Advances in environmental and occupational disorders in 2012

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The year 2012 produced a number of advances in our understanding of the effect of environmental factors on allergic diseases, identification of new allergens, immune mechanisms in host defense, factors involved in asthma severity, and therapeutic approaches. This review focuses on the articles published in the *Journal* in 2012 that enhance our knowledge base of environmental and occupational disorders. Identification of novel allergens can improve diagnostics, risk factor analysis can aid preventative approaches, and studies of genetic-environmental interactions and immune mechanisms will lead to better therapeutics. (J Allergy Clin Immunol 2013;131:668-74.)

Key words: *Allergens, pollens, fungi, pets, air pollution, risk factors, immune mechanisms, asthma, immunotherapy*

Abbreviations used
APC: Antigen-presenting cell
DC: Dendritic cell
FENO: Fraction of exhaled nitric oxide
HDE: House dust extract
iNOS: Inducible nitric oxide synthase
PM2.5: Particulate matter of less than 2.5 μm in diameter
PM10: Particulate matter of 2.5 to 10 μm in diameter
RR: Relative risk
SPT: Skin prick test
STAT: Signal transducer and activator of transcription

The *Journal of Allergy and Clinical Immunology* reported a number of advances in 2012 focused broadly on environmental and occupational factors that affect allergic disease. There were also a number of reports focused on food, insect, fungal, and pollen allergy and exposures to these agents. Environmental influences on atopy included the effect of global climate change on allergen exposure, the effect of pollutant exposure on both exacerbation and induction of asthma, and the relationship of rural and farm exposures on the development of asthma. Immunotherapy also received attention in 2012. Outlined below are the leading contributions to the *Journal* in these areas in 2012.

ALLERGENS: FOODS, DRUGS, AND "BUGS"

Food allergy prevalence in children is increasing, especially in Western industrialized countries. Lack[1] provided an updated review of risk factors that might be involved in this increase. Interestingly, geography can affect the prevalence of food allergy because of several factors, such as the levels of allergen exposure, differences in preparation and processing of allergens, and genetic differences within the population. Several genetic components play an important role in the development of food allergy. A family history of food allergy is well known to be associated with food allergy in children. Ethnicity is under investigation as well. Male sex (at least in childhood) imposes a higher risk (odds ratio, 1.87; 95% CI, 1.32-2.66) for the development of food allergy. Molecular biology studies indicate that genetic polymorphisms and specific gene mutations are associated with an increased risk of food allergy.

Changes in diet (eg, inadequate vitamin D, decreased antioxidants, and obesity) and environmental changes (hygiene hypothesis) might also enhance the development of food allergy. New evidence suggests that cutaneous exposure could be an important route of sensitization. Although oral exposure to food allergens early in life might induce tolerance, investigations to clarify the effects of early oral exposure in reducing food allergy are currently underway.

Identification of new allergen sources and characterization of allergens can lead to a better understanding of the mechanisms of allergic sensitization and improve diagnostic and therapeutic approaches for allergic disease. Latex glove sensitivity is well known. Nitrile gloves are a recommended alternative for use in latex-sensitive patients. Gonzalo-Garijo et al[2] reported on 5 hospital workers with latex sensitivity who had immediate reactions (urticaria and rhinitis) from certain nitrile gloves. The authors found that latex allergenic proteins were present in these gloves, whereas they were not present in other nitrile gloves. Manufacturers, physicians, and patients with latex allergy need to be aware of the possibility of latex-contaminated nitrile gloves.

In an interesting report, Santiago et al[3] found that there was immunologic (IgE) cross-reactivity between the cockroach allergen Bla g 5, a glutathione-S-transferase, and the glutathione-S-transferase of the filarial pathogen *Wuchereria bancrofti*. Human subjects infected with this organism and mice infected with the intestinal nematode *Heligmosomoides bakeri* had IgE antibodies that cross-react with Bla g 5. Molecular mimicry studies of parasites and environmental allergens can increase our understanding of the pathogenesis of allergic diseases.

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Korošec et al[4] reported that the sensitivity of an *in vitro* diagnostic test based on recombinant yellow jacket venom allergens was enhanced by the inclusion of the *Vespula* species recombinant allergens rVes v 1 to rVes v 5. Although the use of whole venom might be more sensitive (because all allergens are included) as a first-line test, the use of recombinant allergens from an insect venom can be useful in more specifically identifying the disease-causing (anaphylaxis) venom allergen.

The diagnosis and management of drug-induced allergic reactions are important parts of clinical practice. Mertes et al[5] identified a possible increased risk for hypersensitivity reactions (anaphylaxis and bronchospasm) induced by the use of methylene blue–treated fresh frozen plasma. Although the precise mechanism for these reactions is unknown, alterations in plasma proteins might be responsible.

Carboplatin and other platinum-based chemotherapeutic agents are often used in cancer treatment. Hypersensitivity reactions (urticaria and anaphylaxis) can occur. Skin testing might be useful in identifying patients who can benefit from desensitization protocols. Patil et al[6] evaluated 39 patients with carboplatin-induced reactions using skin testing. Twelve subjects converted from an initial negative skin test result to a positive skin test result after receiving carboplatin. Because converters are at risk for reactions, the authors suggest that repeat skin testing is necessary for assessing the risk of future reactions.

Aspirin-exacerbated respiratory disease can be improved by aspirin desensitization with subsequent chronic administration of aspirin. Gastrointestinal symptoms (abdominal pain and gastroesophageal reflux) are among the most common adverse effects of this procedure. Hoyte et al[7] reported on 3 patients who were believed to have had acute pancreatitis temporally associated with aspirin desensitization. In an editorial Stevenson et al[8] argued that the evidence for association between pancreatitis and aspirin desensitization was not convincing. However, Durrani and Kelly[9] reported a case in which the patient had normal pancreatic enzyme levels before aspirin desensitization but had abdominal symptoms and increased enzyme levels during the desensitization. Physicians with aspirin desensitization procedures should be aware of this possibility. Additional studies might clarify the issue.

POLLENS

Sensitization to pollen allergens is a major factor in seasonal allergic rhinitis. One of the most important allergens worldwide is grass pollen. In a birth cohort of German children enrolled in 1990, Hatzler et al[10] investigated the evolution of grass pollen sensitization at the molecular level in children and the predictive value of specific IgE responses in the development of seasonal allergic rhinitis. Yearly medical questionnaires were administered, and serum was collected at various age points from ages 1 to 13 years. Children with seasonal allergic rhinitis (170/820) at age 12 years initially had monomolecular/oligomolecular (to 8 purified *Phleum pratense* allergens) IgE responses. At age 3 years, serum specific IgE (≥0.35 kU/L) to *P pratense* predicted seasonal grass pollen–induced allergic rhinitis at age 12 years (positive predictive value, 60% [95% CI, 50% to 82%]; negative predictive value, 84% [95% CI, 80% to 87%]). As the children aged, the concentration and complexity (number of purified allergens involved) increased through a process known as "molecular spreading." Thus early identification of children who are at risk for allergic rhinitis can lead to improved preventive measures.

The increase in the Earth's surface temperature is in part due to the accumulation of anthropogenic gases, especially CO_2. This can affect rainfall, cause severe weather events, and prolong pollen seasons. CO_2 accumulation can directly affect plant physiologic parameters (pollen production). Ziska and Beggs[11] reviewed the potential effects of these climate changes on public health caused by increasing allergen exposure.

Pollen exposure can clearly affect symptoms in sensitized patients with allergic rhinoconjunctivitis and asthma. Caillaud et al[12] investigated the relationship between increasing atmospheric Poaceae pollen concentrations and their effect on nasal and ocular symptoms in allergic subjects. The authors found a sharp positive linear trend of increasing symptoms with increasing pollen levels (up to 80-90 grains/m^3), at which point symptoms reached a plateau. At the beginning of the pollen season, a priming effect was observed, as well as a nonspecific prepriming phenomenon.

The effects of pollen exposure on emergency department visits for asthma were evaluated by Darrow et al[13] in an Atlanta, Georgia, population. Poaceace (grass) and *Quercus* species (oak) pollens were associated with emergency department visits as the pollen concentrations increased in the environment. Oak pollen exposure was particularly important in children (5-17 years old).

These studies clearly show a cause-and-effect relationship between pollen exposure and symptoms of allergic disease. Climatic factors that enhance aeroallergen production and duration can result in increasing morbidity, especially in children.

FUNGI

Fungi play an important role in the pathogenesis of allergic diseases and can be a cause of infection in immunodeficient patients. Engelhardt and Grimbacher[14] reviewed the genetic defects involved in patients with chronic mucocutaneous candidiasis and hyper-IgE syndrome. Various mutations ultimately result in impaired IL-17 immunity, IL-22 immunity, or both. IL-17 and IL-22 have potent antifungal properties, particularly against *Candida* species. Understanding the genetic basis of these conditions might eventually lead to more effective therapies.

Fungal allergen exposure has been linked to the development and severity of asthma. Reponen et al[15] examined the relationship between indoor fungal exposure and the subsequent development of asthma at age 7 years in a birth cohort study of 289 children. Dust samples were collected from the children's homes at age 8 months. Samples were analyzed by using a DNA-based, mold-specific quantitative PCR technique to identify and quantify the presence of fungi in the homes. Asthma was diagnosed at age 7 years in 24% (69/289) of the children. An increased risk for asthma was associated with high scores on the Environmental Relative Moldiness Index, which is composed of concentrations of 36 molds (adjusted relative risk [RR] for 10-unit increase in Environmental Relative Moldiness Index score, 1.8; 95% CI, 1.5-2.2). Summation levels of the fungi *Aspergillus ochraceus*, *Apergillus unguis*, and *Penicillium variable* were associated with asthma at age 7 years (adjusted RR, 2.2; 95% CI, 1.8-2.7). The study adds to our knowledge of the association between

fungal exposure and asthma development. In an accompanying editorial, Rabinovitch[16] pointed out that although the above report is an important advance, the effects were modest, and additional investigations are necessary. Furthermore, dust sample mold levels are a surrogate marker and might not reflect actual respiratory exposure. New methods of assessing fungal exposure are sorely needed.

In a comprehensive review Knutsen et al[17] discussed the association between fungi and lower respiratory tract disease. Sensitization to fungi can contribute to allergic asthma and be associated with severe persistent asthma in adults (severe asthma associated with fungal sensitivity), as well as allergic bronchopulmonary aspergillosis/mycosis. Fungi involved in these conditions, pathogenic mechanisms, and potential therapies are thoroughly presented.

Farmer's lung disease is a common form of occupational hypersensitivity pneumonitis. Several fungi have been implicated as causative agents in Europe, especially *Aspergillus* species from the glaucus group. Millon et al[18] produced recombinant antigens from *Aspergillus* species that were used in an ELISA that resulted in an 89% sensitivity and 84% specificity in identifying subjects with farmer's lung disease versus exposed farmers without disease. Although this approach might offer an improvement in current diagnostic tests, further development will be needed.

PETS

Cat exposure and sensitization have been identified as important risk factors for asthma. A large proportion of households have pet cats (22% to 50%). Birth cohorts have shown that exposure to cats in the home is associated with sensitization to cat allergens. In schoolchildren cat ownership can have an inverse relationship with sensitization. Early childhood exposure to cats might be associated with lower rates of cat sensitization in adulthood. Therefore the timing and intensity of cat allergen exposure might affect outcomes over a person's lifespan.

Olivieri et al[19] reported on the results of a large study of the effects of cat exposure on new onset of cat sensitization in adults because less information is available in this segment of the population. Of 6292 adults (20-44 years old), 231 became sensitized to cats over a 9-year period. Acquiring a cat during the follow-up period (651 subjects) was associated with new-onset sensitization (RR, 1.88; 95% CI, 1.23-2.78) compared with those without a cat (4468) at baseline and follow-up. Other factors, such as pre-existing sensitivities to other allergens, a personal history of atopic diseases, and high total serum IgE levels, were associated with increased risk of cat allergen sensitization. Ownership of cats during childhood was a significant protective factor. Thus adults with a history of atopic diseases and sensitization to other allergens who do not keep cats might be best advised not to acquire a cat.

Sensitization to dog allergens is a common clinical problem affecting up to 20% of the population. Hilger et al[20] identified and molecularly cloned a new allergen, tentatively termed Can f 6, which is a member of the lipocalin family. Sixty-one percent of 54 patients with cat and dog sensitivity determined by means of skin testing exhibited serum specific IgE to Can f 6 by using *in vitro* assays. Extensive IgE cross-reactivity between Can f 6 and the homologous cat allergen, Fel d 4, was demonstrated. In addition, Can f 6 has sequence homology with Equ c 1, the major horse allergen. These findings help explain the high degree of cross-sensitization to animal allergens.

Because allergic diseases caused by sensitization to pets are common, patients frequently seek alternatives to removal of the pet from their environment. Several breeds of dogs (eg, poodle, labradoodle, Spanish waterdog, and Airedale terrier) are touted as being "hypoallergenic." Vredegoor et al[21] compared levels of Can f 1, a major dog allergen, in hair and coat samples from hypoallergenic versus nonhypoallergenic (Labrador retrievers and other breeds) dogs. Airborne and settled dust samples were also evaluated for Can f 1 levels. The hypoallergenic dog breeds actually demonstrated higher Can f 1 levels in their hair/coat samples compared with the control breeds, although Can f 1 levels in the environment were not higher. As pointed out in his accompanying editorial, Lockey[22] concurred with the authors' conclusion that there is no scientific evidence for hypoallergenic dog breeds.

RISK FACTORS AND ALLERGIC DISEASE

There were also a number of articles examining risk factors and lifestyle influences on the development of allergic disease. Holbreich et al[23] examined the allergen sensitization rates in Amish children in northern Indiana. As the Amish emigrated from Switzerland, comparison was made with Swiss farm children, who have been reported to have decreased sensitization as well. Both populations have low rates of atopy, with the Amish having a low rate of 7.2%. Common environmental influences for both populations are exposure to large animals and consumption of unpasteurized milk directly from the farm. Although this study was not large enough to define specific protective factors, it does confirm that early farm exposures and consumption of unpasteurized milk reduce the prevalence of asthma and allergic sensitization.

Illi et al[24] examined a cohort of 8,419 children recruited from an initial sampling of 79,888 children from Austria, Germany, or Switzerland who responded to a screening questionnaire. Of the 8,419 children, blood samples and specific IgE levels were available for 7,682. Asthma was defined broadly based on either symptoms, clinician diagnosis, or treatment. Comparisons were made between farm children with exposure to raw milk, cows, and straw and nonfarm children. Farm children had significantly decreased risk of asthma, hay fever, eczema, or allergen sensitization. However, although the analyses indicated that specific farm factors could be linked to decreased asthma and eczema, this was less clear for hay fever and allergen sensitization. Nonetheless, overall, these 2 studies demonstrate that a traditional farming lifestyle, with direct exposure to raw milk and animals, is protective against the development of allergic conditions.

Lisciandro et al[25] examined neonatal antigen-presenting cell (APC) and naive T-cell ($CD4^+CD25^-CD127^+$ cells) activity in cord blood mononuclear cells collected from newborns from Papua New Guinea and Australia, representing traditional (more rural) versus modern (urban) perinatal environmental exposures. Australian cord blood T cells demonstrated enhanced and more rapid proliferative response to an autologous, APC-dependent culture system, characterized by increased antigen processing and upregulated activation markers with stimulation. Resting Papua New Guinea APCs exhibited higher baseline levels of activation and inhibitory markers and were less responsive or nonresponsive to stimulation. These observations suggest that APC and T-cell activity that is modified by perinatal environmental influences modulates allergen sensitization.

Kim et al[26] examined the effect of endotoxin in house dust on allergen sensitization. In this study from the Cincinnati Childhood

Allergy and Air Pollution study, house dust extracts (HDEs) were obtained from the homes of 99 three-year-old children with at least 1 positive skin test result and 101 matched control subjects with negative skin test results. The relationship between skin test reactivity and HDE endotoxin levels (as assessed by using the limulus assay) or bioactivity of murine splenocytes and bone marrow–derived dendritic cells (DCs) to HDE stimulation, as assessed by cytokine secretion to HDEs alone or HDEs followed by LPS challenge, was assessed. They found that HDEs with higher levels of bioactivity were associated with decreased positive skin prick test (SPT) responses, whereas HDE endotoxin levels alone did not correlate with aeroallergen sensitization profiles of children.

There is also evidence that allergen sensitization decreases with increasing age. This was shown by Warm et al,[27] who undertook interviews and skin testing of 555 subjects in 2004 recruited from a cohort of 666 adults from Northern Sweden to assess changes in allergen sensitization. In 1994, the prevalence of any positive SPT response was highest (55%) in subjects aged 20 to 29 years and lowest (26%) in subjects aged 50 to 60 years. In 2004, the results were similar, with SPT responses being verified by specific IgE measurement. Remission occurred in 32% of the cohort over 10 years, with the main risk factors for allergic sensitization being young age and a family history of allergy. Overall, family history of allergy and age were identified as the primary risk factors for allergen sensitization.

Allergen sensitization also is a risk factor for rhinovirus-induced exacerbation of asthma. This was shown in a study by Soto-Quiros et al,[28] who enrolled 287 children ages 7 to 12 years in Costa Rica into the study, with 96 having acute wheezing, 65 having stable asthma, and 126 being nonasthmatic control subjects. Rhinovirus infection in nasal lavage fluid was identified by using PCR analysis and compared with wheezing, IgE levels, allergen-specific IgE levels, and fraction of exhaled nitric oxide (FENO) values. The greatest risk for wheezing was observed among children with mite-specific IgE titers of 17.5 IU/mL or greater who also had positive test results for rhinovirus (odds ratio for wheezing, 31.5; 95% CI, 8.3-108; $P < .001$). Overall, increased IgE antibody titers to dust mite allergen were common and significantly increased the risk for rhinovirus-induced acute wheezing among asthmatic children.

AIR POLLUTION

There was continued interest in the effect of pollution on allergic disease. Laumbach and Kipen[29] reviewed the effect of pollutant exposure on airway disease, infection, and cardiovascular health, with an emphasis on biomass combustion effects, which are prevalent in the third world. Leung et al[30] also provided a perspective on air quality in Asia. As reviewed by Bauer et al,[31] many of the biological responses to pollutants are mediated by innate immune mechanisms. Both inflammasome and Toll-like receptor signaling can be associated with acute inflammatory responses to pollutants, which are analogous to the effect of acute viral infections in causing acute worsening of disease. Consistent with the idea that innate immune mechanisms modulate response to pollutants is a report by Hirota et al,[32] who found that human airway epithelial cells contain an NLRP3 inflammasome that responds to particulate matter exposure with caspase-1 cleavage and production of IL-1β and that $Nlrp3^{-/-}$ mice have impaired NLRP3-dependent IL-1β and PMN increases in the lung.

Cakmak et al[33] examined the relationship of ambient aeroallergen exposure on hospitalization for asthma, as modified by coexposure to levels of air pollutants in 11 large Canadian cities, using daily time-series analysis. Findings were adjusted for day of the week, temperature, barometric pressure, and relative humidity. Modest increases in the risk for aeroallergen exposure–related hospitalizations were observed with increased exposure to particulate matter of less than 2.5 μm in diameter (PM2.5) and particulate matter of 2.5 to 10 μm in diameter (PM10) exposure. These findings are consistent with human challenge studies that demonstrate that the airway response to aeroallergens can be enhanced by pollutant exposure.

Salam et al[34] assessed the effects of ambient air pollutants, *NOS2* promoter haplotypes, and *NOS2* promoter methylation on FENO values in 940 children from the Southern California Children's Health Study who provided buccal samples and had undergone FENO measurement on the same day. DNA methylation was assessed, and 7 single nucleotide polymorphisms that reflected the haplotype diversity in the *NOS2* promoter were identified. Levels of PM2.5, PM10, ozone, and nitrogen dioxide were compared with FENO values examined 7 days after exposure. Increased 7-day PM2.5 exposure was associated with lower inducible nitric oxide synthase (iNOS) methylation, *NOS2* promoter haplotypes were associated with *NOS2* promoter methylation, and an interaction between 1 common promoter haplotype, iNOS methylation level, and PM2.5 exposure on FENO levels was observed. Overall, promoter variants in *NOS2* and short-term PM2.5 exposure affect iNOS methylation, indicating contributions of both genetic and epigenetic variations in air pollution–mediated phenotype expression. Ji and Khurana Hershey[35] reviewed other literature that also supports the hypothesis that pollutant influences on allergic disease are modulated by epigenetic mechanisms.

Pollutant exposure can also influence the development of allergy. Gruzieva et al[36] examined a birth cohort containing more than 2500 subjects from Stockholm, Sweden, from whom data from repeated questionnaires and blood samples had been collected through age 8 years. Outdoor levels of nitrogen oxides (a marker of automotive exhaust) and PM10 were linked to residential, day care, and school locations by using dispersion models, and the relationship between time-weighted average pollutant exposures and allergen-specific IgE levels for inhalant and food allergens were assessed at ages 4 and 8 years. Nitrogen oxide exposure during the first year of life was associated with an increased risk of pollen sensitization at 4 years of age, with no general increase by age 8 years for pollen allergy. However, the risk of food sensitization associated with early-life pollutant exposure was increased at age 8 years, especially when considered for those children with no food allergy at age 4 years. Overall, these results suggest that traffic-related air pollution exposure does not seem to increase the overall risk of sensitization to common inhalant and food allergens up to school age, but sensitization to certain allergens might be related to exposure during infancy.

Provoost et al[37] examined the role of the CC chemokine receptors CCR2, CCR5, and CCR6 on DC trafficking in the respiratory tract using genetic deletion and adoptive transfer methods in mice. These cells are central to sensitization to allergen. They found that diesel exhaust particle recruitment of monocytes and monocytic DC recruitment to the airway was completely abolished in CCR2 knockout mice and substantially impaired in CCR6 knockout mice, but deletion of CCR5 had little effect on diesel exhaust particle–modulated monocyte and DC trafficking.

Overall, both epidemiologic and mechanistic studies reveal that air pollutants affect both the induction and exacerbation of allergic diseases.

IMMUNE MECHANISMS

There were also a number of articles examining immune mechanisms of host defense and the effect of atopy on host defense. Marodi et al[38] reviewed the literature examining the role of signal transducer and activator of transcription (STAT) mutations and the effect of inadequate STAT1 and STAT3 on host defense against mucocutaneous candidiasis. There is also evidence that T_H2 inflammation downregulates innate immunity. Wu et al[39] reported that IL-13 upregulates IL-1 receptor–associated kinase M, which, in turn, interferes with Toll-like receptor 2 signaling in epithelial cells, suggesting an effect on airway host defense. Hernandez et al[40] reported that asthmatic patients have decreased PMN responses to inhaled endotoxin compared with healthy volunteers, and Sykes et al[41] found that airway macrophages recovered from asthmatic patients have defective IFN-β and IFN-γ production compared with those from healthy volunteers.

BIOLOGY OF ASTHMA SEVERITY

The *Journal* also saw a number of articles that explored various aspects of biology linked to increased asthma severity. Goleva et al[42] reported that PBMC mitogen-induced kinase phosphatase 1 and IL-8 mRNA levels were increased in PBMCs from asthmatic patients found to be resistant to corticosteroid treatment. TNF-α and IL-8 suppression by dexamethasone were reduced and expression of glucocorticoid receptor β was increased in cells from corticosteroid-resistant patients. Shikotra et al[43] examined TSLP expression in the epithelium and lamina propria of bronchial biopsy specimens from asthmatic patients and found that it was increased in tissues from patients with severe asthma. Chang et al[44] found that chemokine production of airway smooth muscle cells from patients with severe asthma has decreased sensitivity to corticosteroids. Farah et al[45] reported that ventilatory heterogeneity predicted response to increased inhaled corticosteroid dosing and worsening with decreased dosing. The same group of investigators also found, using the multiple-breath nitrogen washout technique, that current asthma control was associated with markers of small-airways disease.[46] The use of sensitive methods to detect small-airways function might be helpful in evaluating responses to therapy in asthmatic patients.

Lemiere et al[47] examined features of work-exacerbated asthma (asthma that is also worsened by work exposures) versus classic occupational asthma. They found that work-exacerbated asthma was associated with a noneosinophilic phenotype, contrasting with that seen with occupational asthma. However, both asthma subtypes were associated with greater health care use and 10-fold higher direct costs than asthma not associated with worsening in work settings. Taken together, these observations suggest that increased nonatopic inflammatory responses are linked to worsening of asthma.

IMMUNOTHERAPY

Immunotherapy, whether administered through the subcutaneous or sublingual route, increases allergen-specific immune tolerance. Although immunotherapy is generally safe, systemic reactions do occur, and in some cases these reactions are delayed in onset. Gupta et al[48] surveyed 273 physicians who treat patients with immunotherapy to determine their practices regarding provision of self-injectable epinephrine prescriptions. Thirty-three percent provided all patients with prescriptions, 52.7% risk-stratified patients, and 13.5% did not. Fifty-seven percent of those physicians who prescribe self-injectable epinephrine administer immunotherapy even if the patient does not bring his or her self-injectable epinephrine to the immunotherapy appointment. This study calls for specific guidelines to be developed for the use of self-injectable epinephrine in immunotherapy and the placement of mechanisms to ensure that self-injectable epinephrine is properly used where deemed necessary.

Safety of immunotherapy is primarily directed at the patients undergoing treatment. However, personnel compounding immunotherapy vaccines can also be at risk for systemic reactions. Bandino and Tankersley[49] reported on a technician with preexisting grass pollen allergy who experienced an anaphylactic reaction caused by an inadvertent needle stick from a syringe filled with undiluted grass pollen stock solution. This report emphasizes the proper education of personnel compounding immunotherapy and instituting measures to reduce such risks.

In a reassuring report, Linneberg et al[50] examined the medical records of 18,841 Danish patients receiving subcutaneous immunotherapy and 428,484 subjects receiving conventional pharmacotherapy over a 10-year period for the development of autoimmune diseases, ischemic heart disease, and all causes of mortality. Interestingly, subcutaneous immunotherapy was associated with a lower overall mortality and a lower incidence of acute myocardial infarction, ischemic heart disease, and autoimmune disease. These results confirm the long-term safety of immunotherapy.

Allergenic extracts containing proteolytic enzymes, such as molds, house dust mites, and cockroach, when mixed with tree, grass, and weed pollen (with the exception of ragweed), can degrade the potency of the pollen extracts. To minimize this possibility, the Allergen Immunotherapy Practice Parameters (2003) updated in 2007 recommends that pollen extracts should be separated from high-protease-containing extracts (including molds). An examination of allergen extract vaccines formulated at the US Army Centralized Allergen Extract Laboratory between 1990 and 2010 showed a progressive decrease in overall prescriptions for mold-pollen mixes from 65.2% to 29.8%.[51] However, when immunotherapy was administered as a single injection, mixed mold-pollen prescriptions remained high at 72.3%. The decrease in mold-pollen mixes seemed to occur in conjunction with the publication of the practice parameters, but the reason for the continued high use of these mixtures in single-injection immunotherapy is not clear.

Administration of venom immunotherapy vaccines can be initiated according to different schedules (eg, traditional, semirush, and ultrarush). Brown et al[52] reported on a randomized clinical trial to compare the safety of an ultrarush versus a semirush regimen for initiation of venom immunotherapy. Of 49 patients receiving ultrarush immunotherapy, 65% experienced systemic reactions versus 29% of 44 subjects receiving semirush immunotherapy ($P < .001$). In addition, severe reactions were more common in patients receiving ultrarush immunotherapy (12%) versus 0% in patients receiving semirush immunotherapy ($P = .029$). Not surprisingly, maximal venom-specific IgG_4 levels were achieved earlier in patients receiving ultrarush immunotherapy.

Maintenance doses of 50 μg of venom reduced the risk of repeated reactions, but the efficacy of this dosage in the long-term treatment of insect venom–induced anaphylaxis is unknown. The choice of which initiation method to use will be especially important in patients with predisposing factors for potentially fatal anaphylaxis.

SUMMARY

Environmental and occupational exposures to allergens and air pollutants play an important role in the development and severity of allergic respiratory disease. In 2012, we saw advances in understanding the interaction of genetic and environmental factors in immune responses. The effects of pollen allergens on the initiation of IgE in children and the subsequent decrease in IgE responses in adults were of note. Clearly, genetics, timing, and dose of exposures to allergens and pollutants can both upregulate and downregulate specific immune responses. Climatic changes, which can lead to increases in aeroallergen exposure, are of increasing concern. Identification of new allergens can improve diagnostic approaches. Basic science advances in the genetic basis of allergic disease and the mechanisms of immune responses to environmental factors will aid in the development of new therapies. Several articles published in 2012 have suggested ways to improve the safety and efficacy of immunotherapy. We look forward to further advances in the coming year.

Key advances

- **Helminth glutathione-S-transferase and the cockroach allergen Bla g 5 (a glutathione transferase) share epitopes that induce IgE cross-sensitization.**
- **Climate change can increase exposure to aeroallergens. IgE responses to pollen allergens increase in concentration and complexity in childhood and wane with aging.**
- **Indoor fungal exposure to *Aspergillus* and *Penicillium* species is associated with asthma in children. Fungi play an important role in patients with lower respiratory tract diseases.**
- **"Hypoallergenic" dog breeds do not exist.**
- **Subcutaneous immunotherapy is associated with a reduced incidence of autoimmune disease and ischemic heart disease compared with conventional allergic disease pharmacotherapy. Ultrarush techniques for venom immunotherapy increase the risk and severity of systemic reactions compared with semirush immunotherapy.**
- **Atopy is associated with decreased innate host defense.**
- **Air pollution increases both asthma exacerbation and induction.**
- **Rural environments are associated with protection against atopy.**

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