Rostrum

Is there any role for allergen avoidance in the primary prevention of childhood asthma?

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In this article we discuss 3 hypotheses to attempt to understand why preventive measures thus far studied with the aim of preventing (or delaying) the development of asthma have shown such disappointing results. The most likely explanation is that the development of a multifactorial disease, such as asthma, is extremely difficult, if not impossible, to prevent by eliminating only one risk factor. In a meta-analysis we investigated the effect of a multifaceted and monofaceted intervention in 10 prospective birth cohorts of a total of 3473 children on a diagnosis of asthma. Multifaceted intervention studies had an odds ratio (OR) of 0.73 (95% CI, 0.55-0.97), whereas the monointervention studies had an OR of 1.22 (95% CI, 0.83-1.78) in patients younger than 5 years and an OR of 0.52 (95% CI, 0.32-0.84) versus 0.93 (95% CI, 0.66-1.31) in patients older than 5 years. We therefore hypothesize that studies with a multifaceted approach will have a much greater chance of being successful than studies using a monofaceted approach, with the latter being unlikely to yield a clinically relevant reduction of asthma. (J Allergy Clin Immunol 2007;119:1323-8.)

Key words: Asthma, prevention, multifaceted

It is widely accepted that asthma is a polygenetic disease that can be aggravated by exposure to a range of environmental factors. Genetically predisposed children exposed to specific allergens are believed to be at increased risk of asthma development. On the basis of the understanding that the interaction between genotype and environment plays a crucial role, it is reasonable to assume that reducing exposure to potentially relevant allergens should lead to a reduction in the risk of asthma. This concept is, however, mainly based on observations made in the early 1980s, which found that dramatic reduction of house dust mite (Der p 1) exposure, by moving children with asthma into a hospital or to a mountain sanatorium, could very considerably reduce symptoms of asthma.1,2 But translating these secondary prevention findings into feasible-to-deliver primary prevention strategies has proved extremely difficult, as demonstrated by the disappointing results of large, carefully designed, randomized clinical trials of house dust mite avoidance strategies in birth cohorts.3,4 The reasons behind their lack of effectiveness remain unclear. Based on theoretical consideration, there are 3 main hypotheses:

1. It is not possible to reduce allergen exposure to a clinically relevant extent in real-life circumstances.
2. The concept is wrong: exposure to a specific allergen will not increase but, through induction of tolerance, actually reduce the risk of asthma development.
3. Because asthma is a multifactorial disease, preventive measures will only prove effective if most or all relevant environmental factors for a specific child are simultaneously avoided.

In this article we discuss these 3 hypotheses to attempt to understand why preventive measures thus far studied, which aimed to prevent (or delay) the development of asthma, have shown such disappointing results. Our hope is that these deliberations will assist researchers in progressing beyond the current impasse in relation to investigating the role of allergen avoidance as a primary prevention strategy.

HYPOTHESIS 1: IT IS NOT POSSIBLE TO REDUCE ALLERGEN EXPOSURE TO A CLINICALLY RELEVANT EXTENT IN REAL-LIFE CIRCUMSTANCES

The reduction in exposure needs to fulfill 2 essential criteria: it must be relevant because the child has to be...
A Multi-faceted allergen reduction for the prevention of asthma in children

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Pooled analysis (last observation < 5 years) doctor’s diagnosis

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Pooled analysis (last observation ≥ 5 years) objectively defined

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FIG 1. Numbers of asthmatic children in treatment and control groups are given for different studies at different ages. Pooled analysis of the last observation of the different studies are given for a physician’s diagnosis of asthma (<5 years of age) and for objectively defined asthma (≥5 years of age). PREVASC; Prevention of Asthma in Children; SPACE, Study of Prevention of Allergy in Children in Europe; CAPS, Childhood Asthma Prevention Study; NACmass, NAC Manchester Asthma and Allergy Study.

allergic for the specific allergen studied, and the reduction needs to be of a magnitude sufficient to have a clinical effect.

Most studies in this area have focused on secondary prevention, and the most extensive studied exposure in this respect is the house dust mite in those with established asthma. In studying the success of reducing allergen exposure measures, direct exposure to the allergen is seldom assessed; rather, surrogate parameters like the concentration of house dust mite on bare mattresses or floor covering are typically measured. But even then, not all trials have resulted in clear reductions of house dust mite concentrations. In the latest Cochrane systematic review and meta-analysis of 49 trials (enrolling a total of 2733 patients) investigating the effectiveness of house dust mite avoidance measures for treating asthma,

confirmed mite reduction occurred in only 13 trials and only to a minor extent in the largest trial,

and it was unsuccessful in 24 trials and not reported in the remaining 12. The final conclusion of the reviewers was that current approaches to reducing exposure to mites are ineffective. In arriving at this conclusion, the authors assumed that the absence of an effect was due to an inadequate reduction of mite antigen levels. This interpretation is, however, not necessarily consistent with the evidence because even in a study in which the reduction was clearly successful (ie, >90% reduction in Der p 1 resulting in a geometric mean of less than the accepted absolute threshold value of 2 µg/g), no clinically relevant improvements were observed in FEV1 or asthma symptoms.

Another point that should be considered is that even in the controlled circumstances accompanying most trials, it is still possible that children are exposed and become sensitized to dust mites in other houses.
Although the house dust mite is the allergen to which asthmatic subjects are most frequently sensitive (except in specific areas in the world, such as Colorado or Northern Scandinavia), one could argue that it is unlikely that all subjects studied were allergic to the house dust mite alone. For this reason, we recently performed a trial in which asthmatic subjects were recruited who were sensitive to the house dust mite but not to (or not exposed to) other aeroallergens, such as cat or dog. Despite achieving a reduction in house dust mite allergens of almost 90% (resulting in a geometric mean <1 μg/g), there was only a slight increase in peak flow and no change in symptoms. Therefore from these studies, it is reasonable to conclude that in real-life circumstances it is not possible to reduce the exposure to house dust mite in such a way that it has clinically relevant consequences for asthmatic patients. Whether this conclusion for secondary prevention in asthmatic subjects can be extrapolated to primary prevention of asthma in susceptible children cannot be completely determined. However, as pointed out already, large studies of primary prevention by reducing house dust mite allergens in children with a genetic susceptibility to asthma are not very promising.
HYPOTHESIS 2: EXPOSURE TO SPECIFIC ALLERGENS IN CHILDREN WILL, THROUGH INDUCTION OF TOLERANCE, DECREASE THE RISK OF ASTHMA DEVELOPMENT

What actual evidence do we have that exposure to specific allergens in children will decrease the risk of asthma? Early-life exposure to aeroallergens from cats and dogs has been identified as possibly protecting against allergy, with the proposed mechanism being immune tolerance or concomitant exposure to endotoxin. However, it is important to note that findings suggesting a role for possible tolerance are based on observational (cross-sectional and cohort) studies and not on observations from randomized controlled trials. A fundamental limitation with nonexperimental designs is that it is extremely difficult, if not impossible, to prove a causal relationship. Also, in cohort studies there are validity problems because the exposure is not determined by the play of chance and could be influenced by behavior. Behavior might therefore be a confounder because it can be associated with both exposure and outcome. Could, for example, allergic parents and parents of children with respiratory symptoms be more likely to decide not to have a cat or dog in their households than other parents? Allergic parents might have experienced what effects these pets have on their own health, and parents of susceptible children can take the precaution of avoiding pets. Indeed, behavior of parents is likely to play an important role in the exposure of high-risk children to aeroallergens. In the Prevention and Incidence of Asthma and Mite Allergy study, a randomized clinical trial investigating the efficacy of reducing allergen exposure, the allergen load before the intervention measures was so low that according to the authors this was likely to be caused by increased public awareness of the potential adverse effect of allergen exposure, particularly among atopic families. Moreover, in a large study of more than 14,000 families, it was concluded that pet keeping seemed to be protective for the development of allergy, but this was mainly due to the fact that parents avoided exposing their child to pets because they believed this was a risk factor for the development of allergy. Although in natural cohort studies attempts are often made to control for confounding behavior through multivariate analyses, one has to consider that correction for confounding cannot always exclude residual confounding because, for instance, unknown selection phenomena and poorly measured and unknown confounding factors cannot be adjusted for post hoc.

We would like to emphasize that the mentioned observations do not exclude immune tolerance because the results of the studies of Owney et al and Platt-Mills et al seem to indicate that high levels of allergen exposure to cats (and maybe to dogs as well) were protective for some children and a risk factor for others, possibly genetically determined.

We conclude that on the basis of the present data, there is insufficient evidence to assume that exposure to particular allergens will decrease the risk of asthma development in all children.

HYPOTHESIS 3: A MULTIFACETED APPROACH TO ALLERGEN AVOIDANCE WILL PROVE SUPERIOR TO A SINGLE INTERVENTION

Because asthmatic subjects are usually not only sensitive to one allergen, the successful elimination of that one allergen is only likely to be of limited clinical benefit. It is therefore logical, although experimentally somewhat complex, to test the efficacy and effectiveness of multifaceted approaches to allergen avoidance. The main potential disadvantage of a multifaceted approach is that it is difficult to disentangle the effects of one intervention from those of another.

A number of randomized clinical trials have been conducted in newborn children to investigate whether the development of asthma can be prevented or delayed by reducing exposure to inhalant allergens, feeding allergens, or both. Although the majority of these studies investigated only one measure, others have used a multifaceted approach. Because there is no published systematic review on possible differences between these 2 approaches, we performed a search of the Cochrane Central Register of Controlled trials (Central, issue 1, 2006), Medline (from January 1966 through December 2006), and EMBASE (from January 1989 through December 2006) using an appropriate search strategy (details available from first author). All identified references were screened by the second author. When there was any doubt about whether to select a study, the first author was consulted. Both reviewers assessed the full-article version of the selected studies. Data from the included studies were independently extracted, and disagreements were resolved through consultation with the third author. Familiarity with many of the studies made us aware of the many different outcome parameters and different observation periods. Therefore to make maximum use of available data, our primary outcome measure of interest was agreed a priori as being a physician’s diagnosis of asthma in patients younger than 5 years and an objectively defined diagnosis of asthma in patients older than 5 years. Because of the nature of the question we were addressing in this review, it was likely that there would be some variation in the length of follow-up carried out in each of the studies. We therefore aimed to analyze data on the diagnosis of asthma in 2 ways. First, we analyzed the last observation available in each of the studies, irrespective of time point, because the diagnosis of asthma is more reliable when a child grows older. We also reanalyzed data from multiple time points (as pooled subgroups). A formal test for statistical heterogeneity, the natural approximate $\chi^2$ test, assessed whether the observed variability in effect sizes is greater than would be expected to occur by chance. For dichotomous end points, an odds ratio (OR) and 95% CI were presented by using a random effects model. We used the Cochrane collaboration’s RevMan 4.2 program for the analysis.
In total, 10 high-quality studies enrolling 3473 patients were included, of which 1124 had a multifaceted intervention design and 2349 had a monointervention design. Several studies had repeated measurements on different ages of the children. In Fig 1 we displayed all published observations at different ages from the studies. The Isle of Wight study was published at ages 2, 4, and 8 years. The Canadian Asthma Prevention study was published at ages 2 and 7 years. The Zeiger study was also published at ages 2 and 7 years. The Australian Childhood Asthma Prevention Study was published at ages 3 and 5 years. Fig 1 shows that the multifaceted intervention studies had an OR of 0.73 (95% CI, 0.55-0.97), whereas the monointervention studies had an OR of 1.22 (95% CI, 0.83-1.78) when patients were younger than 5 years and an OR of 0.52 (95% CI, 0.32-0.84) versus an OR of 0.93 (95% CI, 0.66-1.31) when patients were older than 5 years.

These results suggest that a multifaceted approach is effective in delaying or preventing asthma, whereas a monointervention does not seem to have such a protective effect. The multi-faceted Prevention of Asthma in Children trial comparing the combination of miticide intervention, breast-feeding (thereby reducing cow’s milk protein exposure), and smoking cessation versus usual care showed an independent and significant effect of mite allergen reduction, breast-feeding, and maternal smoking on current wheezing at 2 years of age. Epidemiologic observations confirmed the independent effects of different allergens (as well as smoking) on the incidence of asthma and on early indications of asthma in healthy subjects. Also, a secondary prevention (multifaceted intervention in atopic children was clearly shown to be effective when compared with monointervention studies. All these observations support the concept that a multifaceted approach to allergen avoidance is superior in diminishing the development of asthma.

HYPOTHESIS THAT NOW NEEDS TO BE TESTED

It is clear that the enthusiasm induced by early observations that reduction of a single allergen would diminish the development of asthma has not been confirmed in experimental studies. On the basis of the above described data, no definite conclusions can yet be drawn to explain the lack of effectiveness of primary preventive measures on the development of asthma found in most studies. However, the most likely explanation is that the development of a multifactorial disease, such as asthma, is extremely difficult, if not impossible, to prevent by eliminating only one risk factor. We therefore hypothesize that studies with a multifaceted approach will have a much greater chance of being successful than studies with a monofaceted approach, with the latter being unlikely to yield a clinically relevant reduction in asthma. The only way to draw definitive conclusions is to study the effectiveness of separate and combined intervention measures in one and the same study and to compare these effects on the development of asthma. House dust mite allergen avoidance, cow’s milk protein avoidance, and a combination of these approaches could, for example, be investigated in a randomized controlled trial, with the separate and combined measures investigated in separate arms.

To the best of our knowledge, such a trial has not yet been performed, probably because of the large numbers needed for such a trial. Mounting such a necessarily large trial ideally involving at least 6 years of follow-up would be challenging and expensive. If conducted, however, it would, we believe, shed important new light on the role of allergen avoidance measures in preventing the development of asthma in susceptible children.

REFERENCES
24. Hide DW, Matthews S, Tariq S, Arshad SH. Allergen avoidance in infancy and allergy at 4 years of age. Allergy 1996;51:89-93.