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Allergy

NEWSLETTER

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Introduction

Allergy in childhood is common. The cumulative prevalence of asthma in childhood may be 39%. Today there are two common ways of demonstrating IgE antibodies used in everyday clinical care: in vivo allergen skin prick testing (SPT) and in vitro measurement of serum allergen-specific IgE.

Allergen skin testing

This is a safe, practical and highly patient- and parent-acceptable way to look at allergen sensitivity in infants and children. A small amount of standardized allergen is introduced epicutaneously, using a standard single- or double-tined lancet. It is important to note it is no longer accepted practice to use a small-gauge hypodermic needle, or to use a single lancet for multiple allergens. Allergen cross-bridging of IgE fixed on mast cells results in release of vasoactive histamine and other mediators of inflammation. Within 10 min a palpable itchy 'urticarial' papule or wheal appears, not unlike a mosquito bite. The wheal is measured. The older practice of comparing the wheal size to that of response to the histamine control is no longer supported, as clinicians can now use absolute wheal size expressed in mm to predict clinical reactivity, as assessed in a food challenge.

The SPT controls

However, it is still important to always use a histamine positive control, to ensure that the child is actually able to mount a wheal and flare response (thereby validating any wheal response that is elicited by an allergen), and is not taking an anti-histamine, which would block such a response. A negative (saline) control is always used to ensure that the child does not have dermographism or a pressure sensitivity.

The SPT can be undertaken in infants and young children and is noted for its safety and acceptability. Most adverse reactions to SPT occur in subjects with unstable allergic conditions, particularly inhalant allergen-associated asthma. These children are identifiable by history and should have SPT performed in a hospital setting.

In older children and adults the volar (palmar) aspect of the forearm(s) is used; in infants the back is the best, as the infant can be held and comforted against a parent or assistant.

Allergen SPT is difficult if there is widespread eczema. It is said to be unreliable soon after an anaphylactic episode (when the mast cells have all degranulated and require 're-stocking'). Apart from anti-histamines, common drugs have little effect and oral steroids and topical calicineurin inhibitors for eczema such as tacrolimus appear to have no adverse effect.

Prick–prick testing

Some allergens, notably those from fruits and vegetables, are unstable and the best way of demonstrating sensitivity to these [in such cases as the oral allergy syndrome (OAS)] is by using the fresh fruits and vegetables. These are then cut and either a drop of juice is placed on the skin and the lancette is pushed through this or the lancette is inserted into the fruit and then directly into the forearm ('prick–prick method'). Because there is still no universally accepted standardized unit of reactivity for SPT solutions, some units never use commercially available SPT solutions and use only fresh foods, such as cow's milk, egg white, etc.

Intradermal testing, where a much larger dose of allergen (approximately 200 times greater than SPT) is injected into the skin, is now generally reserved for the identification of drug sensitivities. End-point titrated SPT is not part of routine clinical practice but is making a comeback in the setting of deciding start doses for specific oral tolerance induction (discussed below).

It is important not to use too many allergens when testing as SPT is specific, particularly for common food allergens, but it is not sufficiently sensitive. Testing should be restricted to those allergens that are implicated by history [e.g., in asthma test for house dust mite (HDM), cat, grass] or where there is a high likelihood of co-existing allergies (in infants test for milk and egg, e.g. or in older children it is completely justified to skin test peanut allergic children with tree nuts).

Above a certain wheal size for milk, egg and peanut (8, 7 and 8 mm respectively), a universal positive reaction is seen on open food challenge. However, this did not hold for wheat, fish or soya. These published 'decision points' are used widely in practice to decide who would or would not pass a food challenge. They have been developed usually in highly selected populations of subjects who have usually reported clinical reactivity, and/or have undergone formal food challenges; therefore, they are not easily applicable to subjects with high specific IgE levels (e.g. to egg or peanut) but no history of reactivity.

In vitro IgE

Our experience is that measuring total IgE rarely adds to the diagnostic process, as most children seen have raised levels. Total IgE is not an allergy screen, but may be

useful in the interpretation of specific IgE results.

The system used in most UK laboratories to measure allergen-specific IgE in blood is the ImmunoCAP® system. This is a modification of the original radioallergosorbent test (RAST). There is a wide choice of commercially available native allergens and individual 'component' allergenic proteins and recombinant proteins. The results are expressed in international units of IgE (kUA/L) and no longer in RAST classes.

Specific allergic conditions

Food allergy

The largest proportion of the infants and children referred for evaluation are for the clarification of a suspected allergic adverse reaction to food. The story given is usually clear-cut. Exposure to a food (e.g. milk) to which the child is sensitized results in an immediate (within minutes) reaction causing a constellation of symptoms [lip tingling; lip swelling; lip, facial, body urticaria; redness; tiredness; vomiting; laryngeal swelling, stridor; dry cough, wheeze, severe wheeze, cyanosis; older children report a sensation of impending doom; collapse and hypotension (although cardiovascular symptoms are unusual in children)]. The 'usual suspects' in young infants and children are cow's milk, egg and peanut. Occasionally, reactivity to soya and wheat can be verified. In older children reactivity to tree nuts, fish and shellfish become more common. The cited foods, along with lupin, mustard, molluscs, sulphites and seeds, form the list of ingredients that must be declared on ingredient labels in the European Union, irrespective of amount or concentration (Table 1).

However, there is a myriad of foods (and also crossreactions, e.g. between banana, kiwi and latex; cow's milk and goat's milk) which can cause reactions, so the clinical history needs to be taken carefully. Reactions caused by less common allergens such as potato, peach, grape, etc. should not be overlooked. There are important regional variations which reflect local diet.

It is common for parents to ask if it is true that subsequent reactions are more severe than the presenting one. The Cambridge group has shown that subsequent reactions to peanut and tree nuts tend to be similar. When under expert care, nearly all patients self-treat appropriately when they next experience an allergic reaction. Variability of reactions as has been shown for peanut, for example, more probably reflects the interplay of co-factors such as dose, viral infection, the new onset of asthma after the primary diagnosis of food allergy, the effect of exercise and, in adults, use of alcohol and prescribed medication.

Table 1. List of allergens that must be declared on food labels in the European Union, irrespective of amount or concentration.

• Cow's milk	• Eggs	• Fish
• Crustaceans	• Sesame	• Peanuts
• Gluten containing grains (wheat, rye, barley, oats)		
• Tree nuts	• Soya	• Mustard
• Celery	• Sulphites	• Molluscs
• Lupin		

Physical examination is not usually helpful in the diagnosis of food allergy, but the presence of eczema, Dennie-Morgan folds (multiple wrinkles beneath the lower eyelid) and an allergic crease are suggestive. In older children it is critical that asthma is properly identified and controlled.

Food challenge

Only a third of reactions reported in infants can be substantiated by challenge, as other mechanisms of adverse reactions may be operating. Food challenges are also used to investigate asymptomatic sensitization to associated foods detected at diagnosis, and especially to determine resolution of food allergy. It requires experience to time a challenge optimally so that exclusion diets are not sustained for too long. Food challenges are easily blinded, but this is rarely necessary in routine practice.

Once food allergy is confirmed, avoidance of that food is necessary. Experienced dietetic input is critical, especially for infants and smaller children to ensure nutritional adequacy and in older children with multiple food allergies. Soya milk is neither advised for treatment of young infants with cow's milk allergy nor for prophylaxis in asymptomatic infants. An extensively hydrolysed milk formula or an amino acid-based formula which have reduced and no allergenic activity, respectively, are required. Partially hydrolysed formulae are often used in Europe. There is no role for other mammalian milks, such as goat's milk, in the treatment of cow's milk allergy.

Natural history of food allergy

Most infants allergic to milk and egg become tolerant to these foods by school age, although resolution rates in referred populations are lower. Peanut allergy resolves in about 25% of cases. Longitudinal follow-up is therefore needed to distinguish 'resolvers' from 'persisters'.

Eczema

Eczema and food allergy are common bedfellows in infancy and there is a strong association between severe eczema and food allergy in children under 1 year of age. This association attenuates over time. It does not appear useful to screen older children with eczema for food allergies. In infants aggressive treatment should be aimed at all possible aggravating factors (using extensively hydrolysed or amino acid formulae in infancy; potent topical steroids or calcineurin inhibitors, antibiotics, emollients and moisturizers, anti-histamines) to improve the skin quickly; once 'healed' it is less prone to flare. The

diet can then be liberalized one food at a time and the response of the eczema to foods noted. In older children HDM allergy plays an important role, although the distribution of eczema may be different (exposed hands, feet and neck).

Aero-allergen allergy

Allergic conjunctivitis and allergic rhinitis are common and have significant socio-economic effects because of poor school performance, decreased quality of life and other direct and indirect health-care costs. The major allergens are from pollens (grass, tree and weeds), pets (cats, dogs, rabbits, horses) and HDM. Specific IgE assays for to all these allergens are available. HDM and cat are common 'perennial' allergens in the United Kingdom and pharmacological treatment may be needed year-round. Nasally inhaled corticosteroids are very effective in most cases of allergic rhinitis, but do not alter the natural history of the condition. Subcutaneous injected (SCIT) and sublingual immunotherapy (SLIT) for HDM show they are effective treatments in allergic airway disease.

Drug reactions

Adverse reactions to antibiotics may be confused with the underlying infective process, as many viruses cause nonspecific rashes. Not all the mechanisms of drug reactions are IgE-related and the in vivo and in vitro tests for drug-specific IgE are generally not reliable. The gold (and probably only) standard for investigation of an IgE-mediated reaction is a drug challenge in the hospital, but this can be restricted to where an alternate drug is not available and time is available to make the diagnosis. In urgent, serious cases (complicated cystic fibrosis, for example), where no alternative drug is available, it is possible to use a rush desensitization protocol.

Anaphylaxis

Troublesome or poorly controlled asthma appears to be a major adverse risk factor for a fatal outcome in anaphylaxis. Risk of death in a food-allergic child is 1 in 800000. These figures have been criticized as representing only the tip of a much larger iceberg because of the use of an over-restrictive definition of anaphylaxis. Intramuscular injection of the correct dose of adrenaline (epinephrine) is the treatment of choice in infants and children with anaphylaxis.

Who should receive adrenaline?

The former suggests that if a child shows any evidence of sensitivity to an allergen (i.e. a wheal size greaterthan 3 mm) then one is failing in the care of that child if provision is not made to cover all eventualities, and the provisionof injectable adrenaline is mandatory. This is the usual scenario in American practice. Kemp has challenged this approach by suggesting it is unnecessary and expensive. The medical criteria are more selective, based on the severity of the reaction (any wheeze, laryngospasm, asthma, cough, hypotension, collapse or loss of consciousness require adrenaline). A medical consensus is emerging regarding prescription practices.

The primary protection of 'anaphylactic' children is identification of reactivity followed by strategies to avoid the relevant allergen. Following this is the use of an antihistamine and perhaps the provision of injectable adrenaline.

Non-IgE-mediated allergy

There are groups of children who give surprisingly similar histories of 'altered reactivity' and who are referred to an allergy clinic. There are no reliable or proven objective tests for these conditions, although many are offered commercially. Usually these clinical conditions are distinguished easily, and management comprises monitoring improvement clinically during avoidance and deterioration during re-exposure and ensuring that unsubstantiated dietary and lifestyle restrictions are avoided. Non-IgE food allergy has been described and is often associated with vomiting, often delayed. There has been much recent interest in cow's milk allergy, gastro-oesophageal reflux and eosinophilic oesophagitis, discussion of which is beyond the scope of this paper.

Another group of children referred are those where diet is said to alter behaviour, from hyperactivity to the worsening of autistic symptoms. For the former there seems a cluster of foods (oranges, chocolates, cola) that are recalled as causing problems; for the latter, the 'neurotoxic' effects of gluten feature highly. Parents are often desperate for an external cause for what appear to be 'intrinsic' disorders. There is no doubt that some children do experience a 'sugar rush', or their behaviour worsens with a junk-food diet; however, easy objective tests are lackin g. For an individual child's overall management diet may play a small role, but sometimes a very positive one. McCann's controversial findings of an effect of a combination of additives on behaviour in young children will probably need replication with single additives to gain medical acceptance, although the public already seem to have accepted it wholesale.

The chronic urticarias (of which more elsewhere in this series) are rarely allergen-driven. The physical urticarias (hot, cold, solar, pressure) are occasionally seen and have a clear explanation and can usually be demonstrated. Hereditary angioedema is well described in children, and management does not differ greatly from that in adults.

Ref: Clinical Immunology Review Series: An approach to the patient with allergy in childhood. R. Sporik,J. Henderson and J. O'B. Hourihane. Clinical and Experimental Immunology, 155: 378–386.

Food sensitivity frequently occurs early in life and is often a first sign of future atopic disease therefore the prevention of food allergy remains a vexing problem and has been the subject of much current research. Infancy represents a time when an allergic phenotype may be determined. An infant's immune system can either have a T helper cell type 2(Th2)dominance with more secretion of interleukin (IL)-4 or a Th1 dominance with a cytokine balance toward interferon gamma (IFN-γ) production. Therefore, interventions to prevent food allergies and the development of the atopic phenotype are best made early in life. Several dietary manipulations in infancy, such as prolonged breast feeding, maternal avoidance diets during pregnancy and lactation, the use of hypoallergenic formulas, have been proposed as ways of altering the Th1/Th2 balance in infants, with varying degrees of success. The dietary manipulation has been the center of research over the past decades as a form of primary prevention of food allergy and hence atopic disease.

Immunomodulation

Immunomodulatory role of breast milk

The results of studies regarding the effects of breastfeeding and the prevention of allergy remain inconclusive. Even if maternal diets are devoid of allergenic foods, prevention of food allergy in infancy appears to be transient at best. Several factors in breast milk either induce or protect against food allergies (Table1).

Probiotics and Prebiotics

Probiotics are generally called the Lactobacilli and Bifidobacteria. Much of the current research lately has focused on the immunomodulatory effects of probiotics and prebiotics.

A study of the year 2007 showed no reduction of the incidence of AD. A recent study of the year 2008 showed that Lactobacillus rhamnosus, but not Bifidobacterium animalis, significantly reduced the incidence of AD with almost 50% compared to placebo, without any effect on sensitization. In contrast two prevention studies did not show a reduced AD incidence.

A systematic review of RCTs of the year 2009 evaluating the efficacy of probiotics for treating eczema showed that currently probiotics cannot be recommended for treating eczema.

In regards to the immunomodulatory effect of prebiotics in AD prevention a recent study showed that the incidence of atopic dermatitis was significantly lower in the intervention group than in the placebo group. In a more recent study the incidence of AD at the age of 2years was still significantly reduced as were the recurrent wheezing and allergic urticaria. Although these results seem very promishing, a limitation of the study was the large percentage (more than 20%) of infants that were lost to the follow-up during the intervention period.

Exposure to infection

The "hygiene hypothesis" suggests that exposure to common respiratory infections early in infancy may actually decrease the risk of allergic diseases such as asthma by preferentially selecting a Th1-predominant immune system rather than a Th2-predominant atopic immune system. Early infections such as respiratory syncythial virus may predispose infants to develop asthma later in childhood. Much data has been accumulating that children who are either placed in daycare early or have older siblings have higher rates of wheezing during early infancy but lower rates of asthma after age. There is also an association of frequent use of antibiotics in infancy with an increased odds ratio for the development of subsequent asthma. This hypothesis is appealing because it may help to explain the increasing incidence of asthma over the past few decades, although tertiary prevention of asthma involves limiting exposure to infection.

Autoimmunity and atopic disease

The autoallergens represent mainly intracellular proteins, but some of them could be detected as IgE immune complexes in sera of sensitized patients. Several relatively recent findings led to the concept that IgE autoreactivity may play a pathogenetic role in severe and chronic forms of atopy. It was reported that patients predominantly with severe and chronic manifestations of atopy (eg. atopic dermatitis) contain IgE autoantibodies against a variety of proteins.

Predictors of allergy

When attempting primary prevention of food allergy the first question that needs to be asked is which children should be the target of any intervention or manipulation of diet or lifestyle. Several factors have been investigated as predictors of the develpoment of atopic disease, including family history of allergy and cord blood IgE. Numerous genes have been uncovered that can predict allergy in some populations.

Family History and Cord Blood IgE as Predictors of Allergy

Although a genetic test for allergy risk remains elusive, family history remains in practice the most clinically useful determinant of risk of atopy in a child. Studies performed since the 1970s have estimated the risk of atopy to be between 38% to 58% in an offspring with one allergic

parent and as high as 60% to 80% in a child born to two allergic parents.A child with a negative family history has about a 5% chance of developing allergy.

Cord blood IgE, a less practical indicator to obtain, was only 26% sensitive in determining the risk of atopy, whereas it was 74% specific.

Dietary manipulation during pregnancy, lactation and early infancy

Dietary manipulation during pregnancy

Studies which have examined the prophylactic effect of maternal avoidance of highly allergenic foods such as milk and egg during pregnancy in high risk groups showed no beneficial effects in the development of food allergy,if the infant was otherwise maintained on a hypoallergenic diet after birth.It is therefore now widely accepted that maternal avoidance diets during pregnancy should not be recommended as way to prevent allergic disease in children and may be potentially harmful in light of the increased risk of maternal malnutrition.

Breast-Feeding

Undoubtedly, breast feeding is the best nourishment for infants.It is also clear that there is a risk of exposing a child at risk of atopy to highly allergenic foodstuffs through breast milk. It has long been known that β-lactoglobulin, casein and bovine gammaglobulin, three of the most common milk antigens, as well egg, wheat antigens have been detected in breast milk 2-6 hours after ingestion.Peanut proteins may be detected only 1-2 hours after ingestion in lactating women. Studies so far have been controversial.Studies performed in the 1980s showed that breast feeding had no protective effect on the development of food allergy as compared to formula feeding.

A more recent meta-analysis of prospective studies of breast feeding and it's effect on the development of atopic dermatitis from 1966 to 2000 revealed a significant protective effect against the development of atopy by breast feeding.

Based on the previous data the American Academy of Pediatrics (AAP), the European Society for Paediatric Allergology and Clinical Immunology (EAACI) and the European Society for Paediatic Gastroenterology Hepatology and Nutrition (ESPGHAN) strongly recommend exclusive breast feeding for at least 4 months and should be continued till the 6th month of age as a hallmark for allergy prevention.

Maternal avoidance diets during lactation

Several studies have attempted to determine whether sensitization to highly allergenic foodstuffs could be prevented in high risk infants if lactating mothers avoid these foods.

The recommendations of the American Academy of Paediatrics (AAP) present the view of a Cochrane database systematic review. The previous study has shown that in high risk infants who are unable to be completely breast fed, there is evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk (CM) formula reduces infant and childhood allergy and infant cow's milk allergy.

The recommendations of the European Academy of Allergy ane Clinical Immunology (ESPACI) were based on a 2006 Cochrane review including 4 trials and 451 participants which reported that an antigen avoidance diet for high risk mothers is unlikely to reduce their children's of atopic diseases substancially,and that such a diet may adversely affect maternal and/or fetal nutrition.

Because of these contradictory recommendations, maternal avoidance diets during lactation should be instituted on a case by case basis only after evaluating the degree of risk for atopy and the motivation of the family. Care must be taken to make sure that the mother's food intake remains balanced during such a diet to prevent maternal malnutrition. If cow's milk is avoided, one must take care to ensure that the mother is ingesting sufficient calcium, up to 1500mg of elemental calcium daily.

Soy Formula and prevention of allergic disease

There is some evidence that up to 10-15% of children with cow's milk allergy have IgE antibodies to soy. Therefore, although soy formula is certainly nutritious and not deleterious to non-allergic infants, soy formula cannot be recommended for primary prevention of the disease. It can, however be recommended as a safe alternative to cow's milk formula in the majority of infants with cow's milk allergy after screening documents indicate no coexisting soy allergy.

Hypoallergenic formulas and prevention of allergic disease

The ideal protein hydrolysed formulas should not contain peptides larger than 1,5KD,should contain no intact proteins, should demonstrate no anaphylaxis in animals, and should reveal protein determinant equivalents less than 1/1,000,000 of original protein. Most importantly, the formula must be demonstrated safe in milk allergic infants by both double-blind placebo-controlled food challenge and by open challenge.

Acceptable hypoallergenic formulas need to be extensively hydrolyzed in order to be composed of small enough peptides to be considered truly safe in children with milk allergy. Partially hydrolyzed formulas have numerous peptides of more than 4 KD and can cause allergic reactions in 40% to 60% of children with IgE mediated cow's milk allergy and can therefore not be considered a safe alternative for these patients.

Partially hydrolyzed and extensively hydrolyzed formulas

have been studied for their ability to prevent atopic disease for more than 15 years. Most studies of these formulas have focused on infants at high risk of developing allergy.

In studies of infants at high risk of atopy who are not exclusively breastfed for 4 to 6 months, there is modest evidence that the onset of atopic disease may be delayed or prevented by the use of hydrolyzed formulas compared with formula made with intact cow milk protein, particularly atopic dermatitis.

A relatively recent systematic Cochrane meta-analysis regarding the use of hydrolysed proteins on allergy prevention has concluded that in infants at high risk for allergy who are unable to be completely breastfed there is limited evidence that feeding with a hydrolysed formula compared to cow's milk formula reduces allergies.

Recommendations of AAP and ESPACI/ESPGHAN (2008) regarding the hypoallergenic formulas Both the AAP and ESPACI/ESPGHAN commitees recommend the use of protein hydrolysate formulas in primary prevention of allergy in high risk infants who are bottle-fed.

The AAP recommends extensively hydrolyzed formulas or possibly partially hydrolyzed formulas whereas the the European committee suggests a formula with confirmed reduced allergenicity.

The AAP recommendations take into account the higher cost and lower palatability of extensively hydrolyzed formulas that limit their usefulness.The lower palatability may be overcome by their early introduction to infants, before the child has developed a taste for other formulas. Therefore,if cost is not an issue,an extensively hydrolyzed formula should be used in infants at high risk for atopy if they are to be exclusively bottle-fed or if breast feeding is to be supplemented.

Delayed introduction of solid foods

Although not conclusive, several studies suggest that early introduction of solid foods might lead to an increased risk of eczema. The revised AAP report of the year 2008 suggests that solid foods should be delayed until 4 to 6 months of age. The European committees suggest that complementary foods should be introduced after 17 weeks but no later than 26 weeks and concluded that there is no convicing evidence that avoidance or delayed introduction of potentially allergenic foods, such as fish and eggs, reduces allergies in infants either at risk or not.

Table 1: Recommmendations on primary prevention of Food Allergy, incorporating current Guidelines of the ESPACI / ESPGHAN 2008

Interventions	Recommendations
Immunomodulation Pregnancy diet	Still experimental Not recommended
Breast feeding	Exclusive breast-feeding strongly recommended for at least 4 months and should be continued till the first 6 months of life.
Lactation diet	Milk and egg avoidance is not routinely recommended but may be offered on a case-by case basis to highly motivated families;if instituted ,mother must take supplemental calcium
Soy formula Protein hydrolysate formula	Not recommended A formula with confirmed reduced allergenicity is strongly recommened if infant is to be bottle-fed or as a supplement to breast milk.
Delayed introduction of solid foods	Solid food may be added at 6 months (after 17 weeks but no later than 26 weeks)

Table 1 offers an approach to prevention of food allergy in children that incorporates the guidelines of both organizations.

Combined Infant & Maternal Avoidance of Allergenic foods

Studies have examined whether food atopy can be prevented by controlling the intake of highly allergenic foods by a high-risk infant from a variety of sources ,that is,both direct ingestion and indirect ingestion through the breast milk. In prenatally randomized, physician-blinded, parallel-controlled study the effect of multiple food allergen avoidance in both the lactating mothers and their infants was compared to standard feeding practices in children with positive family history of allergy. This study found that children whose intake of allergenic foods from a variety of sources was restricted showed significantly lower incidence of allergic diseases such as atopic dermatitis at 1 year of age because of a lower incidence of food allergy and lower specific IgE to cow's milk up to 2 years of age compared with acceptable infants. There was no effect on the occurance of respiratory allergy or sensitization to environmental allergens from birth to 7 years. These studies suggest that, whereas food allergies can be avoided in the first 1 to 2 years of life by carefully limiting the dietary intake of highly allergenic foods for more than 6 months, this is not followed by a reduction of allergic disease later in childhood.

Ref: Clinical Immunology Review Series: An approach to the patient with allergy in childhood. R. Sporik, J. Henderson and J. O'B. Hourihane.Clinical and Experimental Immunology, 155: 378–386.

Dear Doctor,

Square pharma proudly announce the inauguration of Allergy newsletter.

Allergy usually starts in childhood. So, it is important to understand the pathophysiology and possible intervention to prevent the development of allergy. We try to highlight those aspectes in this issue.

Please let us know your demand, advice and suggestion to improve the publications.

Best regards.

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