PEDIATRIC Perspectives® NEWSLETTER

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To be allergic or not

A question of predisposition and allergen exposure

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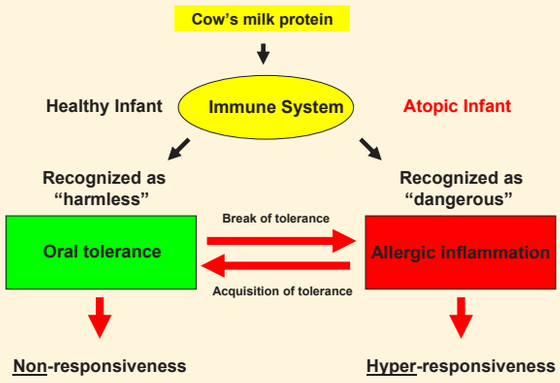
One of the most common allergies in children involves cow's milk, which contains approximately 20 different proteins that can cause allergic reactions. In cow's milk protein allergy, the immune system recognizes normal, harmless cow's milk proteins as "dangerous," resulting in allergy symptoms **(Figure 1)**. Allergic reactions to cow's milk proteins typically begin early in infancy (within the first weeks to months) at the skin, gut and airways.

Figure 1: The Role of Diet in Allergy: Tolerance or Sensitization?

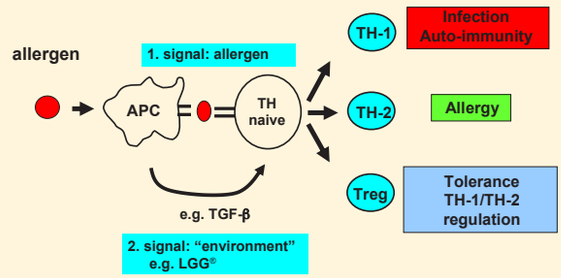


It is well known that some children exhibiting clinical signs of cow's milk protein allergy early in life also develop allergy-related diseases such as rhinitis and asthma later in life. Therefore it is crucial to manage early sensitization and symptoms of cow's milk protein allergy appropriately and effectively, not only to manage the immediate symptoms but also to influence the subsequent "allergic march"[1].

The fundamental pillar in the dietary management of cow's milk protein allergy is the strict allergen avoidance. This avoidance addresses the allergic symptoms by removing the offending proteins. However, the ultimate goal of the dietary management of cow's milk protein allergy is not only to manage the acute symptoms, but concurrently to modify the course of the allergic disease. Achieving oral tolerance, such that the immune system no longer recognizes the protein as dangerous but instead sees it as harmless, is the ultimate goal **(Figure 1)**. Oral tolerance to cow's milk describes an acquired state in which the infant does not react to cow's milk proteins. This state is a highly regulated process in which the T-cells play a crucial role **(Figure 2)**. From an immunological point of view the development of oral tolerance is an active process which requires 2 types of signals. The 1st signal is the recognition of cow's milk protein residues and the 2nd signal determines the type of immune response, allergic versus tolerance, respectively **(Figure 2)**.

In terms of the 1st signal, several studies have assessed the capacity of hydrolyzed cow's milk based formulas in managing cow's milk protein allergy. One important learning from these studies is that the degree of hydrolysis does not predict the capacity of inducing oral tolerance, but rather it is the unique protein and nutrient composition of the formula itself[2]. In these clinical studies, Nutramigen® A+®, an extensively hydrolyzed formula, was shown to be effective in reducing the risk of allergy symptoms associated with the gut and skin[3,4]. The capacity of hydrolyzed cow's milk based infant formulas in allergy management has been extensively reviewed by several expert groups and medical societies including the European Academy of Allergy and Clinical Immunology (EAACI) and recommendations for use are published accordingly[5-8].

Figure 2: The immune system requires 2 signals to develop oral tolerance



APC = antigen presenting cell
LGG® = *Lactobacillus rhamnosus GG* (a licensed trademark of Valio Ltd)

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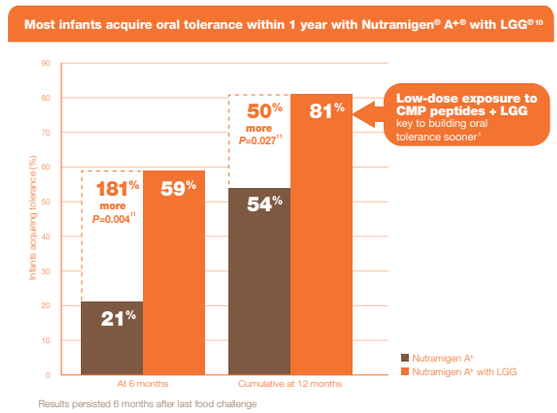
It is well established that exclusively breastfed infants have a lower risk of developing cow's milk protein allergy by building oral tolerance early in life to cow's milk proteins. This result may be related to the combination of very low amounts of cow's milk residue and immunological co-factors favoring the development of oral tolerance present in breast milk. Interestingly, Nutramigen® A+® contains a similar amount of these immuno-reactive cow's milk proteins as found in breast milk[9].

One study has demonstrated that by combining Nutramigen® A+® with Lactobacillus rhamnosus GG, the development of oral tolerance can be accelerated[10] **(Figure 3)**. Additionally, another study noted that the combination of Nutramigen® A+® and Lactobacillus GG helped more infants develop oral tolerance than other formula types commonly used for allergy, such as extensively hydrolyzed, rice, soy, and amino acid-based.*[12] These studies suggest that the combination of low dose exposure to hydrolyzed casein peptides in the formula and Lactobacillus rhamnosus GG seem to direct the immune response to build oral tolerance early in life. While this result indicates that faster oral tolerance development could be a novel approach in the management of CMPA, further research is needed to identify the exact molecular mechanism and to describe the sequences of these peptides in extensively hydrolyzed formulas.

Figure 3



In conclusion, low dose exposure to food allergens in human milk contributes to the efficacy of breast milk in development of oral tolerance early in life. From an immunological point of view, development of oral tolerance requires exposure to cow's milk protein residue in combination with co-factors favoring oral tolerance. The dietary intervention with hydrolyzed cow's milk based formulas in combination with Lactobacillus rhamnosus GG is a feasible approach to promote development of oral tolerance to cow's milk proteins early in life.

* Products tested: EHCF group: Nutramigen (Mead Johnson Italy), Nutriben hydrolyzed (Nutriben Italy), EHCF+LGG group: Nutramigen LGG (Mead Johnson), Hydrolyzed Rice formula: Risolac (Plasmon, Italy), Soy formula: Isomil (Abbott, Italy), Sinelac (Humana, Italy), Nutrilon Soya (Nutricia, Italy), Amino Acid formula: Neocate (Nutricia), Nutramigen AA (Mead Johnson), Sineall (Humana)

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