

Mite Avoidance as a Logical Treatment for Severe Asthma in Childhood Why Not?

Long before IgE was discovered, or the importance of lung inflammation had been appreciated, it was well recognized that some patients develop acute wheezing when exposed to foreign substances such as cat dander (1). After techniques for assessing bronchial reactivity (BHR) were accepted, it was generally assumed that this was a physiological property intrinsic to the asthmatic lung. In 1970, when Cox and Altounyan presented data showing that seasonal exposure of pollen-allergic subjects could increase BHR, and that this reactivity could persist for 3 months after the season, the importance of allergen exposure had still not been acknowledged in the field (2). Around the same time, the first epidemiological studies appeared relating the increase in asthma among children to a high prevalence of dust mite allergy (3). Over the next 10 years, two key elements emerged. First, moving mite-allergic children or adults to a mountain resort or a hospital room was observed to produce highly significant decreases in BHR (4, 5). Second, mite allergy, as judged by either positive skin tests or elevated serum-specific IgE, was linked to asthma among children in Australasia, Japan, South America, and the United States, as well as in Europe. Hence, at that time, it seemed likely that dust mite avoidance would become integral to asthma treatment and prevention (4).

The fundamental challenge then (and now) was how to achieve a decrease in exposure in the environment of a family home to levels that were low enough to impact disease. Perhaps even more pertinent was how to accomplish this in the context of a double-blind controlled trial. Each of these issues is tackled in the report by Murray and colleagues (pp. 150–158) in this issue of the *Journal* (6). This study, which examines the influence of mite allergen exposure in bedding on asthma exacerbations in children, has two key strengths that reflect this group's lengthy experience in analyzing the relationship between allergen exposure and asthma. First, by enrolling children who had experienced a recent asthma exacerbation at 14 hospitals in Northern England, sufficient sample size was attained to objectively monitor changes in acute episodes among mite-sensitized children within a 12-month window. Second, the materials used for active and placebo bedding encasings were carefully selected based on properties of fabrics known to prevent or allow the passage of allergens. The protocol included washing instructions and treatment of relevant beds, recognizing that children are not confined to a single bed. This strategy resulted in a highly significant decrease in levels of the major dust mite allergen, Der p 1, in mattress dust obtained from the active group, which was maintained at 1 year. Moreover, by multivariate analysis, the risk of exacerbations requiring acute

treatment was 45% lower in the active versus the placebo group ($P < 0.006$).

The current findings, which were obtained in children aged 3 to 17 years, are important not only because of the implications for asthma management but also because of their relevance to understanding the mechanisms of severe exacerbations. The results should be considered in relation to recent successful trials demonstrating the efficacy of IgE blockade in reducing events requiring acute intervention among inner-city children with exacerbation-prone asthma (7).

Although the majority of asthma exacerbations in children older than 3 years of age are triggered by infection with human rhinovirus, it is increasingly clear that the risk of either current asthma or exacerbations is related to both the presence and the levels of IgE antibodies to mite or other allergens (Figure 1) (8–10). We would emphasize that the study by Murray and colleagues used a protocol that is allergen-specific and that the relationship of allergen exposure to asthma differs depending on the type of allergen (6). Although there is no doubt that other allergen sources (e.g., cat, dog, cockroach, and *Alternaria*) also contribute to acute exacerbations, approaches to limiting exposure are very different, and evidence of their efficacy is less complete (11, 12). The picture is further complicated by the high prevalence of multisensitization among allergic subjects with asthma and the predominance of mite allergy in many asthma populations. With these aspects in mind, the study by Murray and colleagues reinforces the notion that mite allergy is a principal driver in asthma pathology, consistent with an “allergen hierarchy” that may be geographically determined (6).

As with all studies of avoidance, there are limitations. Murray and colleagues used an intervention focused solely on bedding (6). Although removal of carpets and upholstered furnishings might further reduce the burden of mite allergen, it would clearly be impossible to blind those methods. In relation to this point, analysis of both total and mite-specific IgE could have provided an additional quantitative measure of the efficacy of allergen exposure that might inform the relationship between IgE and the risk for acute asthma. It should also be noted that the large number of sites in the study precluded direct monitoring of parameters of lung inflammation (e.g., expired nitric oxide or cells in induced sputum). There is convincing evidence from Dr. Boner's group in Italy that moving children with asthma to a high-altitude environment where mite exposure is negligible markedly reduces both BHR and lung inflammation (4, 13). It is not clear whether similar effects can be achieved in the home environment, although decreases in BHR have been achieved in many avoidance trials.

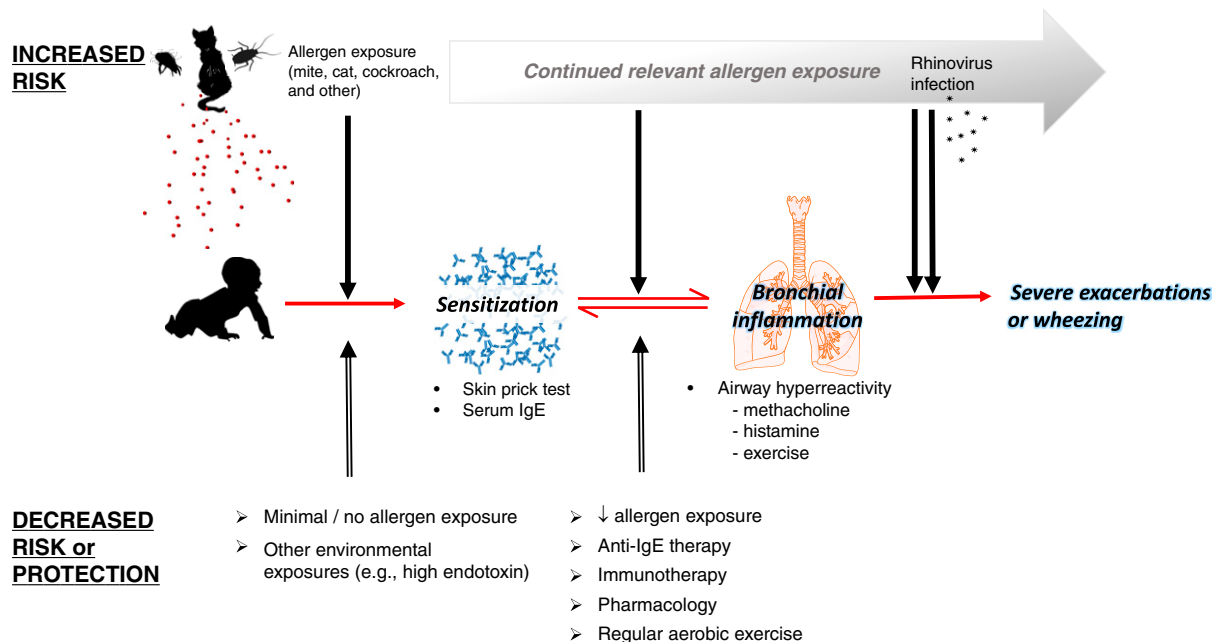


Figure 1. The relevance of allergen exposure at critical steps in the development of severe exacerbations of asthma in at-risk children. Acute exacerbations reflect the culmination of a series of pathogenic processes in the susceptible host, which are influenced at each stage by exposure to airborne particles derived from one or more major allergen sources. Therapeutic interventions that influence asthma exacerbations may act predominantly on the progression from sensitization to bronchial inflammation. The synergistic effects of IgE and rhinovirus depend on the preexisting inflammatory milieu in the asthmatic lung.

In light of the major public health burden exacted by severe asthma exacerbations, the results presented here are clearly relevant to the design of asthma management. It is noteworthy that several recent pharmacological studies failed to show an effect on asthma exacerbations owing to insufficient events in the placebo group (14). Equally, some major trials of allergen avoidance have not achieved significant reductions in allergen levels (15). The current study advances the evidence that allergen-specific intervention can decrease the risk of exacerbations and builds on the substantial work implicating dust mite allergens that derives from other avoidance studies as well as the beneficial effects of specific immunotherapy or IgE blockade (16). The current report adds an important element to the evidence that allergen-specific treatment should play a role in the treatment of chronic asthma in childhood. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Whole-Genome Sequencing in Common Respiratory Diseases Ready, Set, Go!

High-throughput (next-generation) sequencing technologies are becoming increasingly used in studies of common, complex diseases. As with many genomic technologies, studies in cancer have led the way, through projects such as The Cancer Genome Atlas (1). However, these sequencing techniques are becoming more widespread in benign diseases, including respiratory disorders such as asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and pulmonary hypertension (2–5). RNA sequencing has several advantages over microarrays, such as the ability to assay greater number of RNA species with increased sensitivity. Costs are equivalent, if not favorable, for RNA sequencing compared with microarrays.

In the very near future, DNA sequencing is poised to replace genotyping arrays, which have been the standard in genome-wide association studies (GWASs) for more than a decade. Sequencing of the exome, defined as the protein-coding portion of the genome, has served as an intermediate step, as costs were initially too high for whole-genome sequencing (WGS) in large sample sizes. Exome sequencing has been quite fruitful in finding causal mutations in rare Mendelian diseases (6), which are frequently due to nonsynonymous variants that lead to amino acid substitutions. Exome sequencing has not been quite as successful in complex diseases, which are more frequently influenced by variants outside of the coding genome, which likely affect gene regulation (7). WGS is able to overcome this limitation, and costs have decreased to the point where it is now feasible to perform WGS in the sample sizes necessary to find rare variants associated with common diseases.

In this issue of the *Journal*, Radder and colleagues (pp. 159–171) present the first reported WGS study in COPD (8). The investigators used the strategy of studying individuals with extreme phenotypes, a strategy that has been used in many prior genetic studies, including studies of COPD (3). From a Pittsburgh cohort of current or former smokers, they selected cases with both emphysema on the basis of quantitative chest computed tomography scans and severe airflow obstruction ($FEV_1 < 40\%$ predicted), who were compared with control subjects without emphysema or airflow obstruction, matched by age, sex, and smoking history. This yielded a modest sample size of 65 susceptible and 64 resistant smokers with high-quality WGS data. WGS resulted in more than 13 million single-nucleotide polymorphisms across all samples. The subsequent analyses

focused on the 5.5 million rare variants in the cohort (allele frequency $< 1\%$), an average of approximately 80,000 rare variants per subject. In the analyses of individual variants and groups of sequential variants across the genome (within 30-kb windows), none of the findings reached traditional levels of genome-wide significance. Nor were statistically significant results found in an analysis restricted to rare variants located within introns, exons, and 1-kb flanking regions of genes. However, suggestive associations with several genes were identified through this series of tests, including *ZNF816* (zinc finger protein 816) and *CCDC38* (coiled-coil domain-containing 38), the latter of which was previously found in an exome sequencing study of resistant smokers with normal lung function (9).

The most interesting result came from an analysis of nonsynonymous coding variants. In particular, a rare nonsynonymous substitution (rs61754411) in the gene *PTPRO* (protein tyrosine phosphatase, receptor type O) occurred in eight susceptible individuals but was not found in the resistant population. Though the top result, this association did not reach genome-wide significance. The investigators were able to validate this finding by genotyping this variant in the overall Pittsburgh cohort of 686 individuals, demonstrating associations with both FEV_1 and percent emphysema on chest computed tomography scans. Primary human bronchial epithelial cells harboring the mutant allele in *PTPRO* demonstrated reduced epidermal growth factor signaling in response to ligand or exposure to cigarette smoke extract. Although these are preliminary findings, alterations in epidermal growth factor signaling have been previously implicated in the pathogenesis of COPD (10), supporting the possibility that *PTPRO* may represent a novel COPD susceptibility gene. The results are promising, yet additional work is needed to confirm the association of this variant with COPD and emphysema and to further elucidate the role of *PTPRO* in disease pathogenesis.

Although the study by Radder and colleagues (8) is one of the first WGS studies in any common respiratory disease, it follows a considerable history of successful GWAS studies. Some of the lessons learned in the GWAS era of human genetics are immediately applicable to WGS studies, especially the need for large sample sizes to find significant genetic associations in heterogeneous conditions such as COPD. To achieve these sample sizes often requires national or international consortia. Studies of type 2 diabetes (11), serum lipid levels (12, 13), and bone mineral density (14) have incorporated WGS in thousands of subjects. Although sequence alignment and variant detection methods are becoming more standardized (15), there remain many unanswered

Supported by National Institutes of Health grants R01HL125583, R01HL130512, P01HL105339, and P30ES013508.

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