



PEDIATRIC NUTRITION

January 2011

**Nucleotide-fortified Formulas Can Boost Neonate Immunity,
Gastrointestinal Tract Maturation**

Nucleotides present in human milk are believed to be important for the development of neonatal immune function as well as the growth and maturation of the gastrointestinal tract. Given that breast milk remains the gold standard for infant nutrition, research has focused on ingredients that would allow infant formulas to more closely resemble the performance of human milk. Nucleotides represent one of these ingredients. Studies have shown that dietary nucleotides enhance a number of immune responses as well as the growth, differentiation and repair of the gut. Nucleotide supplementation has also been associated with a reduced incidence of diarrhea. Most infant formulas now have some degree of nucleotide supplementation; however, the amounts added are not always the same and supplementing infant formula with nucleotide levels that are similar to those in human milk is felt to offer the best opportunity to approximate the benefits of natural nucleotides in the formula-fed infant.

Human breast milk is the gold standard by which all other sources of infant nutrition are compared. Amongst its many advantages, it offers considerable immune benefits to the newborn baby's immature immune system. To meet the environmental challenges that occur after birth, an infant's immune system must develop rapidly during the first 2 years of life.

Human milk contains a variety of natural compounds that help the development of the infant's immune system. Nucleotides are one of the immunomodulating factors found in human milk. They serve as building blocks of DNA and RNA for cells in the body, including important immune system cells. According to Schlimme et al. (*Br J Nutr* 2000;84 (suppl 1):S59-S68), nucleotides are involved in essential metabolic reactions in cells. This is particularly important for the gut, where cell turnover is high and nucleotides are constantly required in the formation of these new cells. Furthermore, it is important to note that the gut plays a key role in the immune system. Approximately 70%-85% of the body's immune system is located there.

Rapidly growing infants need nucleotides for protein synthesis and cell growth. Nucleotide requirements are met by a combination of de novo synthesis, salvage (from endogenous sources) and from the diet. During periods of additional demand—rapid growth or illness, for example—infants may not be able to synthesize or salvage enough nucleotides and dietary nucleotide sources may be necessary

to supplement nucleotide synthesis (Carver JD. *Acta Paediatr* 1999;88(suppl 430):83-8).

In a meta-analysis of nucleotide-supplemented infant formula, Gutiérrez-Castrellón et al. (*Br J Nutr* 2007;98 (suppl 1):S64-S67) reviewed available evidence to establish the efficacy, safety and dose-response effect of nucleotide-supplemented infant formula. Nine studies were included in the analysis which showed that nucleotide-fortified formulas were associated with better antibody responses to immunization with *Haemophilus influenzae* type b (Hib) vaccine, diphtheria toxin and oral polio vaccine (OPV) compared to formula without nucleotides (control formula). Nucleotide-fortified formulas were also associated with fewer episodes of diarrhea than control formula. Moreover, they report considerably greater effects for the selected end points as well as significantly larger clinical and statistical differences in the infants who received formulas with a higher level of supplementation. Consequently, they concluded that while the evidence supports the supplementation of formula at levels of at least 33 mg/L, "It is important to note that 50% of the evidence from studies with formula supplemented with 72 mg/L show greater effects on end point variables."

Although nucleotides have been added to infant formula since 1997, most Canadian infant formula companies supplement only up to 28 mg/L. The only brand of infant formula with a higher level of nucleotide supplementation is Similac, providing 72 mg/L.

Immune Status

Schaller et al. (*Pediatr Res* 2004;56:883-90) specifically analyzed the effect of supplemental nucleotides on infant immune status as measured by antibody responses to routine infant immunizations. A cohort of human milk-fed infants was also included. Infants received Hib vaccine, diphtheria tetanus acellular pertussis (DTaP) vaccine and OPV at 2, 4 and 6 months of age and antibody responses were assessed at 2, 6, 7 and 12 months.

Results indicated that infants who received the formula supplemented with nucleotides had significantly higher OPV type 1 neutralizing antibody (PV-VN1) responses than infants who received the same formula minus the nucleotides. Indeed, PV-VN1 responses in infants fed human milk were not different from infants who were fed the nucleotide-fortified formula.

In contrast, PV-VN1 responses were significantly higher at 6 months among infants who were fed human milk than among those who received the unfortified formula. However, responses to Hib, diphtheria, tetanus toxoid, OPV-specific IgA and PV-VN3 were not significantly different among infants fed the nucleotide-fortified formula than responses seen in either the human milk-fed infants or those fed the unfortified formulation, even though there was a trend towards increased Hib and diphtheria antibody response among the nucleotide group.

In summary, the group fed formula fortified with nucleotides at 72 mg/L had higher antibody responses following 3 doses of oral poliovirus vaccine compared to the control group and, statistically, the levels were not different from that of the breast-fed infants.

Additionally, growth measures were similar between the 2 formula-fed groups and both showed comparable growth to infants fed human milk.

Immune Function, Diarrhea, Birth Weight

The same infant cohorts were also investigated by Buck et al. (*Pediatr Res* 2004;56:891-900), who sought to determine whether dietary nucleotides altered immune cell phenotypes or function in the first year of life. They concluded that nucleotide-associated increases in memory/effector T-cell populations as well as changes in natural kill (NK) cell subtypes observed in the nucleotide group provide evidence that infant formula supplemented with levels of nucleotides similar to levels in human milk may facilitate maturation and immunoregulatory

shifts in some lymphocyte populations consistent with those seen in human milk-fed infants. "These shifts might support increased antibody responses and immune cell protection," they added, "while the nucleotide-associated changes in immunoregulatory NK cell subsets may also enhance innate immune responses against tumours and/or intracellular pathogens." Their research showed that infants fed formula supplemented with nucleotides at 72 mg/L had immune cell profiles that more closely resembled those of babies fed human milk compared to infants fed formula without nucleotides.

Yau et al. (*J Pediatr Gastroenterol Nutr* 2003;36:37-43) similarly randomized infants between 1 and 7 days old to receive a formula fortified with 72 mg/L nucleotides or a control formula without nucleotides. At 48 weeks of age, investigators found that serum IgA concentrations—a component of humoral immunity—had increased in both groups; however, at every subsequent measurement, serum IgA concentrations were higher in infants fed the nucleotide-fortified formula than in controls. The risk of diarrhea was also about 25% lower among infants fed the nucleotide-fortified formula and stools were more frequent and softer than those of control infants. Softer stools are characteristic of breast-fed infants and are therefore desirable.

As observed in a different analysis (Yu V. *J Paediatr Child Health* 2002;38:543-9), the number of first episodes of diarrhea was found to be significantly lower in another group of infants fed a nucleotide-supplemented formula compared to those who were fed a non-supplemented formula, although no significant differences were found in the presence or type of enteropathogens between the 2 groups.

Carver (*Acta Paediatr* 1999) noted that an infant recovering from diarrhea requires nucleotides to replace intestinal mucosal cells and to maintain normal growth; as such, they may benefit from supplemental nucleotides in a period of high demand.

Summary

Nucleotides are increasingly considered by nutrition experts to be "conditionally essential," in that they may become essential when the endogenous supply is insufficient to meet elevated demands. Under conditions of rapid growth, for example, dietary nucleotides may optimize the function of rapidly dividing cells, including cells in the GI tract and the immune system. Given that no adverse effects have been reported in healthy infants fed nucleotide-supplemented formulas, these have the potential to offer tangible health benefits for young infants. □

To view an electronic version of this publication along with related slides if available, please visit www.mednet.ca/2010/ho11-003e.

© 2010 Health Odyssey International Inc. All rights reserved. INTEGRATIVE MEDICINE REPORT® is an independent medical news reporting service providing educational updates reflecting peer opinion from accredited scientific medical meetings worldwide and/or published peer-reviewed medical literature. Views expressed are those of the participants and do not necessarily reflect those of the publisher or the sponsor. Distribution of this educational publication is made possible through the support of Abbott Nutrition Canada under written agreement that ensures independence. Any therapies mentioned in this publication should be used in accordance with the recognized prescribing information in Canada. No claims or endorsements are made for any products, uses or doses presently under investigation. No part of this publication may be reproduced in any form or distributed without written consent of the publisher. Information provided herein is not intended to serve as the sole basis for individual care. Our objective is to facilitate physicians' and allied health care providers' understanding of current trends in medicine. Your comments are encouraged.

Health Odyssey International Inc.
132 chemin de l'Anse, Vaudreuil, Quebec J7V 8P3
A member of the Medical Education Network Canada group of companies

