

Advances in environmental and occupational disorders in 2014

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In 2014, the *Journal* published a number of studies that have advanced our understanding of the effects of various environmental factors and immune responses in patients with allergic diseases. In this review we emphasize reports that have appeared in the *Journal* over the past year that deal with environmental and occupational respiratory disorders and novel approaches to their treatment. The review will focus on the effects of environmental factors and immune responses in allergic airway diseases, identification of new allergens, and risk factors in stinging insect allergy, development of asthma in different age groups, effects of viral infections, and benefits of new therapies. (*J Allergy Clin Immunol* 2015;136:866-71.)

Key words: Air pollution, allergens, anaphylaxis, viral infections, immune responses, asthma

The *Journal of Allergy and Clinical Immunology* published a number of articles focused on environmental factors that affect allergic diseases. Other reports advanced our knowledge of therapeutic approaches to these conditions. Areas involved in the advances included (1) studies on the effects of environmental exposure on immune responses and disease pathophysiology, (2) identification and characterization of new allergens, (3) description of risk factors in systemic allergic reactions, (4) investigations of the role of viral infections in airway disease, and (5) reports on new therapies. In this review we highlight the advances in environmental and occupational disorders reported in the *Journal* in 2014.

EFFECTS OF ENVIRONMENTAL EXPOSURE ON IMMUNE RESPONSES AND AIRWAY DISEASES

In a comprehensive review Miller and Peden¹ discussed the effects of air pollution on immune responses in patients with

Abbreviations used

COPD: Chronic obstructive pulmonary disease
CRSsNP: Chronic rhinosinusitis without nasal polyps
CRSwNP: Chronic rhinosinusitis with nasal polyps
HRV: Human rhinovirus
PAF: Platelet-activating factor
PAF-AH: Platelet-activating factor acetylhydrolase
SOCS3: Suppressor of cytokine signaling protein 3
STAT3: Signal transducer and activator of transcription 3
TLR: Toll-like receptor

allergic respiratory diseases. Exposure to ambient fine particulate matter (particulate matter of 2.5 μm) and ozone account for a large number of asthma exacerbations, emergency department visits, and hospitalizations for asthma. Further exposure to these and other pollutants, such as polycyclic aromatic hydrocarbons and nitrogen dioxide, can result in decreased lung function. Children appear to be especially vulnerable to reduced lung growth and predisposed to chronic airway inflammation caused by these exposures. Atopy, stress, and obesity can enhance the adverse effects of air pollution. The authors describe a number of alterations in innate and adaptive immune responses that result from air pollutant exposure, including Toll-like receptor (TLR) signaling, damage-associated molecular pattern production, and proinflammatory epithelial responses. Furthermore, pollutants can upregulate $\text{T}_\text{H}2$, IL-17, and dendritic cells and impair regulatory T-cell function. In addition, gene-environment interactions can alter oxidative stress genes and cause epigenetic changes that result in increased inflammatory responses. Potentially, antioxidants might have therapeutic benefits in reducing pollutant-induced airway disease. Legislative initiatives to reduce air pollution have reduced asthma morbidity, but further research into the mechanisms and treatment of air pollution-induced airway disease are needed.

In another thorough review Bublin et al² described the role of lipids in the allergic sensitization process. Many allergens from pollens, house dust mites, pets, cockroaches, and food contain binding sites for lipid ligands that can enhance $\text{T}_\text{H}2$ responses. The authors provide a comprehensive discussion of the allergens, lipid mediators, mechanisms of action, and immune responses involved in allergic sensitization and disease. TLR4- and TLR2-dependent and CD1d-restricted mechanisms are especially relevant. Moreover, lipids can protect food allergens from proteolysis and enhance their uptake by intestinal epithelial cells. Because allergens are associated with lipids in a variety of contexts, this review is especially significant.

The role of environmental factors (allergens) in nonatopic asthma is not entirely clear. Increased total serum IgE levels are associated with an increased risk for asthma, regardless of atopic status. To evaluate the role of local specific IgE production in

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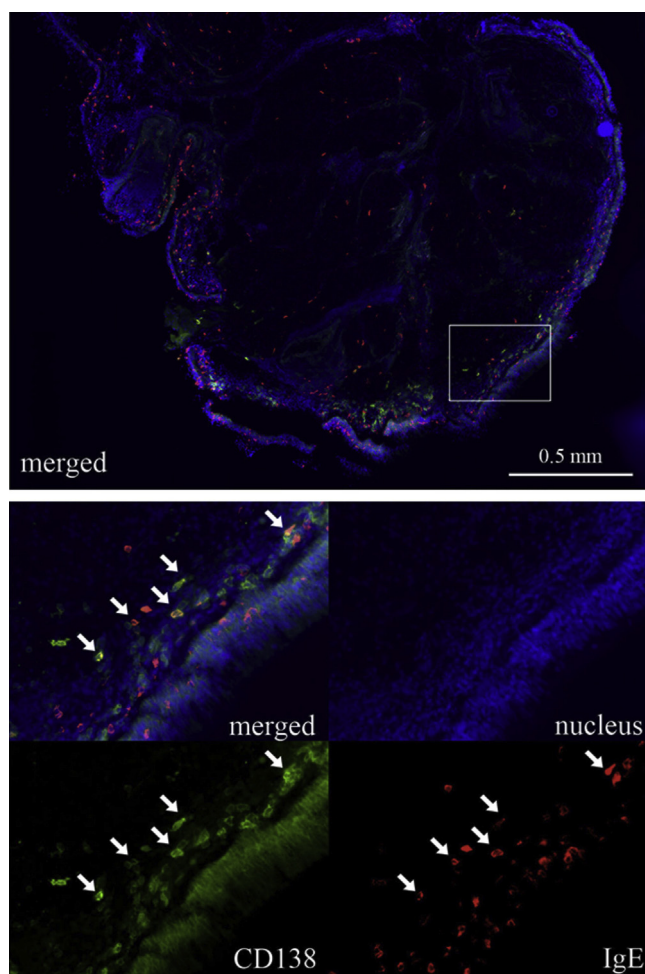


FIG 1. Immunofluorescence image of a bronchial biopsy specimen from a nonatopic asthmatic patient stained for plasma cells (CD138; green), IgE (red), and nucleus (blue). *Top*, View of the whole biopsy specimen showing area of magnification. *Bottom*, Magnified view with a merged image and individual stains. Arrows indicate cells with dual staining (plasma cells expressing IgE). From Pillai et al.³

patients with nonatopic asthma, Pillai et al³ performed bronchial mucosal biopsies on patients with nonatopic asthma, patients with atopic asthma, and nonasthmatic control subjects ($n = 10$ in each group) and examined the tissue for total and specific IgE to 100 known allergens. Biopsy specimens from both asthmatic groups showed increased total IgE levels compared with those in nonasthmatic control subjects. Specific IgE to the allergens tested was not detectable in biopsy specimens from nonatopic asthmatic patients. Although the data suggest that local IgE production occurs in nonatopic asthmatic patients, it is directed against targets other than allergens. Further studies will be needed to determine the exact role of this finding (Fig 1).³

Chronic rhinosinusitis with nasal polyps (CRSwNP) is believed to reflect a T_H2 response, whereas chronic rhinosinusitis without nasal polyps (CRSSNP) is characterized by neutrophilic inflammation. However, the immune response in patients with either condition are complex. Previous studies suggest that increased expression of suppressor of cytokine signaling protein 3 (SOCS3) is associated with T_H2 -mediated diseases, and

increased SOCS3 protein levels were found in ethmoid tissue in both patients with CRSwNP and those with CRSSNP.

To further evaluate the role of phosphorylated signal transducer and activator of transcription 3 (STAT3) and SOCS3 in nasal polyp tissue, Hulse et al⁴ studied these proteins in uncinate tissue from control subjects ($n = 5$), patients with CRSSNP ($n = 18$), and patients with CRSwNP ($n = 24$) and polyp tissue ($n = 31$). Levels of phosphorylated STAT3 were diminished in uncinate tissue and polyps from the patients with chronic rhinosinusitis compared with those in control subjects. Total STAT3 levels were similar in all groups. Surprisingly, SOCS3 levels were decreased in uncinate and polyp tissue from patients with CRSwNP. The fact that these findings differed from those of previous work suggests that tissue sampling (ethmoid vs uncinate tissue) and patient demographics (eg, ethnicity) might affect the results. Thus further investigations will be needed to better understand the role of potential environmental factors in the pathogenesis of CRS.

ALLERGENS

Identification of allergens and their characterization is important in the development of new diagnostic and therapeutic approaches to allergic diseases. Pollen-induced allergic rhinitis and asthma are common clinical problems. Grass pollen allergens are a major source of sensitization in many parts of the world. Group 5 grass pollen allergens, including Phl p 5 from timothy grass, are recognized as the most frequent and potent sensitizers. Focke-Tejkl et al⁵ examined the immune-dominant IgE and T-cell recognition sites on the Phl p 5 protein molecule. Using synthesized peptides of 31- to 38-amino-acid sequences, they found that Phl p 5 IgE epitopes are conformational and located on both the N- and C-terminal domains of Phl p 5. One peptide, P4, stimulated strong T-cell responses but was not part of the strongest IgE-reactive region. The dissociation of the major IgE- and T-cell-reactive domains in Phl p 5 could lead to novel therapeutic approaches.

Identification and characterization of new allergens can lead to new diagnostic tests. Mas et al⁶ conducted a complete immunoproteomic study of ash pollen extracts using 1-dimensional electrophoresis and molecular cloning. They identified 6 new allergens and showed a high degree of sequence identity with olive pollen allergens. Similarly, in studies of the allergens of *Plantago lanceolata* (English plantain) by Gadermaier et al,⁷ reactivity to English plantain pollen was largely due to IgE cross-reactivity to profilin that was probably induced by grass pollen sensitization. However, they identified the nonglycosylated rPla l 1 as a potential marker for true plantain sensitization. Lastly, Goldblum et al⁸ investigated the IgE-binding epitopes on the major mountain cedar pollen allergen Jun a 1. The molecule displayed at least 4 distinct IgE epitopes that are brought together by means of protein folding (conformational). These studies can lead to novel therapeutic approaches and serve as a model for studying the structural basis of allergenicity of protein allergens.

Allergen microarray-based assays are increasingly used to diagnose IgE-mediated allergic diseases. Cabauatan et al⁹ pointed out the limitations of such an approach in selected populations. They found that subjects residing in tropical climates exhibited a very high frequency of IgE sensitization to grass pollen-derived carbohydrate epitopes and little or no IgE reactivity to grass

pollen protein allergens. Consideration of climate factors that can affect glycosylation of plant pollen proteins must be taken into consideration when using microarrays for diagnostic purposes.

Pets are a major source of allergen exposure, and sensitization to pet allergens is a significant cause of allergic airway disease. Conversely, early childhood exposure to cat and dog allergens has been associated with decreased sensitization in some studies. Although this might be attributed to the presence of IgG antibodies to pet allergens, the association is not entirely clear. Curin et al¹⁰ sought to clarify the potential protective role of IgG responses to pet allergens using microarray assays for IgE and IgG to a number of cat, dog, and horse allergens. The investigators found a dissociation between allergen-specific IgE and IgG responses, which might explain why allergen-specific IgG responses might not always be protective.

Keeping rabbits as pets seems to be becoming more common. It is well known that occupational exposure to rabbits can induce allergic airway disease. Many known rabbit allergens can cross-react with other mammalian proteins, and therefore there is a need for identification of a novel rabbit allergen for determining specific sensitization. To this end, Hilger et al¹¹ isolated a new major rabbit lipophilin allergen, Ory c 3, which belongs to the secretoglobulin protein family. Although there appears to be structural similarity between Ory c 3 and the major cat secretoglobulin allergen Fel d 1, no IgE cross-reactivity was found. The identification of this allergen could be used to more accurately diagnose IgE sensitization in patients with allergic airway disease who are exposed to rabbits.

RISK FACTORS IN SYSTEMIC REACTIONS TO STINGING INSECTS AND DRUGS

Identification of risk factors for systemic reactions to stinging insect venoms and drugs can reduce adverse outcomes.

Sturn et al¹² examined the role of sensitization to stinging insect venoms in patients without a history of a systemic reaction. IgE antibodies to venoms are detected by *in vitro* testing in 27.1% to 40.7% of the general population who have no history of a stinging insect reaction. To further investigate the potential of future systemic reactions in the general population with asymptomatic sensitization, these investigators performed 131 bee and/or wasp sting challenges in 94 such subjects. Five (5.3%) experienced systemic reactions (urticaria, tachycardia, and mild hypotension and/or gastrointestinal symptoms [grade 1-3]), and 41 (43.6%) had large local reactions. Serum specific venom IgE antibody titers increased by an average of 3.5-fold (range, 0.2- to 34.0-fold) from baseline 4 weeks after the challenge. Eighteen randomly selected subjects were re-stung to further assess the significance of this increase. Nine (50%) had large local reactions, but none had a systemic reaction. The authors conclude that currently available tests for specific IgE to venoms are not able to distinguish between patients who will continue to have asymptomatic sensitization and those who will go on to experience large local reactions or, more importantly, systemic reactions on subsequent stings. Indiscriminate testing for IgE to venoms in patients with no prior history of reactions is unwarranted and can lead to misdiagnosis and unnecessary treatment.

Conversely, patients with a history of a systemic reaction to a sting with negative specific IgE measurements to commercially available venom extracts present a diagnostic dilemma. Because 0.05% to 2% of the population have had systemic sting reactions,

intradermal skin testing to venoms is lacking in sensitivity (26% to 89%), and measurement of specific serum IgE to venom is not ideal. Cifuentes et al¹³ examined the use of recombinant venom allergens in the diagnosis of systemic sting reactions when results of commercial tests are negative. Using assays for IgE to recombinant yellow jacket venom allergens (rVes v 1-5) increased the sensitivity compared with current extract tests from 42.1% to 84.2%, and similarly, the use of recombinant honey bee venom allergens (rApi m 1-5) increased sensitivity from 37.5% to 100%. Although current testing has improved over the past decade, detection of specific IgE to a panel of recombinant venom allergens can further improve diagnosis.

Platelet-activating factor (PAF) plays an important role in hypotension associated with anaphylaxis. PAF is quickly degraded by the enzyme platelet-activating factor acetylhydrolase (PAF-AH). Low PAF-AH levels have been found in children with fatal anaphylaxis. Pravettoni et al¹⁴ examined basal PAF-AH levels in 169 adults with a history of Hymenoptera venom-induced anaphylaxis and 60 control subjects. Patients with a history of grade III or IV anaphylaxis had the lowest PAF-AH levels, with 73.7% for grade II and 89.2% for grade IV having enzyme activity of less than 20 nmol/mL/min (the lowest cutoff level). Use of PAF-AH activity levels can predict those at risk for future stinging insect venom-induced anaphylactic reactions. The kinetics of PAF-AH and genetic studies of polymorphisms are fertile areas to be explored.

Allergic reactions to platelet transfusion occur in 2% or more of recipients. Savage et al¹⁵ sought to identify the risk factors involved in these reactions. In comparing factors in patients (n = 124) with reactions to platelet transfusion with those who did not have such reactions (n = 44), the investigators found a direct relationship between the concentration of aeroallergen-specific and total IgE and the occurrence of an allergic transfusion reaction. Furthermore, they found that transfusion reaction rates decrease with increasing transfusion exposure and that atopy in donors is not associated with reactions in recipients. Evidence that mast cell degranulation and leukotriene pathway activation are the mechanisms underlying these reactions was presented. Therapies that inhibit these processes might be useful in preventing reactions in platelet transfusion recipients at risk (eg, with hay fever).

IDENTIFYING RISK FOR ASTHMA FROM INFANCY TO ADULTHOOD

Several articles examined specific tests or markers of asthma risk across several age ranges. Mendola et al¹⁶ examined the effect of maternal asthma on pregnancy outcomes. This team examined a cohort that included 223,512 singleton deliveries at 23 weeks' gestation or later. Health outcomes of infants born to women with asthma (n = 17,044) were compared with those of infants born to nonasthmatic mothers. They found that risk of preterm birth was increased in women with asthma after 33 weeks' gestation. Infants born to asthmatic mothers also had increased risk for being small for gestational age, requiring neonatal intensive care unit admission, and having hyperbilirubinemia, respiratory distress syndrome, transient tachypnea of the newborn, and birth asphyxia. Term infants (≥ 37 weeks' gestation) had increased risk for intracerebral hemorrhage and anemia.

TABLE I. Key advances

Advance	References
Air pollution is a significant factor in asthma. Dissection of the immune mechanism can improve therapy.	Miller and Peden ¹
Lipids can increase IgE responses to allergens.	Bublin et al ²
Recombinant allergens can improve the identification of patients with Hymenoptera venom allergy.	Cifuentes et al ¹³
Novel allergens from rabbits, ash tree, and English plantain were identified.	Gadermaier et al, ⁷ Hilger et al ¹¹
Novel approaches in analyzing available data might greatly improve our ability to identify subgroups of persons at risk for airway pathophysiology associated with asthma.	Howrylak et al, ¹⁷ Marcon et al ¹⁸
The effect of viral infections associated with increased asthma risk might be associated with coinfection with other viruses, existing airway bacterial colonization, or novel host factors.	Lukkarinen et al, ¹⁹ Hyde et al, ²⁰ Iwasaki et al, ²¹ Hong et al, ²² Cho et al ²³
Theophylline can have actions on airway sensory and vagal nerves that account for antitussive actions.	Dubois et al ²⁵
Voriconazole is not an effective adjunct for decreasing allergic asthma associated with <i>Aspergillus fumigatus</i> .	Agbetile et al ²⁶
There are continued advances in our understanding of the biology of asthma driven by novel immunobiological agents, approaches to modify corticosteroid response, and allergen immunotherapy that will lead to improved treatments for asthma.	Hatchwell et al, ²⁴ De Boever et al, ²⁷ Mosbech et al ³⁰

Howrylak et al¹⁷ used spectral cluster analysis approaches with posttreatment pulmonary function anti-inflammatory treatment response data obtained over 48 months from 1041 participants in the Childhood Asthma Management Program. They identified 5 patient clusters from 3 groups of asthma phenotypic features: atopic burden, airway obstruction, and exacerbations that predicted long-term asthma control based on oral prednisone use, need for additional controller medications, or longitudinal differences in lung function. Two clusters with the most exacerbations had unique responses to inhaled corticosteroids relative to the other clusters, one with a positive response to budesonide and nedocromil (vs placebo) and the other being nonresponsive to intervention. These results suggest that such analyses can be used to identify those who need targeted interventions.

In an analogous study Marcon et al¹⁸ examined 3851 persons aged 20 to 44 years at the time of study entry who underwent methacholine challenge at baseline and 8 years later, with methacholine response determined by the dose-response slope. They examined the change in this slope with the incidence of asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis, finding those with the lowest slope had increased risk for these diseases. This was true even if those with the lowest slope did not have a greater than 20% decrease in FEV₁ after challenge. Taken together, these reports all suggest that novel approaches in analyzing available data might greatly improve our ability to identify subgroups at risk for airway disease.

VIRAL INFECTIONS AND ASTHMA

Although viral infections are a long appreciated risk factor for induction and exacerbation of asthma, there were a number of interesting reports in the 2014 issues of the *Journal* examining viral infections in the setting of asthma. An intriguing report by Lukkarinen et al¹⁹ examined infants in Finland infected

with the RNA virus rhinovirus and the DNA virus human bocavirus either alone or together. They found that wheezing and inflammatory responses were tempered in those children with bocavirus, including the effect of rhinovirus in those children who were coinfecting. This suggests that in addition to host-virus interactions, virus-virus interactions modulate human airway biology. There might also be bacteria-virus interactions that are important in expression of viral airway disease. Hyde et al²⁰ reported that upper airway colonization with bacteria from the Proteobacteria family, especially *Haemophilus influenzae* and *Moraxella catarrhalis*, was increased in children with bronchiolitis caused by respiratory syncytial virus or human rhinovirus (HRV).²⁰

However, host response was also altered during viral infection in those with airway disease. Iwasaki et al²¹ reported that 96 asthmatic children had greater HRV IgG₁ response to viral capsid proteins from HRV-A and HRV-B compared with 47 nonasthmatic children. HRV-C responses tended to be lower in both groups and not different between them. Overall, these data suggest a greater immune response to HRV-A and HRV-B in asthmatic children. Data from Hong et al²² suggest that the age of HRV infection might be an important factor in asthma risk because of increased response to IL-25-driven T_H2-type responses. They demonstrated this using a murine model in which neonatal and adult mice were infected with rhinovirus, in which the response in neonates was associated with increased IL-25 and IL-13 responses involving expansion of IL-13-secreting type 2 innate lymphoid cells. Cho et al²³ reported that levels of plasminogen activator inhibitor 1 were increased in airway and nasal lavage fluids from asthmatic patients compared with those in patients without asthma and increased even further after viral infection. This mediator inhibits both the fibrinolytic system and the matrix metalloproteinase system, which allows airways remodeling to occur. Finally, Hatchwell et al²⁴ used a murine model to show that salmeterol exerts anti-inflammatory effects on allergen- and rhinovirus-induced

inflammation by increasing levels of protein phosphatase 2A, which decreases CCL11, CCL20, and CXCL2 expression. Clearly, viral respiratory tract infections influence inflammation seen in asthmatic patients, and host responses to viral infections are a key factor.

NEW TREATMENTS FOR AIRWAY DISEASES

2014 continued to see a number of reports focused on novel interventions or novel uses of established interventions for airway disease. Theophylline received a fresh look as an antitussive agent in studies reported by Dubois et al.²⁵ Among their findings were that theophylline inhibited C-fiber afferent nerves *in vivo*, depolarization of human and guinea pig vagus fibers *in vitro*, and antitussive activity in guinea pigs exposed to cigarette smoke. Agbetele et al.²⁶ re-examined the idea that antifungal agents can affect allergic asthma associated with IgE sensitization to *Aspergillus fumigatus*. They randomized 65 patients with moderate-to-severe asthma and skin test reactivity to *A. fumigatus*, with 59 patients starting a planned 3-month treatment with either voriconazole (n = 32) or placebo (n = 27) and no improvement being observed in the active treatment group.

In a study of the action of a novel humanized mAb that inhibits IL-13 binding to IL-13 receptor $\alpha 1$ and $\alpha 2$ in patients with severe asthma, De Boever et al.²⁷ found that intervention had little effect in patients with severe asthma compared with placebo (n = 99 for both groups). An *in vitro* study by Milara et al.²⁸ of the effect of the phosphodiesterase 4 inhibitor roflumilast N-oxide (the active metabolite of roflumilast, which is approved to reduce the risk of exacerbations in patients with severe COPD) demonstrated that these drug polymorphonuclear neutrophils from patients with COPD and smokers had decreased corticosteroid resistance. This observation supports the strategy of developing treatments to modify steroid responsiveness in patients with asthma endotypes characterized by steroid resistance.²⁹ Finally, Mosbech et al.³⁰ reported that in a study of 600 volunteers with allergic rhinitis and mild-to-moderate asthma randomized to treatment with one of 3 standardized sublingual house dust mite immunotherapy doses or placebo, the highest dose was associated with the ability to decrease inhaled corticosteroid doses while maintaining adequate asthma control.

SUMMARY

In this review we examined reports in the 2014 volumes of the *Journal*. There were important reports and reviews for air pollution, novel allergen identification, treatment of stinging insect allergy (an issue likely to increase as populations of stinging insects change habitats), new ways to categorize asthma endotypes, viral and microbial influences in airway disease, and new treatments. We anticipate that the 2015 *Journal* submissions will be equally provocative and informative. The key advances reviewed in this article are summarized in Table I.^{1,2,7,11,13,17-27,30}

REFERENCES

1. Miller R, Peden DB. Environmental effects on immune responses in patients with atopy and asthma. *J Allergy Clin Immunol* 2014;134:1001-8.
2. Bublin M, Eiwegger T, Brieteneder H. Do lipids influence the allergic sensitization process? *J Allergy Clin Immunol* 2014;134:521-9.
3. Pillai P, Fang C, Chang YC, Shamji MH, Harper C, Wu SY, et al. Allergen-specific IgE is not detectable in the bronchial mucosa of nonatopic asthmatic patients. *J Allergy Clin Immunol* 2014;133:1770-2.e11.
4. Hulse KE, Chung K, Seshardi S, Suh L, Norton JE, Carter RG, et al. Suppressor of cytokine signaling 3 expression is diminished in sinonasal tissues from patients with chronic Rhinosinusitis with nasal polyps. *J Allergy Clin Immunol* 2014;133:275-7.e1.
5. Focke-Tejkl M, Campana R, Reininger R, Lupinek C, Blatt K, Valent P, et al. Dissection of the IgE and T-cell recognition of the major group 5 grass pollen allergen Phl p 5. *J Allergy Clin Immunol* 2014;133:836-45.
6. Mas S, Torres M, Garrido-Arandia M, Salamanca G, Castro L, Barral P, et al. Ash pollen immunoproteomics: identification, immunologic characterization, and sequencing of 6 new allergens. *J Allergy Clin Immunol* 2014;133:923-6.e3.
7. Gadermaier G, Eichhorn S, Vejvar E, Weinböck L, Lang R, Briza P, et al. *Plantago lanceolata*: an important trigger of summer pollinosis with limited IgE cross-reactivity. *J Allergy Clin Immunol* 2014;134:472-5.e5.
8. Goldblum R, Ning B, Endsley MA, Estes DM, Judy BM, van Bavel J, et al. IgE antibodies to mountain cedar pollen predominantly recognize multiple conformational epitopes on Jun a 1. *J Allergy Clin Immunol* 2014;134:967-9.e7.
9. Cabauatan C, Lupinek C, Schieblhofer S, Weiss R, Focke-Tejkl M, Bhalla PL, et al. Allergen microarray detects high prevalence of asymptomatic IgE sensitizations to tropical pollen-derived carbohydrates. *J Allergy Clin Immunol* 2014;133:910-4.e5.
10. Curin M, Swoboda I, Wollmann E, Lupinek C, Spitzauer S, van Hage M, et al. Microarrayed dog, cat, and horse allergens show weak correlation between allergen-specific IgE and IgG responses. *J Allergy Clin Immunol* 2014;133:918-21.e6.
11. Hilger C, Kler S, Arumugam K, Revets D, Muller CP, Charpentier C, et al. Identification and isolation of a Fel d 1-like molecule as a major rabbit allergen. *J Allergy Clin Immunol* 2014;133:759-66.
12. Sturm GJ, Kranzelbinder B, Schuster C, Sturm EM, Bokanovic D, Vollmann J, et al. Sensitization to Hymenoptera venoms is common, but systemic sting reactions are rare. *J Allergy Clin Immunol* 2014;133:1635-43.
13. Cifuentes L, Vosseler S, Blank S, Seisemann H, Pennino D, Darsow U, et al. Identification of Hymenoptera venom-allergic patients with negative specific IgE to venom extract by using recombinant allergens. *J Allergy Clin Immunol* 2014;133:909-10.
14. Pravettoni V, Piantanida M, Primavesi L, Forti S, Pastorello EA. Basal platelet-activating factor acetylhydrolase: prognostic marker of severe Hymenoptera venom anaphylaxis. *J Allergy Clin Immunol* 2014;133:1218-20.
15. Savage WJ, Hamilton RG, Tobian AA, Milne GL, Kaufman RM, Savage JH, et al. Defining risk factors and presentations of allergic reactions to platelet transfusion. *J Allergy Clin Immunol* 2014;133:1772-5.e5.
16. Mendola P, Männistö TI, Leishar K, Reddy UM, Chen Z, Laughon SK. Neonatal health of infants born to mothers with asthma. *J Allergy Clin Immunol* 2014;133:85-90.
17. Howrylak JA, Fuhlbrigge AL, Strunk RC, Zeiger RS, Weiss ST, Raby BA. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. *J Allergy Clin Immunol* 2014;133:1289-300.
18. Marcon A, Cerveri I, Wjst M, Antó J, Heinrich J, Janson C, et al. Can an airway challenge test predict respiratory diseases? A population-based international study. *J Allergy Clin Immunol* 2014;133:104-10.
19. Lukkariinen H, Söderlund-Venermo M, Vuorinen T, Allander T, Hedmann K, Simell O, et al. Human bocavirus 1 may suppress rhinovirus-associated immune response in wheezing children. *J Allergy Clin Immunol* 2014;133:256-8.e4.
20. Hyde ER, Petrosino JF, Piedra PA, Camargo CA, Espinola JA, Mansbach JM. Nasopharyngeal Proteobacteria are associated with viral etiology and acute wheezing in children with severe bronchiolitis. *J Allergy Clin Immunol* 2014;133:1220-2.e3.
21. Iwasaki J, Smith WA, Khoo SK, Bizzintino J, Zhang G, Cox DW, et al. Comparison of rhinovirus antibody titers in children with asthma exacerbations and species-specific rhinovirus infection. *J Allergy Clin Immunol* 2014;134:25-32.
22. Hong JY, Bentley JK, Chung Y, Lei J, Steenrod JM, Chen Q, et al. Neonatal rhinovirus induces mucous metaplasia and airways hyperresponsiveness through IL-25 and type 2 innate lymphoid cells. *J Allergy Clin Immunol* 2014;134:429-39.
23. Cho SH, Hong SJ, Chen H, Habib A, Cho D, Lee SH, et al. Plasminogen activator inhibitor-1 in sputum and nasal lavage fluids increases in asthmatic patients during common colds. *J Allergy Clin Immunol* 2014;134:1465-7.e2.
24. Hatchwell L, Girkin J, Dun MD, Morten M, Verrills N, Toop HD, et al. Salmeterol attenuates chemotactic responses in rhinovirus-induced exacerbation of allergic airways disease by modulating protein phosphatase 2A. *J Allergy Clin Immunol* 2014;133:1720-7.

25. Dubois E, Wortley MA, Grace MS, Maher SA, Adock JJ, Birrell MA, et al. Theophylline inhibits the cough reflex through a novel mechanism of action. *J Allergy Clin Immunol* 2014;133:1588-98.
26. Agbetile J, Bourne M, Fairs A, Hargadon B, Desai D, Broad C, et al. Effectiveness of voriconazole in the treatment of *Aspergillus fumigatus*-associated asthma (EVITA3 study). *J Allergy Clin Immunol* 2014;134:33-9.
27. De Boever EH, Ashman C, Cahn AP, Mocantore NW, Pverend P, Pouliquen IS, et al. Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: a randomized trial. *J Allergy Clin Immunol* 2014;133:989-96.
28. Milara J, Lluch J, Almudever P, Freire J, Xiaozhong Q, Cortijo J. Roflumilast N-oxide reverses corticosteroid resistance in neutrophils from patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2014;134:314-22.
29. Koenderman L, Chilvers E. Future treatment in patients with chronic obstructive pulmonary disease: to reverse or not reverse steroid resistance—that is the question. *J Allergy Clin Immunol* 2014;134:323-4.
30. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-75.

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