

EDITORIAL

Considering 25 years of research on allergy prevention – have we let ourselves down?

DOI:10.1111/pai.12092

Almost 25 years ago pediatric allergists in Europe and other parts of the world started to get organized in working-groups and small national societies, many driven by a strong interest in the development of the infantile immune-system, as related to the manifestation of allergic disorders. In their activities they shared a common enthusiasm for early prediction of chronic atopic manifestations as well as primary and secondary prevention of allergic sensitization and different atopic phenotypes (1–4).

Today, after two and a half decades of intense basic as well as clinical research, it seems – in spite of some optimistic reports (4) – we have to admit that most of the concepts and proposals have failed to be effective. In fact we have to face that few areas in pediatric research have a comparably frustrating lack of successful results.

Alimentary strategies for primary prevention

Measures for primary prevention are aimed at a population that is still healthy but may be at an increased risk for the disease.

The effect of breastfeeding has not really been studied in a randomized controlled trial—which is considered to be unethical by most authorities today. Therefore, the extent breastfeeding's preventive effect remains controversial. Several other beneficial aspects justify recommendations for exclusive breastfeeding for at least 4 months. But whether or not the beneficial effects are explained by the avoidance of 'foreign' food proteins from cow's milk or soy is still unclear (5). Global recommendations for breastfeeding during infancy remain based mainly on political emotions and ideological prejudices rather than clear evidence for an effective allergy prevention.

The use of hydrolyzed infant formulas is recommended in some areas, particularly in Europe, if maternal breastmilk is not sufficiently available during the first months of life (6). Here the effect on atopy prevention has been extensively studied these last two decades. Some early studies indicate that extensively hydrolyzed formulas in combination with avoidance of cow's milk proteins and solid foods for at least 4 months in children with a positive family history of atopy does have some preventive effect, which, however, is only related to the food proteins that were avoided. This approach, therefore, cannot be considered as a long-lasting prevention of atopic manifestations of the skin or the airways in general (1).

Extensively and partially hydrolyzed formulas with moderately reduced allergenicity were investigated later in large randomized prospective studies (e.g. German Infant Nutrition Intervention Study). We learned that the feeding of hydrolysates may result in a reduced incidence of atopic dermatitis in

infancy which is carried over throughout the first decade of life. Neither IgE-mediated sensitization to food or inhalant allergens nor the development of upper or lower airway-disease is in any way affected (6).

After the supplementation of prebiotic oligosaccharides to an infant formula had been shown to have immunomodulatory effects in experimental animals (upregulation of TH₁ and downregulation of TH₂ responses), it was studied in infants without susceptibility for atopy in their families. As with hydrolysate feeding, we learned that the incidence of atopic dermatitis is significantly reduced in infancy; however, there was no effect on the development of allergic sensitization (7).

The debate over effects and effect sizes of alimentary approaches aimed at primary prevention of atopy remains ongoing, and this journal will provide the forum for future contributions in this area (8–11).

Elimination of environmental allergens

Early studies tried to reduce the load of environmental allergens in the first years of life, particularly indoor allergens from house-dust mites and cats. The results of the few published intervention studies were not really very encouraging, although one study from the Isle of Wight demonstrated an intervention effect of indoor allergen elimination together with a hydrolyzed infant formula (12,13). During the last decade we learnt from the transient latex allergy 'epidemic', that complete avoidance of allergen exposure over a critical period of time can be a reasonable concept (14).

Exposure to bacterial compounds

After epidemiological surveys suggested that the exposure to certain infectious agents or microbial molecules might have some preventative effect, investigators tried and are still trying to identify the protective mechanisms that have been so frequently addressed in research related to the so-called 'hygiene hypothesis.' The ultimate aim is to integrate protective components in the environment (like the one from Bavarian farm stables in Germany) and try to mimic the exposure early in life, possibly by some 'anti-allergic' vaccine. Candidates such as *Acinetobacter Iwofii* have already been extensively studied. Animal experiments with lipopolysaccharides and other bacterial cell wall components, which can be found abundantly in stables with pigs, cattle and poultry, did have encouraging antiallergic effects in mice (15). Unfortunately, clinical trials in humans with a strong genetic susceptibility for atopy failed to demonstrate strong intervention effects, so that up to now no label of any drug for allergy prevention exists anywhere in the world (16).

Pharmacological studies for secondary prevention

Based on the concept that early manifestation of infantile eczema is directly linked to the subsequent development of allergic airway disease ('allergic march') and that these two manifestations cannot be simply considered as co-expression of two different atopic phenotypes, a variety of pharmacological interventions in young infants with atopic dermatitis were performed: (17)

Antihistamines (Cetirizine, Levocetirizine and Desloratadine) were studied in large cohorts of young children with atopic dermatitis, toward reducing the incidence of allergic asthma during subsequent years (18). Later on, Pimecrolimus applied topically on the skin of infants with atopic dermatitis was investigated. All these studies clearly failed to demonstrate any intervention effect on either allergic sensitization or the development of airway disease (19).

Independently, the disease modifying effect of inhaled corticosteroids was studied in children with recurrent wheeze after the age of 2 yr. We learned that, despite an impressive effect on symptomatic control, after termination of corticosteroid treatment symptoms rapidly reappeared, thus providing us no evidence of any disease-modifying effect (20).

What is the message for future research?

Obviously, research approaches aimed at allergy prevention need completely new concepts. These might be entirely

different when it comes to the prevention of food allergy, atopic dermatitis, allergic rhinitis or asthma. Today it seems very unlikely that one single strategy could turn out to be preventative for all areas of atopic disease (21,22).

Patrick Holt recently suggested focusing on both viruses and indoor allergens for preventing allergic asthma. It seems that certain viruses such as RSV or Rhinovirus, both of which turn out to be extremely important in the initiation of pediatric asthma, deserve the development of specific vaccines. On the other hand, in high-risk groups of children for allergic airway disease the early application of allergens by different routes (transdermal, sublingual, intralymphatic) should be studied (23).

In the field of food allergy, it is currently proposed that early application via the oral route might result in tolerance and a reduced incidence of manifest food allergy. However, the results of available studies are far from clear.

Overall, pediatric allergists have to realize that very little of the research performed over the last two and a half decades has resulted in applicable effective prevention strategies. The time has come to develop novel ideas and more promising approaches in order to win the battle against the epidemic of the 21st century.

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