    - perturbations to the normal healthy colonization patterns of the gut can result in lifelong disease (Di Mauro et al, 2013). Such perturbations can be specifically caused by the use of infant formula which changes the bacterial population. Breastmilk's protective action relies mainly on its ability to modulate intestinal microflora composition during the early days of life (Guaraldi & Salvatori, 2012). The early bacterial colonizers of the infant's gut regulate the gene expression of the cells that line the digestive tract, creating a favorable environment for themselves which inhibits the growth of potentially pathogenic bacteria.
- in susceptible families, breastfed babies can be sensitized to cow's milk protein by the giving of just one bottle of infant formula, (inadvertent supplementation, unnecessary supplementation, or planned supplements), in the newborn nursery during the first three days of life (Host, Husby, Osterballe, 1988; Host, 1991). Small doses of allergens in the newborn nursery should be avoided to prevent allergic manifestations when subsequently challenged with cow's milk (Cantani & Micera, 2005)
    - infants at high risk of developing atopic disease has been calculated at 37% if one parent has atopic disease, 62-85% if both parents are affected and dependant on whether the parents have similar or dissimilar clinical disease, and those infants showing elevated levels of IgE in cord blood irrespective of family history (Chandra, 2000)

- cross reactivity exists between cow's milk protein and human milk protein (Bernard et al, 2000). Only 1 nanogram of bovine b-lactoalbumin is required to sensitize a susceptible infant (Businco et al, 1999)
- in breastfed infants at risk, hypoallergenic formulas can be used to supplement breastfeeding; solid foods should not be introduced until 6 months of age, dairy products delayed until 1 year of age, and the mother should consider eliminating peanuts, tree nuts, cow's milk, eggs, and fish from her diet (Zieger, 1999; AAP, 2000)
- stored frozen breast milk is the optimal choice for supplementing a breastfed baby, especially in the presence of high atopic risk; in the absence of stored breast milk, an extensively (not partially) protein hydrolyzed formula is recommended (Zeiger, 2003)
- study results on asthma and atopy can be confounded by the early introduction of infant formula, as small amounts of early formula may be damaging to the development of an infant's immune system; this should be considered in research analysis, even if a mother goes on to predominantly breastfeed (Oddy et al, 2003)

- in susceptible families, early exposure to cow's milk proteins can increase the risk of the infant or child developing insulin dependent diabetes mellitus (IDDM) (Mayer et al, 1988; Karjalainen, et al, 1992)
  - human insulin content in breast milk is significantly higher than bovine insulin in cow's milk; insulin content in infant formulas is extremely low to absent; insulin supports gut maturation
  - in animal models oral administration of human insulin stimulates the intestinal immune system generating active cellular mechanisms that suppress the development of autoimmune diabetes
  - the lack of human insulin in infant formulas may break the tolerance to insulin and lead to the development of type 1 diabetes (Vaarala et al, 1998)
  - the avoidance of cow's milk protein for the first several months of life may reduce the later development of IDDM or delay its onset in susceptible individuals (AAP, 1994)
  - infants who are exclusively breastfed for at least 4 months have a lower risk of seroconversion leading to beta-cell autoimmunity
    - short-term breastfeeding and the early introduction of cow's milk based infant formula predispose young children who are genetically susceptible to Type 1 diabetes to progressive signs of beta-cell autoimmunity (Kimpimaki et al, 2001)
  - sensitization and development of immune memory to cow's milk protein is the initial step in the etiology of IDDM (Kostraba, et al, 1993)
    - sensitization can occur with very early exposure to cow's milk before gut cellular tight junction closure
    - sensitization can occur with exposure to cow's milk during an infection-caused gastrointestinal alteration when the mucosal barrier is compromised allowing antigens to cross and initiate immune reactions
    - sensitization can occur if the presence of cow's milk protein in the gut damages the mucosal barrier, inflames the gut, destroys binding components of cellular junctions, or other early insult with cow's milk protein leads to sensitization (Savilahti, et al, 1993)
  - beta cell autoimmunity is increased in children who are not breastfed or breastfed for a short time. Early introduction of cow's milk based formula increases the risk for developing type 1 diabetes up to 5 years of age in the general population (Holmberg et al, 2007)

The Nutritional Committees from the American Academy of Pediatrics and jointly the European Society for Pediatric Allergology and Clinical Immunology and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommend exclusive breastfeeding as the hallmark for food allergy prevention (Zeiger, 2003; Muraro, et al, 2004))

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