

Advances in environmental and occupational respiratory diseases in 2009

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The year 2009 led to a number of significant advances in environmental and occupational allergic diseases. The role of exposure to environmental pollutants, respiratory viruses, and allergen exposure showed significant advances. New allergens were identified. Occupational asthma and the relationship of complementary and alternative medicine to allergic diseases were extensively reviewed. New approaches to immunotherapy, novel vaccine techniques, and methods to reduce risks for severe allergic disease were addressed. (*J Allergy Clin Immunol* 2010;■■■■:■■■-■■■.)

Key words: Environmental pollutants, respiratory viruses, allergens, occupational asthma, complementary and alternative medicine, allergic diseases, immunotherapy, vaccines

The Journal published a number of significant advances in 2009. Major advances included the identification of environmental exposures and risk factors for severe allergic diseases as well as risk factor reduction techniques. New allergen identification and characterization were described. Novel approaches to immunotherapy were addressed. The articles reviewed here detail these findings.

ALLERGEN IDENTIFICATION AND CHARACTERIZATION

Several new allergens were identified in the past year. Building on previous studies, the importance of carbohydrate moieties was expanded. Grönlund et al¹ demonstrated that individuals sensitized to cat IgA show significant IgE binding to the carbohydrate galactose- α -1,3-galactose. Clearly, carbohydrate moieties on proteins derived from nonprimate mammals are a significant allergen source.

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Abbreviations used

CAM: Complementary and alternative medicine

OA: Occupational asthma

Another allergen from animal source was reported by Mattsson et al.² The authors identified prostatic kallikrein as an important allergen component of dog urine. There appears to be extensive cross-reactivity with human prostate-specific antigen, which is important in IgE-mediated reactions to seminal plasma in women.

Two new food allergens have been identified. Ayuso et al³ reported on a major shrimp allergen that is a sarcoplasmic calcium-binding protein belonging to the EF-hand-type family. Ohgiya et al⁴ molecularly cloned and characterized the major allergen cochine in carmine, a natural red dye derived from the bodies of insects. The allergen showed sequence homology to phospholactases. Further investigations of allergens are critical, and it is anticipated that we will see further advances in 2010.

OCCUPATIONAL ASTHMA

Dykewicz⁵ discussed the diagnostic approaches to occupational asthma (OA). Distinguishing between work-related asthma and OA is critical. Often there is a latency period between the occupational exposure and the development of asthma. In contrast, irritant-induced asthma, also known as reactive airway dysfunction, occurs in the absence of pre-existing asthma after a single exposure to a high concentration of vapor, fumes, or smoke. Patients may need objective testing, including spirometry and, in some situations, a specific inhalation challenge. Induced sputum cell counts may be another useful method for evaluating OA.

In a prospective study of laboratory animal workers, Krop et al⁶ found that new sensitization was correlated most closely with pre-existing evidence of atopy (positive skin test to inhaled allergens) and a total IgE level <100 IU/mL. Pre-employment counseling aimed at such individuals may be able to reduce occupational sensitization by up to 45% to 50%.

Agents involved in OA were thoroughly reviewed by Malo and Chan-Yeung.⁷ High-molecular-weight agents, which are often proteins, are likely to induce IgE sensitization. However, low-molecular-weight agents (metals, isocyanates, and so forth) may produce sensitization, but specific IgE antibodies are not readily identified.

Gill et al⁸ evaluated processing workers with sensitization to snow crab. The majority of the patients showed at least 4 different proteins that bound IgE. Further characterization of these allergens may improve diagnostics and approaches to management.

Maestrelli et al⁹ discussed the mechanisms of OA. The development of OA includes not only environmental factors but also

intrinsic characteristics of the causative agent and host factors such as genetic polymorphisms. Recent advances have shown that OA may also involve innate immune responses.

Takeda et al¹⁰ evaluated patients with acute irritant-induced asthma (reactive airway dysfunction). The study demonstrated that significant eosinophilic and neutrophilic inflammation as well as airway remodeling occurs as long as 10 years or more after the initial exposure.

Smith and Bernstein¹¹ reviewed management approaches to patients with work-related asthma. Exposure avoidance and pharmacologic approaches are key. The ultimate goal of OA management is its prevention.

IMMUNOTHERAPY

Over the past year, a number of important advances occurred in immunotherapy. Molecular biology was applied to improved immunotherapeutic reagents. Walgraffe et al¹² purified a hypoallergenic form of Der p 1, a major house dust mite allergen. This may be useful as a therapeutic agent after its investigation in human beings.

Roesler et al¹³ used mRNA allergen constructs in a murine model. This technique elicited benefits similar to those seen with DNA-based vaccination with an improved safety profile.

Hofmann et al¹⁴ reported on the safety of oral peanut immunotherapy, whereas Jones et al¹⁵ reported on the clinical efficacy and immune response to this treatment. The effectiveness of oral immunotherapy indicates that clinical desensitization to peanut can be achieved and that long-term immunologic benefits occur.

Maintz et al¹⁶ examined the contribution of histamine metabolism to tachyphylaxis during the buildup phase of rush immunotherapy. Scranton et al¹⁷ evaluated the incidence and clinical characteristics and risk factors for biphasic reactions after allergen-specific immunotherapy. These were significantly less severe compared with the initial reaction, did not occur in children, and did not require additional epinephrine. Further advances in immunotherapy with new agents, new techniques, and improved safety can be anticipated in the coming years.

EXPOSURES, SENSITIZATION, AND EXPOSURE REDUCTION

A number of articles addressed research examining changes in the patterns of sensitization, environmental exposures that may enhance the likelihood of sensitization or exacerbation of existing allergic disease, and reduction of such exposures. Ronmark et al¹⁸ examined 2 cohorts of children from Sweden (age 7-8 years) who underwent skin testing to 10 common allergens for this region in 1996 (n = 2148) and 2006 (n = 1700). They found that the prevalence of having a positive skin test rose from 21% in 1996 to 30% in 2006 ($P < .001$), although there was no change in asthma, rhinitis, or eczema. Family history of atopy was a risk factor for developing a positive skin test, but exposures that protected against atopy (rural living and having many siblings) in 1996 were not protective for the 2006 cohort. Parental smoking and incidence of infections were decreased in 2006. These findings suggest that protective factors (rural living and presumably innate immune activation) lost their ability to prevent atopy. However, despite increased sensitization, decreased environmental smoking and decreased infections may have countered the impact of increased atopy, because symptoms did not change. Erwin et al¹⁹

examined the relationships among ryegrass, mite, and cat-specific IgE in persons who were sensitized with wheeze versus control volunteers with no wheeze. Ryegrass-specific IgE proved to be a risk factor in patients with wheeze, whereas this was not the case for mite or cat. Likewise, ryegrass-specific IgE correlated with total IgE. It may be that the pollen allergens elicited a more robust IgE response because they are more phylogenetically distinct from mammalian antigens such as mite, and more notably cat, which may better resemble human molecules.

Balmes et al²⁰ examined traffic exposure as a risk factor for decreased lung function and respiratory health. They examined the relationship between the distance to the nearest roadway (and distance to nearest major roadway) and lung function and quality of life (by using the SF-12 questionnaire) and found significant effects of distance from the nearest road and nearest major roadway and lung function but not quality of life. They concluded that proximity to a roadway (and likely pollutants) notably increased risk for lung disease. Zock et al²¹ identified 3626 participants of the European Community Respiratory Health Survey II in 10 countries who did the domestic house cleaning and for whom data on specific serum IgE to 4 environmental allergens were available. Frequency of bleach use and respiratory symptoms were obtained by questionnaire. They found that bleach use was linked to decreased atopy but increased respiratory symptoms. Lopez-Souza et al²² examined the susceptibility of cultured nasal and bronchial epithelial cells from 5 healthy volunteers and 6 subjects with asthma to rhinovirus infection *ex vivo*. They found that inflammatory responses to infection were lesser in nasal cells, suggesting that nasal cells had increased resistance to viral infection. They also failed to confirm that cells from subjects with asthma had increased susceptibility to viral infection than those from normal volunteers. Taken together, these observations point out important changes in allergen sensitization, occurrence of symptoms, and clarification of whether subjects with asthma have increased likelihood for rhinovirus-induced inflammation. Such data will be essential for understanding more precisely the interplay between environmental factors and occurrence of disease, especially as global climate change will likely modify exposures to both allergens and nonspecific irritants.

RISK REDUCTION FOR SEVERE ALLERGIC DISEASES

Another area of research that garnered attention in the 2009 Journal was risk reduction for severe allergic disease or asthma. Rueff et al²³ examined the occurrence of severe allergic responses to hymenoptera in 926 volunteers as well as tryptase concentration, age, sex, culprit insect, cardiovascular medication, and the number of preceding minor systemic reactions before the index field sting. They found that 206 (21.4%) patients had a severe anaphylactic reaction after a field sting, and that this was related to elevated tryptase concentrations, vespid venom allergy, older age, male sex, angiotensin-converting enzyme inhibitor medication, and 1 or more preceding field stings with a less severe systemic reaction. They concluded that patients with *Hymenoptera* venom allergy and baseline serum tryptase levels had increased risk for severe anaphylactic reactions and that, when possible, angiotensin-converting enzyme inhibitors should be replaced with a different type of antihypertensive. Pieretti et al²⁴ reported a study in which 20,241 food products were surveyed to determine whether they contained advisory labels for food allergens.

Seventeen percent did have such warnings, although there was remarkable variation in the type of warning language, with up to 25 different types of advisory terminology identified. Much of this language was confusing or used nondescript terms (eg, “spices” or “flavorings”) that could not be linked to specific food allergens. The authors suggested that better standardization of how food allergens are described would lessen confusion for patients with food allergy and increased public safety. Finally, with regard to anaphylaxis and urticaria, it was also reported that high doses of desloratadine were more effective at controlling urticaria than typical doses.²⁵

Haselkorn et al²⁶ examined the relationship between markers of very poorly controlled asthma as outlined by the most recent version of the National Heart, Lung, and Blood Institute Guidelines and risk for developing exacerbations of disease requiring systemic corticosteroids. They found that subjects with very poorly controlled asthma were at increased risk acute exacerbation compared with those who had regained asthma control and suggested that monitoring these features might identify those at increased risk for acute exacerbation. It is also thought that risk for cardiovascular disease in subjects with asthma may be a result of β -agonist use, although this has frequently been difficult to examine. Appleton et al²⁷ assessed the relationship between incident cardiovascular disease (CVD)/stroke and asthma and the effect of atopy while controlling for β_2 -agonist use in a representative adult population cohort free of CVD at baseline. They surveyed more than 6000 people in the North West Adelaide Health Study for doctor-diagnosed asthma and CVD (myocardial infarction and angina)/stroke, smoking status, atopy medication use, and spirometry. Asthma (but not atopy) and β -agonist use was linked to increased risk for CVD in women. Men had few events, but those who did were more likely to be atopic and have increased cough with decreased FEV₁. The increased risk for CVD in women may be linked to β -agonist use, with further studies needed to understand the mechanisms for this risk in women.

COMPLEMENTARY MEDICINE

An area that received notable attention in the Journal and at the 2009 Annual Meeting of the American Academy of Allergy, Asthma & Immunology²⁸ was the role for complementary and alternative medicine (CAM) in allergy and immunology. It was noted that a large number of patients (as high as 40% and growing) seek CAM therapy, often without disclosing use of such treatments with their allergy specialists. Such treatments, although considered by many to be “natural,” do have toxicities and may interact with pharmaceutical agents. Practicing allergists/immunologists need resources to understand the known actions and interactions of CAM agents. Engler et al²⁹ reviewed the currently available resources available to physicians for such information.

In addition, many CAM therapies have potent anti-inflammatory and antioxidant actions, and as translational research from basic science to the clinic progresses in this area, many may prove to be useful adjuncts for treatment of allergic disease. Mainardi et al³⁰ reviewed the current literature regarding the antioxidant and anti-inflammatory actions of many CAM agents. Li and Brown³¹ described the anti-inflammatory actions of herbs classically used in traditional Chinese therapy, including agents that are currently under study for treatment of food allergy and asthma. Allergists need to be aware of the use of CAM therapy in patient communities and appreciate that many CAM interventions may

represent novel new treatments that eventually become established medical interventions, not unlike the extract of willow bark known to many as “aspirin.”

The year 2009 has advanced the understanding of a variety of environmental exposures and their impact on respiratory disease. The symposium on OA provides guidance for new directions for research. CAM is an interesting facet with which the practicing clinician should be familiar. As in previous years, new allergens have been characterized and identified. New approaches to therapy will improve the care of patients with environmental allergic respiratory diseases.

Key advances in environmental and occupational respiratory diseases, 2009

- Identification of new allergens: dog, cat, snow crab.
- Description of the long-term pathologic features of acute irritant-induced asthma.
- Efficacy and safety of oral peanut immunotherapy.
- Appreciation for changing patterns of allergen sensitization.
- Identification of risk factors for severity of allergic disease.
- Appreciation of uses of complementary medicine in allergy and immunology.

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