

Advances in environmental and occupational respiratory disease in 2007

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This review of key articles appearing in the Journal in 2008 represents significant advances in the understanding of the interrelationships between the environment and allergic respiratory diseases. New allergens have been identified and characterized. Improvements in diagnostic techniques and methods to assess environmental allergen exposure have been developed. The novel therapeutics and refinements of allergen avoidance approaches will improve patient care. A fuller appreciation of the complexities of environmental factors in allergic diseases can lead to better preventative measures. Lastly, the increasingly important role of pollutants on inflammatory processes is evolving. The articles discussed will add to our increasing knowledge base and advance the ability to more effectively treat patients with allergic respiratory diseases and expand research opportunities. (J Allergy Clin Immunol 2008;121:1359-62.)

There were a number of noteworthy contributions to the Journal addressing environmental and occupational diseases in 2007. Areas of investigation included identification of allergens and their biochemical structures, methods for diagnosing allergic diseases, the effectiveness of environmental modifications in minimizing disease, new treatments for disease (Table I), environmental allergen exposures and the development of allergic disease, and the impact of pollutants on inflammatory processes (Table II). In this review, we summarize key articles published in the Journal in 2007 from these research areas.

ALLERGENS

A comprehensive review of allergen nomenclature and structural biology indicates that current databases contain more than 120 distinct protein families that are allergens.¹ Modern molecular biology techniques not only provide information regarding the amino acid sequences of allergens but also assist in determining

Abbreviation used

OR: Odds ratio

the structural biology of allergens, as well as defining targets for both diagnostic and therapeutic purposes.

A new indoor allergen source has recently been described, the Asian ladybug (*Harmonia axyridis*). The proteins from Asian lady beetles that are important allergens included Har a 1 and Har a 2. The 10-kd Har a 1 allergen has unique amino acid sequences, whereas Har a 2 shares amino acid sequence homology with a dehydrogenase from the red flour beetle. Cross-reactivity of these allergens with *Blattella germanica* was found but was significant only in patients who had been primarily exposed to cockroach.²

In addition to the Asian lady beetle, other insect allergens may play a role in allergic respiratory disease. Mosquito-inhalant allergens may play an important role in sensitization in many parts of the world. Kausar et al³ describe several inhalant proteins from mosquitoes with molecular weights of 24 to 30 and 33 kd as major allergens.

House dust mites are a known important source of allergen exposure. A new major allergen from *Blomia tropicalis*, Blo t 21, was not cross-reactive with the known major *Blomia* allergen, Blo t 5, although it shares some sequence and structural identity.⁴ Another study that looked at cross-reactivity between house dust mite, *Dermatophagoides pteronyssinus*, and the storage mite *Glycyphagus domesticus* showed that the storage mite may act as a primary sensitizer independent of house dust mite in patients exposed to both species.⁵ Inclusion of *Glycyphagid* extracts may be necessary for proper diagnosis and treatment of patients exposed to both.

A number of allergens have been identified as causes of epidemic asthma during thunderstorms. Pulimood et al⁶ demonstrated the role of *Alternaria alternata* sensitivity as a predictor of epidemic asthma in patients with seasonal asthma and grass pollen allergy. It is well known that other pollens such as *Parietaria* may also be involved.

Mouse-allergen sensitivity is recognized as an important factor in children with asthma living in inner cities. Matsui et al⁷ evaluated children living in inner-city environments with asthma who underwent skin testing and serological analysis for sensitivity to mouse allergens. The prevalence rate of mouse sensitization was 25% and did not consistently increase with increasing levels of Mus m 1 exposure. High-level exposure to mouse allergen was associated with attenuated responses to all immunoglobulin isotypes, which suggests that protection against allergic sensitization by high-level allergen exposure may not be mediated by preferential production of IgG over IgE. Phipatanakul et al⁸ evaluated the role of mouse allergen sensitivity and asthma morbidity among women residing in the Boston area, which demonstrated an

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TABLE I. Key advances in environmental and occupational respiratory diseases in 2007

1. The Asian lady beetle has become an important seasonal indoor allergen.
2. Glycophagid (mite) allergens can act as primary sensitizers independently of mite allergens in some patients exposed to both.
3. *Alternaria* sensitivity is an important contributor to episodes of thunderstorm-associated asthma.
4. Mouse-allergen sensitivity is a significant factor in inner-city children with asthma and in women, and the indoor levels of mouse allergen vary over time.
5. New technology (fluorescent multiplex arrays) permits simultaneous measurement of multiple allergen-specific IgE levels in small amounts of sera and quantitation of multiple indoor allergens from settled dust samples.
6. Nonwoven mattress encasements may trap cat and house dust mite allergens in contrast with woven fabric encasements.
7. Reductions in cockroach allergen levels can be achieved by reducing infestations but are highly dependent on the thoroughness and effectiveness of the eradication efforts.
8. Novel genetically engineered (eg, DNA shuffling, hybrid proteins, and synthetic peptides) may lead to improvements in allergen immunotherapy.

TABLE II. Key advances in mechanisms of environmental and occupational respiratory diseases in 2007

1. The role of overall environmental exposure on disease expression is becoming better understood.
2. Allergen exposure remains a risk for allergic disease, but the role for this in adults is less clear than for children.
3. Pollutants may enhance antigen presentation capability.
4. Mechanisms by which environmental agents signal innate immune responses are being identified.

association between physician-diagnosed asthma and asthma morbidity regardless of race, ethnicity, and socioeconomic status with the presence of sensitization to mouse allergen. Matsui et al⁹ found that mouse allergen levels in inner-city homes varied over time, suggesting that a single point evaluation may not be sufficient to determine exposure levels or demonstrate that effective control measures have a significant impact. Thus, exposure and sensitization to mouse allergens occur outside the research laboratory setting and are important factors in asthma related to indoor allergen exposure.

DIAGNOSIS OF ALLERGIC RESPIRATORY DISEASE

The American Academy of Allergy, Asthma & Immunology Work Group reported clinical practice parameters for the diagnosis of allergic sensitization, discussing the appropriate use of both skin testing and *in vitro* testing coupled with the medical history and physical examination for the proper diagnosis of allergic disorders.¹⁰

A new technology, fluorescent suspension multiplex array, permits the simultaneous measurement of total and allergen-specific IgE in small quantities of sera in a single test.¹¹ The assay is comparable to current ELISAs in terms of reproducibility. Its use will facilitate epidemiologic studies and will be advantageous in pediatric populations.

It is well known that delayed reactions to skin testing may occur, especially with intradermal skin testing. However, in a case report, Johnson et al¹² describe a patient who developed a pathergy response (a rare cutaneous erythematous and pustular reaction 24 hours after skin trauma that is associated with a vasculitic histologic picture) after prick-puncture skin testing.

ALLERGY EXPOSURE ASSESSMENT AND REDUCTION

In addition to the application of fluorescent multiplex array technology for diagnostic purposes, it can also be used to quantify levels of multiple allergens in a single settled dust sample.¹³ This

could lead to an increased ability to conduct clinical studies, large population-based environmental surveys, and assessment of allergen avoidance techniques.

A study of nonwoven mattress encasements showed that they may accumulate cat and dust mite allergens on their surfaces compared with woven encasements, raising questions regarding their effectiveness in allergen avoidance recommendations.¹⁴

In a cockroach allergen abatement study, insecticide baits placed by entomologists and commercial pesticide treatment were compared with untreated control homes. Both active methods reduced infestation and cockroach allergen levels, but the magnitude of reduction was dependent on the thoroughness of the eradication effort.¹⁵

TREATMENT OF ALLERGIC RESPIRATORY DISEASE

Novel approaches to allergen immunotherapy are under investigation. Larche¹⁶ reviewed the use of synthetic peptide fragments of allergen molecules for immunotherapy. Such approaches may reduce IgE-mediated adverse events and may act through increased IL-10 production from allergen-specific regulatory T cells. Further studies with larger numbers of subjects will be needed to determine the overall safety and efficacy of such therapy.

Gonzalez-Rioja et al¹⁷ reported that hybrid proteins derived from *Parietaria* pollen resulted in reduced IgE reactivity. Skin tests showed that the hybrid protein had significantly less potential to induce cutaneous reactions compared with the purified native allergens and whole pollen extracts. The engineering of hybrid proteins may be a safe and effective approach to allergen immunotherapy, which, in addition, shortens the course of therapy.

Wallner et al¹⁸ examined the generation of multivaccines created by DNA shuffling of tree pollen allergens. Genes of the Bet v 1 family were used to produce recombinant proteins that displayed low release of inflammatory mediators but increased T-cell immunoreactivity compared with the parent allergen. Further studies will be necessary to determine the effectiveness of this approach.

ALLERGEN EXPOSURE AND OTHER FACTORS IN RESPIRATORY DISEASES

The relationship between indoor allergen and environmental exposure and immune response was again an area of active research. Diet is a form of environmental exposure. It has long been thought that ω -3 and ω -6 fatty acids might protect against the development of allergy. However, a recent Journal study does not confirm this idea.¹⁹ The hygiene hypothesis was examined more closely by Ege et al,²⁰ who examined features in rural lifestyle and development of allergy in a study of included 8263 school-age children from rural areas in 5 European countries. They reported that specific features of rural life were linked with protection against atopy, as opposed to simply living in a rural area. Pig keeping (odds ratio [OR], 0.57; 95% CI, 0.38-0.86), farm milk consumption (OR, 0.77; 95% CI, 0.60-0.99), frequent stay in animal sheds (OR, 0.71; 95% CI, 0.54-0.95), child's involvement in haying (OR, 0.56; 95% CI, 0.38-0.81), and use of silage (OR, 0.55; 95% CI, 0.31-0.98; for nonatopic asthma) in Germany for agriculture (OR, 0.34; 95% CI, 0.22-0.53) were all protective against development of atopy. These protective factors were also related with higher expression levels of genes of the innate immunity.

Arbes et al²¹ examined data from the Third National Health and Nutrition Examination Survey, in which volunteers age 6 to 59 years were skin-tested with 10 allergens, with atopy being defined as having at least 1 positive skin test result. In the United States, 56.3% of the asthma cases were attributable to atopy, and 29.3% were associated with sensitization to cat allergen, suggesting an important link between cat allergy and asthma. Chen et al²² examined the relationship between cat allergen exposure in infancy and childhood and the development of sensitization to cat and development of allergic diseases to age 6 years in a longitudinal analysis of 2166 subjects. House dust samples were collected 3 months after birth and assessed for cat allergen levels, blood samples were collected at ages 2 and 6 years, and questionnaires were used to obtain data on the allergic symptoms of children and doctor-diagnosed allergic disease at each follow-up visit. Cat allergen exposure in infancy was linked with sensitization at age 2 years but not at age 6 years. Although there was no link between cat allergen exposure in infancy and allergic symptoms to age 6 years, cumulative exposure burden caused by regular cat contact increased the risk of cat sensitization to age 6 years.

In a study of 274 adults in the inner city with persistent asthma, Wisnivesky et al²³ examined the relationship between atopy and asthma severity. These investigators reported prevalences of sensitization to cockroach, dust mite, cat, mold, and mouse of 60%, 43%, 41%, 21%, and 14%. On univariate as well as stratified and multivariate analyses, patients sensitized to each allergen did not have worse asthma control or higher resource utilization compared with nonsensitized individuals. This was true even after controlling for self-reported exposure to indoor allergens and other potential confounders. Jarvis et al²⁴ examined the relationship between exposure to cats and mattress mite allergen levels and respiratory symptoms and mite and cat allergen-specific IgE, IgG, and IgG₄ from 2780 adults to determine whether increased IgG₄ was associated with decreased atopy. Cat-specific IgG and IgG₄ was higher in subjects who had a cat that was allowed in the bedroom than in subjects without a cat, and levels of house dust mite-specific IgG and IgG₄ were similar in subjects with undetectable and high (>20.22 μ g/g) mattress Der 1 levels.

Together, these observations suggest that allergen exposure is linked to development of atopy. However, IgG₄ response was not protective against development of atopy.

Overall, in adults atopy was generally not linked to asthma severity, unlike observations in children. However, adults do develop occupational asthma, including disease induced by sensitization to the legume lupin, as well as wheat lipid transfer protein. These occupational diseases highlight the potential to develop occupational airway allergy with exposure and sensitization to plant-based food allergens.

POLLUTANTS AND OCCUPATIONAL DISORDERS

Although allergens are by definition the leading environmental agent associated with asthma and allergic disease, pollutants in the ambient and workplace environment are also important triggers of asthma. In the past year, the innate immune responses of pollutants received significant attention from Journal contributors. Lay et al²⁵ reported that in addition to PMNs, ozone exposure enhanced CD80, CD86, and MHC class II molecule expression of airway monocytes and macrophages and increased the numbers of cells that are likely dendritic cells, suggesting that this pollutant enhances the ability to present antigen. Such an effect might be a contributing factor to ozone-induced exacerbation of allergic asthma.

Another leading source of environmental irritants is airborne particulate matter. Endotoxin is an important component of these particulates and is associated with both acute exacerbation of lung disease and development of chronic obstructive pulmonary disease in those chronically exposed. Brass et al²⁶ examined the role of IL-1 in the airway remodeling process by examining the ability of chronic endotoxin exposure to induce remodeling in IL-1 receptor-deficient animals. They report a notable attenuation of endotoxin action when responsiveness to endotoxin is ablated. However, derived particulate matter may have actions independent of LPS. Poole et al²⁷ demonstrated this with their report of the effect of swine PM on human THP-1 cells. They found that swine exposure induced significant protein kinase C α , δ , ϵ , and ζ activation, which peaked at 30 to 60 minutes. This was notably attenuated with repeated exposures, and inhibition of PKC α and PKC ϵ reduced dust-induced TNF- α secretion.

Sato et al²⁸ found that bronchoalveolar lavage cells from patients with chronic beryllium hypersensitivity secreted increased amounts of TNF on stimulation with beryllium compared with cells from exposed but unaffected volunteers. However, examination of the polymorphisms for the promoted region of the TNF promoter did not reveal risk polymorphisms for enhanced response to beryllium. Overall, these data demonstrate that nonallergen irritants have a significant impact on innate responses in the airway, although specific risk factors remain incompletely identified.

SUMMARY

Environmental and occupational causes of allergic disease remain a vibrant element of the research effort in allergy and immunology. We anticipate that continued exploration of the role of innate immunity in environmental airway disease as well as better appreciation of the role of allergen exposure in modulating allergic disease will continue in 2008.

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