

Atopy and Asthma Prevention

New Paradigms?

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The aim of the present issue on current opinion is to bring together the collective knowledge of experts from the United States and Europe to discuss the role of allergens in the onset of atopy and in the development of symptoms, with pro and con versions.

Three major topics are developed: primary allergen avoidance, pros and cons of high-dose allergen exposure leading to tolerance, and the pros and cons of secondary prevention. First, it is necessary to define prevention. Primary prevention leads to reduced risk of disease onset; secondary prevention reduces the rate of deterioration of disease through a number of measures, including early diagnosis, treatment, allergen avoidance, and patient education; and tertiary prevention deals with rehabilitation.

Concerning primary prevention, according to Dr. Allan Becker, only multifaceted intervention programs have been successful as a primary prevention strategy for the development of asthma in young children. The decrease in exposure to inhalant and ingestant allergens and in environmental tobacco smoke during the first year of life in children at high risk for the development of asthma has the potential to be protective. However, it is important to

reassess children as they reach school age to determine whether multifaceted intervention was effective. Moreover, it is increasingly clear that gene-directed environmental manipulation is critical in the primary prevention of allergy and allergic diseases such as asthma.

One major problem, as stated by Dr. Susan Lau, is the fact that all primary prevention trials had different study protocols, often combining one or several intervention strategies, and comparability is not evident. It appears clear that smoking in families, especially during pregnancy, favors later sensitization, notably to inhalant allergens in children. Exposure to cigarette smoke is also a risk factor for wheezing. Therefore, it is highly recommended that parents avoid smoking during pregnancy and early infancy.

The role of high allergen exposure as a risk factor for asthma, allergic diseases in general, and for tolerance is very controversial. Many published studies dealing with associations between allergen exposure, sensitization, and asthma have incongruent results. The strong association between asthma and sensitization to indoor allergens has been confirmed in many population-based studies. However, a causal

relationship between allergen levels, sensitization, and asthma would best be supported by evidence of a dose-response relationship between exposure and symptoms. Only the Sporik study demonstrated this type of relationship (1). A subsequent prospective study demonstrated that there was no relationship between early indoor allergen exposure and the prevalence of asthma, wheeze, or bronchial hyperresponsiveness at age 7 yr, suggesting that sensitization and asthma may be determined by independent factors (2). The association between sensitization and asthma was interpreted as a causal relationship between exposure and disease. The results of a very large number of studies have shown that high exposure to cat or dog allergen reduces the risk of subsequent sensitization and disease. However, the community prevalence of cats in the children's areas, the role of direct and indirect exposure, and the atopic background were very important biases in these studies.

Dr. Catarina Almqvist suggests that one possible way to assess the effect of early exposure to cat allergen is to perform a multicenter prospective study that includes a population of children unexposed to cat allergen (which is not so easy to find) as a reference group and to estimate total levels of personal allergen exposure (direct and indirect) over time.

Although the epidemiological data regarding the relationship between exposure and sensitization to Fel d 1 is conflicting, the ability of high doses of Fel d 1 to induce a characteristic nonallergic immune response with a modified T-helper (Th) 2 response to cat allergen was proposed by Drs. Judith Woodfolk and Tom Platts-Mills. A modified Th2 response to cat allergen could be a sign of tolerance to the allergen. However, one major question remains: does a nonallergic response constitute tolerance? To fulfill the criteria for immunological tolerance, the phenomenon should be antigen-specific and mediated by clonal deletion, by T-cells synergy, or through regulatory T-cell

effects. Dr. Woodfolk suggests that among human lymphocyte antigen DR7-positive subjects with an allergic predisposition exposure to high doses of cat allergen favors interleukin (IL)-10 induction within the respiratory tract above a critical threshold and results in tolerance. She also found that the T-cell repertoire for cat allergen consists of distinct Th and regulatory T-cell subsets with defined T-cell receptor specificities. Indeed, novel immunodominant regions on the amino terminal portion of Fel d 1 chain 2 has been identified. These two peptides P2:1 and P2:2 preferentially induce IL-10 and interferon- γ in T-cell responses to Fel d 1 in allergic-modified Th2 responders and controls. By contrast, another peptide on Fel d 1 chain 1 (P1:2) induces strong proliferation in allergic and modified Th2 responders but not in nonallergic controls.

The cat paradox, whereby increased exposure leads to decreased prevalence of sensitization, presents a dilemma for clinicians. For Drs. Almqvist and Woodfolk, there is no doubt that an allergic patient living in a house with a cat will have more symptoms, a higher degree of bronchial hyperresponsiveness, and will need more medication than a patient living in a house with no cats. Thus, for a child with allergic parents, the prediction would be that exposure to high doses of cat allergen favors a modified Th2 response in the presence of the DR7 genotype, whereas there is a lack of expression of DR7 increases the risk of sensitization.

From a practical point of view, families should look for early symptoms of allergic diseases and be advised to remove the pet (or not to get one) if one or more individuals in the family react to the pet.

Secondary prevention of mite allergy appears to be a logical choice. However, several recent studies failed to demonstrate the clinical efficacy of this approach. A meta-analysis by Gotzsche et al. (3), suggested that current chemical and physical methods aimed at reducing

exposure to allergens from house dust mites might be ineffective. However, in a majority of these studies, techniques that are now known to have little effect on mite levels were used. Another meta-analysis performed by the same group found that when only chemical methods for detection of mite allergen were used, there was a statistically significant adverse effect on symptoms ($p = 0.03$), whereas when only physical methods were used, there was a statistically significant beneficial effect ($p = 0.02$) (4).

According to Drs. Romei and Boner, there are a number of reasons for the failure of allergen avoidance to improve clinical symptoms:

1. The allergens that are avoided are not relevant to the etiology and pathogenesis of the disease.
2. Multiple allergens are involved in the etiology and pathogenesis of the disease.
3. Noneffective measures were used.
4. There was low adherence to the measures suggested.
5. There was inadequate or incomplete application of the measures.
6. Exposure to the responsible allergens occurred outside the home.
7. Some parts of the house that should obviously have been treated were not or could not be treated.
8. The period of observation or of low allergen exposure was not long enough.
9. Comparison was with placebo mattress covers that provided significant protection.
10. The long-term duration of the disease had resulted in irreversible pathological changes in the target organ.

Finally, it appears that patients must be exposed to high enough allergen levels if they are to have an opportunity to reduce their symptoms after applying methods aimed at reducing allergen levels. Moreover, application of allergen-reduction procedures should be considered globally, with advice given by the patient's physician or, perhaps even better, by a medical indoor environmental counselor

(5). This point of view is supported by the results of two published studies, one dealing with asthma and one with rhinitis. Both failed to obtain a positive clinical result, most likely because the amount of allergen present at the beginning of the studies was too low (6,7). Therefore, in these two studies, allergen avoidance had no effect in the actively treated groups compared with the control groups. The results imply that when susceptible patients are involved and when the avoidance measures are adequately performed (meaning with a global allergen reduction), then secondary allergen avoidance is associated with a clinical benefit. In the future, for Romei and Boner, a successful strategy should include both advice on how to reduce allergen exposure, as well as advice aimed at implementing other related factors. This was confirmed by a multicenter study including more than 900 inner-city children from seven centers. They clearly demonstrated the efficacy of secondary prevention on allergic asthma (7).

In conclusion, there is currently only limited understanding of the effectiveness of the methods used to reduce the risk of the development of allergic disease through induction of immunological tolerance. Hence, we must continue to advise patients about other relevant risk factors, those that have been demonstrated to decrease the risk of disease onset. According to the results of epidemiological studies regarding the relationship between allergen exposure and allergic symptoms, secondary allergy prevention appears to be the logical approach. However, to be clinically effective, secondary prevention must be properly performed, remembering that atopic diseases are the result of interactions on a given genetic background and also on other specific factors.

References

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