

Advances in environmental and occupational disorders in 2013

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In this review of articles published in the *Journal* in 2013, we report on the significant advances in environmental and occupational disorders. Research advances have led to the identification and defined the structure and function of several major allergens. A meta-analysis confirmed the importance of mold exposure in patients with allergic rhinitis, and a new immunologic classification of aspergillosis emerged. Insights into the role of diesel exhaust particles in patients with severe asthma were clarified. Improvements in stinging insect allergy diagnostics were reported. Genetic, immunologic, and biomarker studies advanced the understanding of adverse drug reactions. New practice parameters for cockroach allergen control were presented. The pathologic role of viruses and bacterial agents in patients with asthma and chronic obstructive pulmonary disease were further defined. An excellent review of allergen bronchoprovocation testing was reported. The roles of bronchoprovocation and bronchodilator responsiveness in asthma diagnosis were further clarified. A biomarker for neutrophilic asthma was identified. Therapeutic advances in asthma research include the inhibition of IL-13 by lebrikizumab, use of montelukast in asthmatic smokers, and a thorough review of bronchial thermoplasty in patients with severe asthma. Lastly, maternal asthma was linked to a number of adverse neonatal outcomes. (*J Allergy Clin Immunol* 2014;133:1265-9.)

Key words: Allergens, fungi, venoms, adverse drug reactions, viral infections, asthma, bronchoprovocation

In this review of articles published in the *Journal* in 2013, we will address advances in our knowledge of a number of environmental and occupational disorders that include allergens, fungi, irritants, venoms, and drugs (summarized in [Table I](#)). We also examine the role of infectious agents in patients with respiratory disease and

Abbreviations used

BT:	Bronchial thermoplasty
CF:	Cystic fibrosis
COPD:	Chronic obstructive pulmonary disease
DEP:	Diesel exhaust particle
DRESS:	Drug reaction (rash) with eosinophilia and systemic symptoms
GM:	Galactomannan
HDM:	House dust mite
HRV:	Human rhinovirus
NTHi:	Nontypeable <i>Haemophilus influenzae</i>
OR:	Odds ratio
RT-PCR:	Real-time PCR
TLR:	Toll-like receptor

advances in diagnostic techniques and biomarkers for asthma. Finally, we will address improved methods of therapy for asthma, which include pharmacotherapy, bronchial thermoplasty (BT), and environmental allergen control measures (summarized in [Table II](#)).

ENVIRONMENTAL FACTORS AND ALLERGIC DISEASE

Allergens

The keeping of indoor mammals as indoor pets is a common activity in many parts of the world. Rabbits have become increasingly popular pets in recent years. Unfortunately, sensitization to pet allergens is responsible for a significant burden of allergic respiratory disease. Although several important rabbit allergens have been identified, Hilger et al¹ identified, isolated, and characterized a novel major rabbit allergen termed Ory c3. This molecule is a lipophilin that belongs to the secretory globulin protein family similar to the major cat allergen Fel d 1. However, no IgE cross-reactivity between Ory c 3 and Fel d 1 was detected. The identification and characterization of this new allergen will aid in the diagnostic testing for rabbit allergen sensitization and assays for its detection in environmental samples.

Research on the structure of allergens can enhance our understanding of their function, mechanisms of sensitization, and assessment of exposure. Mueller et al² determined the structure of the major cockroach allergen Bla g 1 using x-ray crystallography, mass spectrometry, and nuclear magnetic resonance spectrometry. These studies revealed the ability of Bla g 1 to bind hydrophobic ligands (lipids), which can potentially act as adjuvants for allergic sensitization. Because assays for environmental assessment of Bla g 1 have been expressed in arbitrary units, this new information can lead to assays expressed in absolute units. Such assays can be used to better compare assessment of exposure to different allergenic proteins.

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Sensitization to house dust mites (HDMs) is a significant cause of allergic respiratory disease. Ruebsaet et al³ reported on the effects of the major HDM allergen Der p 1 on regulatory T cells. T cells from HDM-sensitive children stimulated *in vitro* with Der p 1 generated a population of forkhead box protein 3–positive GATA3⁺ cells, whereas CD4⁺ cells from non-HDM-sensitive children did not. These forkhead box protein 3–positive GATA3⁺ cells suppressed proliferation of other T cells and T_H1-associated cytokines but not T_H2 cytokines. Therefore these cells might contribute to the polarization and amplification of T_H2 responses in sensitized subjects rather than suppressing these responses.

Fungi and irritants

Home dampness and indoor mold growth have been associated with asthma and other respiratory symptoms, but data linking these exposures to rhinitis have been lacking. Jaakkola et al⁴ conducted a systemic review and performed a meta-analysis of published literature, which showed that exposure to indoor dampness was associated with an increased risk for rhinitis. Mold odor was associated with an increased risk for rhinitis (odds ratio [OR], 2.18 [95% CI, 1.76-2.71]; absolute risk, 1.87 [95% CI, 0.95-3.68]). Although visible mold increased the risk for rhinitis (OR, 1.82 [95% CI, 1.56-2.12]; absolute risk, 1.51 [95% CI, 1.39-1.64]) and rhinoconjunctivitis (OR, 1.66 [95% CI, 1.27-2.18]). Thus controlling indoor dampness and subsequent mold growth might reduce the burden of rhinitis.

Aspergillus fumigatus complicates the clinical course of cystic fibrosis (CF) in adults and children. Baxter et al⁵ sought to better classify the spectrum of *Aspergillus* species sensitization in adults with CF. On the basis of sputum galactomannan (GM) assays and real-time PCR (RT-PCR) for *Aspergillus* species, as well as serum specific IgE and IgG levels, they proposed a new classification of aspergillosis in these patients: class 1, nondiseased (negative sputum GM and RT-PCR results); class 2, positive sputum GM result, RT-PCR result, and increased total and specific IgE and IgG levels to *Aspergillus* species (serologic allergic bronchopulmonary aspergillosis); class 3, negative sputum GM result with or without positive RT-PCR result, and increased specific IgE, but not specific IgG, levels (*Aspergillus* species sensitized); and class 4, positive sputum GM result, positive RT-PCR result, and increased specific IgG, but not specific IgE, level (*Aspergillus* species-induced bronchitis). These classifications might improve phenotyping studies and pathologic evaluation and enhance the management of patients with CF.

Diesel exhaust particles (DEPs) are a contributing factor in allergic rhinitis and asthma. Although the mechanisms are not clearly defined, Brandt et al⁶ investigated the role of DEPs in the generation of IL-17A in an animal model and in children with allergic asthma. Mice exposed to DEPs together with HDM allergen had enhanced airway hyperresponsiveness to methacholine and generated a mixed T_H2 and T_H17 response (IL-13⁺IL-17⁺ T cells). Neutralization of IL-17A prevented DEP-induced airway hyperresponsiveness. In allergic asthmatic children exposure to high DEP levels was associated with more frequent asthma symptoms over a 12-month period and 6 times higher serum IL-17A levels compared with values seen in those with low exposure levels. Strategies to abrogate IL-17A might reduce the burden of asthma in patients with allergic asthma exposed to traffic-related air pollution.

Venoms

The diagnosis and treatment of stinging insect reactions can be complicated by the presence of IgE antibodies to cross-reactive carbohydrate determinants on venom glycoproteins. Paper wasps (Polistinae) are common in Europe and North America, where they can cause stinging insect venom-induced anaphylactic reactions. Blank et al⁷ demonstrated that *Polistes* species venoms are devoid of cross-reactive carbohydrate determinants, which suggests that serum specific IgE to the venom indicates true sensitivity. However, discriminating between *Polistes* species venom and *Vespula* (yellow jacket) species venom is still difficult because of protein-based cross-reactivity and requires additional testing (eg, IgE inhibition assays).

Currently available *in vitro* diagnostic tests for yellow jacket venom-specific IgE (ImmunoCAP; Phadia, Uppsala, Sweden) might lack sensitivity. Using recombinant Ves V 5 to spike the ImmunoCAP yellow jacket venom assay, Vos et al⁸ showed that the sensitivity of the test for specific IgE antibodies increased from approximately 83.4% to 96.8%. These 2 reports indicate significant progress in our ability to more accurately diagnose and tailor specific treatment for systemic reactions to stinging insect venoms.

Adverse drug reactions

Allergists are frequently consulted regarding immunologically mediated hypersensitivity reactions to drugs. These can range from macular rashes to severe systemic reactions, such as drug reaction (rash) with eosinophilia and systemic symptoms (DRESS) syndrome. These reactions involve peptides modified by drugs (haptens) interacting with HLA molecules to activate T cells. Carbamazepine, an antiseizure medication, has been associated with drug rashes and more severe reactions. Previous genetic studies suggest that HLA-B*31:01 and HLA-B*15:02 genotypes predispose to a variety of carbamazepine hypersensitivity reactions. Because carbamazepine is metabolized to more than 30 metabolites in human subjects, Farrell et al⁹ studied the immunologic responses to unmetabolized carbamazepine and its halogenated derivatives in T cells from a HLA-B*31:01–positive subjects with DRESS syndrome caused by carbamazepine and a carbamazepine-naïve HLA-B*15:02–positive subject. T cells from both subjects demonstrated proliferative responses to unmodified carbamazepine, as well as some of the halogenated derivatives. Thus T-cell activation by carbamazepine does not require metabolism.

In another report Schnyder et al¹⁰ examined the role of HLA-B*57:01 in reactions to abacavir, an antiretroviral drug. Interestingly, abacavir-specific CD8⁺ cells are detectable in the circulation of abacavir-naïve HLA-B*15:01 subjects. To further explore the relationship between abacavir reactions and DLA-B*57:01, abacavir-reactive circulating T cells were evaluated from HLA-B*57:01 HIV-infected patients with hypersensitivity, HLA-B*57:01 HIV-positive patients without abacavir exposure and HLA-B*57:01 HIV abacavir-naïve subjects. All were skin patch tested to abacavir. All subjects had circulating abacavir-reactive T cells, but only subjects with abacavir hypersensitivity had positive skin patch test results. These 2 reports enhance our knowledge of adverse immunologically-mediated drug reactions. Further studies of genetic predisposition to drug hypersensitivity will be useful to individualize pharmacotherapy and reduce the risk of adverse drug reactions.

Drug hypersensitivity reactions that involve fever and rashes (especially to antibiotics) are difficult to diagnose in patients with infectious diseases and *vice versa*. Yoon et al¹¹ reported that serum procalcitonin might be a useful biomarker for distinguishing drug hypersensitivity from bacterial infections and was better than C-reactive protein levels in this regard. Serum procalcitonin levels were higher in patients with bacterial infections compared with levels seen in those with drug hypersensitivity reactions. Serum procalcitonin levels in drug reactions were usually less than 1.67 ng/mL, and the procalcitonin levels had better sensitivity and specificity than C-reactive protein levels. Therefore the use of serum procalcitonin levels might be helpful in identifying patients with delayed-type drug hypersensitivity from systemic bacterial infections. Additional studies of simple biomarkers will aid physicians dealing with systemic febrile drug reactions.

ENVIRONMENTAL CONTROLS AND IMMUNOTHERAPY

Cockroach allergen exposure and sensitization are significant factors in allergic respiratory disease (especially asthma) morbidity. This is particularly true in environments in which cockroach infestation is common, such as inner cities. Children with asthma and sensitization with exposure to cockroach allergens are especially vulnerable. Several decades of research have been directed at assessing environmental exposure to cockroach allergens and methods to reduce this exposure. On the basis of these studies, Portnoy et al¹² developed a practice parameter for environmental assessment and cockroach exposure reduction. Among the strongest recommendations were the following: (1) exposure to cockroach allergens in homes should be minimized to reduce the risk of cockroach sensitization, (2) integrated pest management should be used to decrease cockroach exposure to reduce asthma morbidity, and (3) reservoirs of cockroach contaminants should be cleaned or removed to prevent additional exposure to occupants. The development of these practice parameters will be of great value to the practicing clinician.

Allergen immunotherapy is an effective treatment for allergic rhinitis. However, because the benefits generally require frequent outpatient visits and a long-term commitment to achieve maximum effects, patient "dropout" is a problem.

Patient satisfaction and expectations play a significant role in patients' decisions regarding their treatment. Until now, no validated patient satisfaction survey for allergen-specific immunotherapy has been developed. Justicia et al¹³ reported on the validation of a questionnaire (the Satisfaction Scale for Patients Receiving Allergen Immunology [ESPIA] questionnaire) for assessing patient satisfaction with regard to allergen immunotherapy. In a Spanish population the questionnaire demonstrated appropriate psychometric validity for its use in clinical practice. The use of this instrument might be helpful in monitoring patient satisfaction with treatment and enhancing compliance with allergen immunotherapy regimens.

INFECTIOUS AGENTS AND RESPIRATORY DISEASE

2013 saw a number of interesting studies on the effect of infection in patients with respiratory disease. Viral illness is a significant cause of asthma pathogenesis. Kaiko et al¹⁴ used mice

in which Toll-like receptor (TLR) 7 had been genetically deleted (TLR7^{-/-}) to determine whether experimental infection with pneumovirus could induce an asthma phenotype in TLR7^{-/-} mice. Pneumovirus infection of TLR7^{-/-} mice was associated with tissue eosinophilia, mast cell hyperplasia, IgE production, airway smooth muscle alterations, and airways hyperreactivity linked to memory CD4⁺ T cells. Additionally, pneumovirus infection promoted allergic sensitization to inhaled cockroach antigen in the absence, but not the presence, of TLR7 in these mice. Thus TLR7 deficiency coupled with pneumovirus infection is associated with an abnormal adaptive response that might underlie virus-induced asthma exacerbations in later life.

Linder et al¹⁵ reported the results of a prospective study of children less than 5 years of age over a 21-year period in Tennessee in which nasal lavage samples from those children who presented with upper or lower respiratory tract illness were tested for human rhinovirus (HRV). From 1982 to 2003, 190 of 527 samples recovered from a cohort of 2009 children had positive HRV test results. Thirty-six percent of the positive samples were HRV-C. HRV-C was significantly more likely to be found in children with lower respiratory tract illness compared with HRV-A ($P = .014$), with more overall infections occurring in winter. The observed variation in overall disease seasonality with increased severity associated with HRV-C has implications for diagnostic and intervention strategies for respiratory disease.

The role of infection with nontypeable *Haemophilus influenzae* (NTHi) in patients with chronic obstructive pulmonary disease (COPD) was reported by King et al,¹⁶ who had access to lung tissue from 69 patients with lung cancer who required lobectomies. Thirty-nine of these 69 patients had COPD, with the remaining 30 without COPD examined as control subjects. The lobectomy samples were dispersed into single-cell suspensions and challenged with live NTHi, and cells were labeled with antibodies for 5 important inflammatory mediators and assessed by means of flow cytometry. T_H cells and cytotoxic T cells from the COPD cohort responded vigorously to NTHi, with increased secretion of TNF- α , IL-13, and IL-17 in both CD4⁺ and cytotoxic T-cell subsets. By dividing the control subjects on the basis of smoking history, it was possible to identify a progressive increase in the numbers of T cells producing cytokines based on smoking-based exposure or disease (nonsmoking control subjects < smoking control subjects < patients with COPD). Thus smoking appears to promote the inflammatory response of T cells after NTHi exposure, suggesting a mechanism by which smoking increases the risk for COPD caused by infection.

BRONCHOPROVOCATION AND BIOMARKERS

2013 also saw a number of both original articles and reviews on bronchoprovocation and biomarkers to assess airway biology. Diamant et al¹⁷ reviewed allergen bronchoprovocation techniques and the use of these techniques in intervention development for asthma and a number of technical guidelines for these studies. They noted that allergen bronchoprovocation is a well-established model of acute allergic asthma that allows study of several clinical and pathophysiologic features of asthma in sensitized subjects, including T_H2-derived asthma responses and relationship of this biology to airway pathology during the late-phase response. Because this procedure is reproducible, it can be used for early screening of new interventions, having a fair positive predictive response for successful agents and excellent ability

TABLE I. Key advances in environmental exposures in 2013

Advance	Reference no.
The new major rabbit allergen, Ory c 3, was identified.	1
The structure of Bla g 1 was determined.	2
Der p 1 enhances T _H 2 responses.	3
Indoor dampness and mold growth are associated with rhinitis.	4
New classification of aspergillosis in adult CF was reported.	5
DEPs induce IL-17A release.	6
Improved diagnostic tests for stinging insect venom allergy were developed.	7, 8
New insights into the genetics and immunologic responses in adverse drug reactions were defined.	9, 10
Differentiated bacterial infections versus delayed-type adverse drug reactions were differentiated, aided by serum procalcitonin level measurement.	11
Practice parameters for the assessment and control of cockroach allergens were published.	12
Validation of a patient satisfaction questionnaire will assist in patient adherence to allergen immunotherapy regimens.	13

to exclude ineffective agents. This procedure is safe and reproducible, especially when used by qualified and experienced investigators.

Marcon et al¹⁸ undertook a study of 3851 subjects with asthma, COPD, and allergic rhinitis who underwent spirometry and methacholine challenge during a baseline assessment (years 1991-1993; age range, 20-44 years) followed by follow-up assessments between 1999 and 2002 as part of the European Community Respiratory Health Survey. They found that subjects with increased airway responsiveness had the greatest chance of having asthma, COPD, and allergic rhinitis (incidence rate ratios of 10.82, 5.53, and 4.84, respectively; all $P < .01$). Thus methacholine reactivity predicted new-onset asthma, COPD, and allergic rhinitis. Hilton et al¹⁹ also described the use of capsaicin challenge to assess chronic cough. Using nonlinear mixed-effects modeling, they reported that maximal capsaicin-induced cough responses better discriminate health from disease and predict spontaneous cough frequency. These observations provide important new insights into the mechanisms underlying chronic cough.

Tse et al²⁰ examined bronchodilator responsiveness in 1041 asthmatic patients (59.7% male; mean age, 8.9 ± 2.1 years) and 250 control subjects (46.8% male; mean age, 8.7 ± 1.7 years) with mean bronchodilator responses of $10.7\% \pm 10.2\%$ and $2.7\% \pm 8.4\%$, respectively. Bronchodilator response could differentiate asthmatic patients from nonasthmatic patients with a moderate accuracy (area under the curve, 73.3%). However, although there was reasonably good specificity, a cutoff of 12% reactivity was associated with poor sensitivity for asthma (35.6%). These observations reveal poor sensitivity associated with the commonly used 12% cutoff for bronchodilator response as a criterion for asthma. However, Saito et al²¹ reported that sputum hydrogen sulfide was a promising test for identifying neutrophilic asthma.

The importance of identifying asthma was highlighted by a study undertaken by Mendola et al,²² who examined the effect of maternal asthma on neonatal outcomes using the Consortium on Safe Labor (2002-2008), a retrospective cohort with 223,512 singleton deliveries at 23 weeks' gestation or later. They found

TABLE II. Key advances in infections and asthma: asthma physiology assessment and therapeutics in 2013

Advance	Reference no.
TLR7 mediates pneumovirus enhancement of T _H 2 sensitization.	14
HRV-C is an important cause of asthma exacerbation.	15
Smoking enhances NTHi induction of COPD.	16
Allergen, methacholine, and capsaicin bronchoprovocation are important research tools.	17-19
Bronchodilator response might not be sensitive enough to diagnose asthma.	20
Asthma during pregnancy is associated with significant neonatal morbidity.	22
BT remains effective 5 y after the procedure in patients with severe asthma.	25

that maternal asthma was linked to preterm delivery after 33 weeks' gestation. Maternal asthma also increased the adjusted odds of being small for gestational age (OR, 1.10 [95% CI, 1.05-1.16]) or having neonatal intensive care unit admission (OR, 1.12 [95% CI, 1.07-1.17]), hyperbilirubinemia (OR, 1.09 [95% CI, 1.04-1.14]), respiratory distress syndrome (OR, 1.09 [95% CI, 1.01-1.19]), transient tachypnea of the newborn (OR, 1.10 [95% CI, 1.02-1.19]), and asphyxia (OR, 1.34 [95% CI, 1.03-1.75]). Findings persisted for term infants (≥ 37 weeks' gestation) who had additional increased odds of intracerebral hemorrhage (OR, 1.84 [95% CI, 1.11-3.03]) and anemia (OR, 1.30 [95% CI, 1.04-1.62]). Thus maternal asthma was associated with prematurity and small for gestational age infant outcomes, and other adverse neonatal outcomes, including respiratory complications, hyperbilirubinemia, and neonatal intensive care unit admission, were increased in association with maternal asthma even among term deliveries.

NEW ASTHMA THERAPIES

There continue to be research into new asthma therapeutics. Price et al²³ examined the use of montelukast and fluticasone on asthma control in asthmatic patients who are active smokers, finding that both agents resulted in fewer days of acute asthma. In terms of new interventions, Noonan et al²⁴ examined the effect of 12 weeks of treatment with lebrikizumab (an anti-IL-13 mAb) in 212 asthmatic patients, focusing on prebronchodilator FEV₁ at 12 weeks of treatment compared with baseline values. Anti-IL-33 treatment was generally well tolerated but insufficient to improve lung function in this group of asthmatic patients not receiving steroid treatment.

BT is another new intervention that has been reported to improve asthma control in patients up to 2 years after the procedure in patients with severe persistent asthma. Wechsler et al²⁵ examined the effectiveness and safety of BT in asthmatic patients 5 years after the procedure. They found that 162 (85.3%) of 190 BT-treated subjects completed 5 years of follow-up and found notable 5-year durability of the benefits of BT with regard to both asthma control (reduced severe exacerbations and emergency department visits for respiratory symptoms) and safety.

SUMMARY

A number of observations were reported in 2013, revealing characteristics of several allergens, parameters for aspects of

environmental control, and tools for improved patient-reported outcomes for immunotherapy. There were also important observations regarding the effect of infections, innate immunity, and lung inflammation in patients with airway diseases. There were also observations demonstrating that BT remains effective in patients with severe asthma as long as 5 years after the procedure. We look forward to continued advances in 2014.

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