

Immunological Basis and Management of Food Allergy

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ABSTRACT

One of the most common allergies in children involves cow's milk, which contains approximately 20 different proteins that can cause allergic reactions. It is well known that children exhibiting signs of cow's milk allergy early in life often go on to develop allergy-related respiratory diseases; thus, management of early sensitisations and symptoms of food allergies is crucial to preventing subsequent allergic complications. Constant allergen exposure and other environmental factors determine whether a sensitised individual will become chronically allergic and experience persistent symptoms. Management of food allergies in children focuses on minimising sensitisation and encouraging immune system maturation through the exposure of children to exogenous stimuli known to prime the immune

system. Hypoallergenic molecules or allergen avoidance can also be used to induce tolerance in allergy-prone children. Available evidence suggests that the onset of the sensitisation phase and the degree of inflammation can be modulated by external factors such as nutrition, and guidelines outlining the most effective dietary regimen for the prevention of allergic disease have been published. The underlying mechanisms of tolerance induction and the potential benefits of prophylactic treatment for food allergies remain to be determined. *JPGN* 47:S54–S57, 2008. © 2008 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

From an immunological viewpoint, food allergies comprise a diverse set of diseases with major health implications. Food allergies are more frequent in children (6%–10%) than in adults (3%–4%), and the most common allergies involve cow's milk (in children), and eggs and peanuts. The symptoms of an adverse reaction to foods may include immediate gastrointestinal (GI) symptoms, eosinophilic gastroenteritis, urticaria, atopic dermatitis, bronchospasm, asthma, coeliac disease, and anaphylaxis.

Cow's milk allergy (CMA) and peanut allergy reach peak prevalence between birth and 2 years of age. Although 50% of cases of CMA are diagnosed within the first month of life, its prevalence largely declines by 3 years of age. In contrast, peanut allergy is maintained as a lifelong allergy and allergen avoidance is the most common management option.

It is also well established that early allergic manifestations of CMA are often associated with the later development of respiratory allergic manifestations. As the sensitisation to food allergens declines during the first few years of life, that to aeroallergens increases; this is paralleled by a switch of the affected organs from skin and the GI tract to the lungs. Most of the infants (64%) who are sensitised early to cow's milk and have severe skin-related manifestations subsequently develop asthma

in later childhood. The challenge is to appropriately manage early sensitisations and clinical symptoms to food allergens to reduce the risk for later onset of respiratory diseases.

PRIMARY AND SECONDARY PREVENTION STRATEGIES

Although food allergies comprise a diverse set of diseases, they share a common immunological basis that is characterised by sensitisation to food allergens and local inflammation at the site of allergen exposure. The onset of allergies involves complex interactions between exogenous factors such as allergen exposure, infections and other environmental stimuli, and genetically determined factors (Figure 1; see also Helen Cox's article in this supplement). It is well known that the risk for neonates' developing allergies is strongly influenced by genetic factors: infants with a mother or sibling with food allergies have a 50% to 70% risk for developing some kind of an allergic manifestation. Although there is no doubt that the genetic background predisposes to the development of allergies, the immediate environment also plays a crucial role in determining the time of onset, maintenance, and severity of allergies.

Allergy development can be divided into 2 phases: sensitisation and chronification. The sensitisation phase is characterised by the development of an allergen-specific

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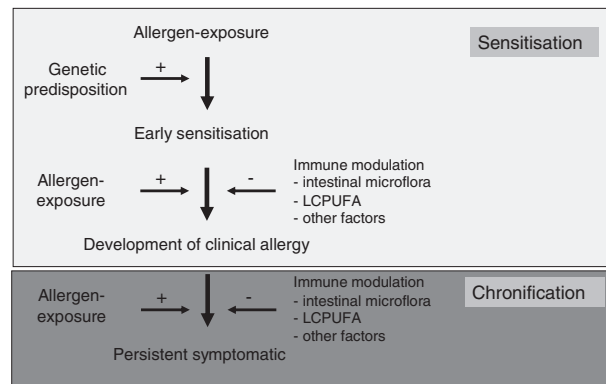


FIG. 1. Primary and secondary strategies in prevention of allergy. LCPUFA, long-chain polyunsaturated fatty acids.

immunoglobulin E (IgE) antibody response. During the past few decades our knowledge of the immunological basis of allergy has dramatically increased. Many cells, immunological factors, and pathways related to how an allergen induces an allergic immune response have been identified. In principle, at the site of exposure allergens are taken up by antigen-presenting cells (APC). Those APCs located in the gut and lung mucosa present processed allergen fragments to naïve T helper (Th) cells. These APCs together with other stimuli determine whether the T helper cells develop a phenotype that regulates the onset of allergic sensitisation (Th2 type T cells) or whether the T helper cells develop tolerance (T regulatory cells)

(Figure 2). Th2 T cells secrete mediators such as cytokines (eg, interleukin [IL]-4, IL-5, IL-13), which trigger B cells to produce antibodies of the subclass IgE. Cross-linking of IgE antibodies on the surface of mast cells triggers histamine release and immediate onset of reactions (immediate type 1 hypersensitivity reaction) after exposure to small volumes of cow's milk. The effector phase of an allergic reaction, which occurs within 12 to 24 hours, is characterised by an acute inflammatory immune response at the site of allergen exposure. This response is also regulated by Th2 T cells by acting on the development, maturation, and recruitment of effector cells such as eosinophils and neutrophils at the site of allergen exposure.

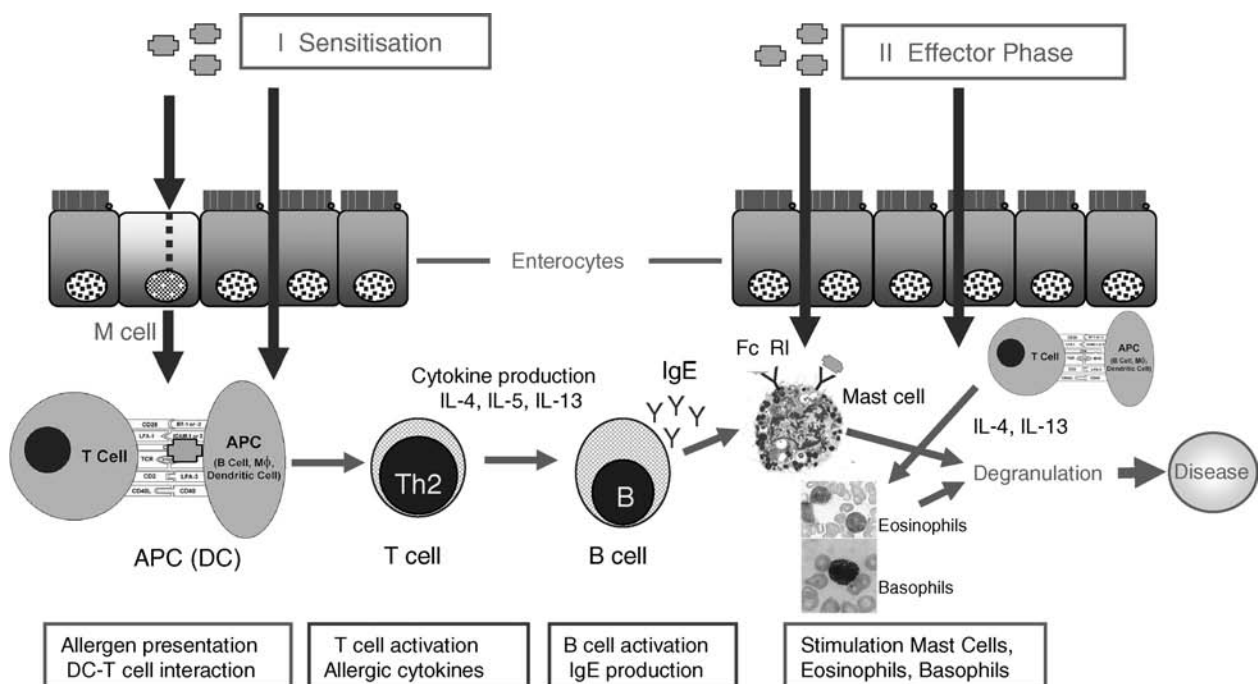


FIG. 2. Immunopathogenesis of allergy. APC, antigen-presenting cell; DC, dendritic cell; IgE, immunoglobulin E; IL, interleukin. Reproduced with permission from E.A.F. van Tol, Mead Johnson Nutritionals, USA.

T cells also play a critical role in the second phase of the development of allergic manifestation: the chronification of the disease state. T cells regulate the development, maturation, and recruitment of effector cells such as eosinophils and neutrophils, but are also involved in the onset and perpetuation of tissue remodelling. This chronification process results in structural mucosal changes that limit therapeutic options at this disease stage. Therefore, strategies for preventing the onset and the persistence of an allergic manifestation are needed.

There is promising evidence that the onset of the sensitisation phase as well as the degree of inflammation can indeed be modulated by external factors such as nutrition (eg, long-chain polyunsaturated fatty acids [LCPUFA], probiotics, prebiotics). The efficacy in allergy prevention for some of these factors has been studied in prospective, randomised double-blind placebo-controlled studies in individuals followed up to 7 years old. More studies are needed to further evaluate the underlying mechanism of mucosal tolerance induction (1–3).

There are also critical environmental factors such as the intestinal microflora and LCPUFA, which promote or prevent the onset of allergic diseases that may play a role in determining whether a particular individual will have allergic manifestations. Continuous allergen exposure and other environmental factors determine whether an individual will enter the chronification phase and experience persistent symptoms. At this stage therapeutic options are limited to anti-inflammatory medication plus specific immune therapy.

DIAGNOSIS AND MANAGEMENT OF CMA

In the management of food allergy in young children, there are a number of diagnostic tests and procedures that may help establish an early allergy diagnosis (4,5). The double-blind placebo control food challenge (DBPCFC) has become the gold standard for diagnosis of food allergy, and this test should be performed at specialised centres. A pragmatic approach to the diagnosis of CMA was recently published and provides guidance for IgE-mediated as well as for non-IgE-mediated symptoms suggestive of CMA (6). Clear-cut cases such as those with a history of anaphylactic food reactions should undergo an elimination diet. In infants with suspected CMA, a comprehensive history (including a family history of atopy) and careful physical examination form the foundation for further diagnostic tests such as the skin prick test, atopy patch test, and determination of specific IgE, which could aid in disease management.

There are approximately 20 different proteins in cow's milk that cause allergic reactions. Infants exhibit individual IgE reactivity profiles and, therefore, all

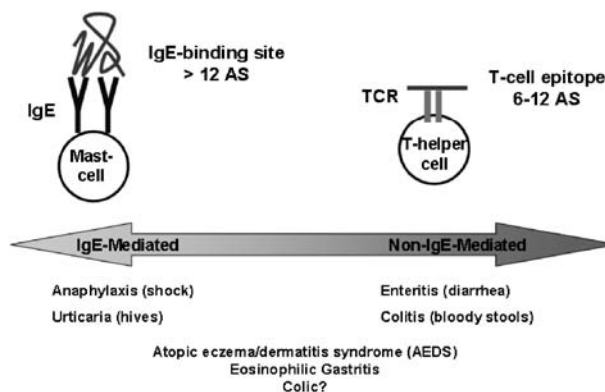


FIG. 3. The principle of hypoallergenicity involves destroying conformational and linear epitopes. IgE, immunoglobulin E; TCR, T cell receptor.

cow's milk allergens must be destroyed; this is the concept of hypoallergenicity. It is of particular importance that both conformational and linear epitopes must be destroyed (Figure 3). There are a number of technologies that reduce the allergenicity of a protein including heating, enzymatic hydrolysis, and ultrafiltration (7). A combination of these technologies is most commonly used in the production of infant formula. IgE-mediated reactions are triggered by proteins of >12 amino acids in length, which have conformational epitopes. Non-IgE-mediated reactions are triggered by T cell epitopes, which cover 6 to 12 amino acids in length. Extensive hydrolysis produces proteins consisting of a maximum of 2 to 3 amino acids. In principle, the higher the degree of hydrolysis the lower the chain length, which is often shown by the molecular weight profiles (<500 kDa), and the lower the residual allergenicity of a protein/peptide. IgE and T cell receptor binding are absent at <500 kDa.

In clinical terms, hypoallergenic formulas are defined as those that are tolerated by $\geq 90\%$ of infants with documented CMA (minimum of 30 patients tested) who are exposed to the tested formula following an elimination diet (8,9). Hypoallergenicity should be assessed separately in infants with IgE-mediated and non-IgE-mediated CMA.

DIETARY INTERVENTION IN ALLERGY PREVENTION

In healthy infants, cow's milk protein triggers immune memory and tolerance occurs. In contrast, in atopic infants sensitisation occurs and the immune system is triggered upon subsequent exposures to cow's milk. Whether the immune system develops immunological tolerance or an allergic immune response depends on many factors. It is now generally accepted that allergen sensitisation begins

in utero. In the early postnatal period, the allergic immune response is restricted by maturing T regulatory cells and/or Th1 immunity, and by 5 years of age normal patterns of immunity appear to be established in nonatopic individuals (10). There is accumulating evidence that in at-risk infants this maturation process begins at a lower level and may not reach the patterns of immunity established in nonatopic individuals. This maturation of the immune system requires environmental stimuli. During the first 12 months of life, there appears to be a critical period during which exogenous stimuli prime the immune system (9). Certain environmental stimuli that affect the development of allergies including tobacco smoke, breast-feeding, LCPUFA, gut microbiota, probiotics, and allergen exposure have been identified.

Hypoallergenic molecules and/or allergen avoidance may be 1 additional possible route to inducing immunological tolerance in allergen-prone infants. The role of partially hydrolysed and extensively hydrolysed formulas for the prevention of atopic disease has been the focus of many studies (8,11). Recently a large, prospective, multi-centre study from the German Infant Nutritional Intervention Program has investigated the allergy preventive effect of 3 hydrolysed formulas compared with cow's milk formula in the first 3 years of life. The 3 hydrolysed formulas were a partially hydrolysed whey-based formula, an extensively hydrolysed whey-based formula, and an extensively hydrolysed casein-based formula. Only the extensively hydrolysed casein formula was shown to prevent the onset of allergic manifestations such as atopic dermatitis, allergic urticaria, and GI manifestations relative to cow's milk formula (12). One notable conclusion from the German Infant Nutritional Intervention Program is that the degree of hydrolysis, the resulting molecular weight, and the protein source have little predictive value for the immunogenic or allergenic effect or the capacity to prevent the onset of allergies (13–15). This study, however, provided evidence that prophylactic treatment with a hypoallergenic fragment of cow's milk may prevent the onset of sensitisation.

SUMMARY

Milk allergy is the first manifestation of the “allergic march.” Cow's milk has a number of allergens and hypoallergenicity is an important principle for the dietary management of food allergy. Dietary intervention is effective in the prevention of allergic diseases in high-risk infants, particularly in early infancy with regard to food allergy and eczema. The current guidelines recommend that the most effective dietary regimen is as follows (16–18):

- Exclusive breast-feeding for at least 4 to 6 months
- Formulas with documented reduced allergenicity for at least the first 4 months, combined with

avoidance of solid food and cow's milk for the first 4 months.

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