



PEDIATRIC NUTRITION

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Enriching Infant Formulas for Optimal Health: A Review of the Evidence

It is well established that breast-feeding is best for all newborns. However, whether for medical or other reasons, not all mothers are able or choose to breast-feed their infant exclusively for the first six months. The alternative is an infant formula that best mimics breast milk. Formulas enriched with nucleotides help boost an infant's naïve immune system and offer better protection against pathogens. Not all formulas contain supplemental nucleotides, however, and pediatricians who are counselling mothers may wish to direct them to the appropriately supplemented formula brands.

Most new mothers do attempt to breast-feed their infants. Not all, however, succeed, and few manage to breast-feed exclusively for at least six months, as is recommended by the World Health Organization (WHO), among others. Indeed, according to results from a 2008 Canadian survey (<http://www.statcan.gc.ca/pub/89-599-m/89-599-m2008005-eng.htm>), fewer than half (47.4%) of mothers surveyed by Statistics Canada at the time breast-fed for at least six months and only about half of this group breast-fed exclusively. Thus, with so many mothers having difficulty with breast-feeding early on, it is important for physicians and other caregivers to recommend supplementation with an infant formula that closely mimics breast milk.

The Role of Nucleotides

To begin, mothers should be told that nearly all infant formulas will foster normal growth, even though they lack most of the protective factors contained in human breast milk that bolster the infant's immune system. Nucleotides—present in nearly all foods with the exception of cow's milk, which is particularly low in nucleotide content—serve as building blocks in the genetic code and help support the cellular proliferation of antibodies when an antigen or a vaccine triggers an immune reaction. However, nucleotide-supplemented formulas do contribute to the maturation of a naïve immune system and help protect infants against any number of pathogens.

Until infants begin eating solid foods, standard formulas may offer a relatively limited supply of nucleotides and this at

a time when their dietary supply would appear to be especially important, when infants are growing rapidly. Experimental analyses carried out on human milk indicate that it contains a total of 72 mg/L of nucleotides.

Today's formulation of Similac Advance contains the same amounts of nucleotides and studies support the beneficial effects of formulas supplemented to nucleotide levels identical to those of breast milk. Earlier findings indicated significantly higher antibody responses to both the *Haemophilus influenzae* type b (Hib) vaccine and the diphtheria vaccine were demonstrated at seven months in infants fed a nucleotide-fortified formula (72 mg/L) compared with a control formula. The higher Hib antibody responses also persisted at the age of 12 months in the supplemented cohort while significantly more infants in the supplemented group also achieved protective Hib antibody levels than infants fed control formula. Antibody levels in fortified formula-fed infants were also not different from those of breast-fed infants. In a subset analysis, infants fed the nucleotide-supplemented formula also had significantly fewer diarrhea episodes than those fed the unsupplemented formula.

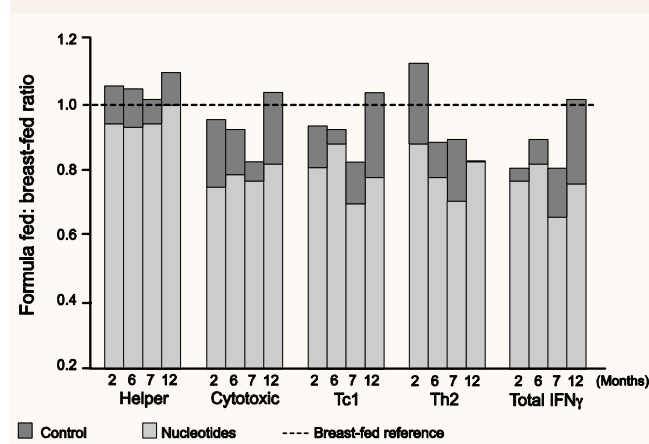
Among the more recent studies are those led by Buck et al. (*Pediatr Res* 2004;56:891-900) and Schaller et al. (*Pediatr Res* 2004;56:883-90). Both authors reported that infants fed nucleotide-supplemented formula had enhanced humoral and cellular responses compared to those who were not fed the supplemented formula (Figure 1).

In Schaller et al., infants fed the supplemented formula developed significantly higher levels of antibodies to one of

two poliovirus serotypes compared to infants who were fed an unsupplemented formula. Meanwhile, Buck et al. reported that nucleotide-fortified formula increased memory-effector T-cell subsets to a greater extent than unsupplemented formula and that levels of most T-cell subsets were very close to those of breast-fed infants.

Findings from Hawkes et al. (*Eur J Clin Nutr* 2006; 60:254-64) provide additional support for the beneficial effects of nucleotides on immune function. In this study, infants fed a nucleotide-supplemented formula (33 mg/L) for the first seven months of life exhibited a modest improvement in antibody response to tetanus vaccination at seven months compared to infants fed unsupplemented formula. Interestingly, the same supplemented feeding had no effect on antibody responses to either diphtheria toxoid or the Hib vaccine. This may be because the supplemented formula used in this study contained only 33 mg/L of nucleotides, far below the levels contained in either human breast milk or formula, where results demonstrated a favourable effect from nucleotide supplementation on antibody responses to both the Hib and the diphtheria vaccine.

Figure 1. Nucleotides Increased Memory-effector T-cell Subsets Similar to Breast-fed Infants



Adapted from Buck et al. *Pediatric Res* 2004;56:891-900.

Further evidence for a reduced incidence of diarrhea in infants who received a nucleotide-supplemented formula was again provided in a large observational study carried out in Italy (*Minerva Pediatr* 2000;52:699-711). In this prospective

observational study, 3315 infants were assigned to one of four groups: exclusively formula-fed infants whose formulas were (group 1) or were not (group 2) supplemented with nucleotides; human-milk-fed infants mixed-fed with either a nucleotide supplemented formula (group 3); or infants fed an unsupplemented formula (group 4). The relative risk of an infant having a diarrheal episode was approximately half that in group 1 compared with group 2, and approximately 75% lower in group 3 compared with group 4.

Yau et al. (*J Pediatr Gastroenterol Nutr* 2003;36:37-43) similarly observed that a nucleotide-supplemented group of one- to seven-day-old infants had higher levels of serum IgA than control infants while the incidence of diarrhea was again significantly lower in infants fed the same nucleotide-enhanced formula between weeks 8 and 28, with the trend continuing out to 48 weeks.

Collectively, these findings suggest that infants fed formulas containing levels of nucleotides equal to those in mother's milk may have an immune system advantage compared with infants fed formulas with lower nucleotide content. Nucleotide-supplemented formulas also appear to be associated with fewer diarrhea episodes, a not inconsequential finding, not only in terms of the potential effect that persistent diarrhea can have on growth but from a quality of life perspective as well.

Summary

As Schaller et al. concluded in their review of the ribonucleotides and their effect on immune function and diarrhea in infants (*Semin Fetal Neonatal Med* 2007;12:35-44), most relevant studies demonstrate that the addition of nucleotides to formulas are associated with clear immunologic benefits not seen with unsupplemented formulas. Furthermore, the studies also show that the immunological benefits associated with nucleotide-supplemented formulas are similar to those provided by human milk. These benefits include positive changes in immune cell populations, enhanced antibody responses to various vaccine antigens and reduced episodes of diarrhea. Collectively, it can thus be stated that supplementation of infant formulas with appropriate levels of nucleotides support immune development and function and that this finding is consistent with the concept that nucleotides are conditionally essential as nutrients for the developing neonate, as Schaller et al. concluded. □

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