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A Synopsis of Allergy and Asthma Literature, Resulting from an Unbiased, Comprehensive Review of Twenty Major Medical Journals.

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## FEATURE ARTICLES

### 'LEAP-On' Study: Peanut Allergy Prevention Appears to Be Durable!

The LEAP trial ("Learning Early About Peanut Allergy") found that sustained peanut consumption starting before age 1 can prevent peanut allergy in high-risk infants. A 12-month extension phase evaluated whether this protective effect persists in children who stop consuming peanuts for a year.

The LEAP-On study included 556 children from the primary trial: 282 assigned to peanut avoidance and 274 to peanut consumption. At the end of the LEAP trial, both groups were instructed to avoid peanuts for 1 year; mean age at that time was 61.3 months. At 72 months, rates of peanut allergy were compared by oral peanut challenge.

Analysis included complete outcome data for 550 children. Rates of peanut avoidance during the LEAP-On year were 90.4% for children assigned to peanut avoidance and 69.3% for those assigned to peanut consumption. At 72 months, 18.6% of children in the peanut-avoidance group had peanut allergy, compared to 4.8% in the peanut-consumption group.

Among children initially assigned to peanut consumption, there was no significant change in allergy prevalence during the LEAP-On year: from 3.6% to 4.8%. Children in the peanut-consumption group were less likely to have elevated levels of peanut-specific or Ara h 2-specific IgE, but continued to have higher levels of peanut-specific IgG4 and a higher peanut-specific IgG4:IgE ratio.

The LEAP-On results suggest that the protective effect of early introduction of peanut in high-risk children persists after a 1 year period of peanut avoidance. After this extension study, the prevalence of peanut allergy remains 74% lower for children assigned to early peanut consumption. The researchers conclude, "Four years of consuming peanut was sufficient to induce stable unresponsiveness to • • •



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- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Journal of Asthma
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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peanut, independent of the level of subsequent consumption of peanut."

**COMMENT:** When the LEAP study children stopped eating peanuts at age 5, there was no increase in the prevalence of peanut allergy at age 6. This suggests that the preventive strategy of introducing peanut consumption early in high-risk children is not only an effective way to avoid becoming allergic to peanuts, but that this peanut tolerance is durable after a year of avoidance. It is important to keep in mind that the study selected children at high risk of peanut allergy; time will tell if this kind of primary and secondary prevention works in lower-risk children. If so, then the epidemiology of peanut allergy may be dramatically different 10 years from now.

S.A.T.

Du Toit G, Sayre PH, Roberts G, et al: Effect of avoidance on peanut allergy after early peanut consumption. N Engl J Med. 2016; 374:1435-1443.

Keywords: allergen avoidance, early introduction, peanut allergy

## EAT Study: Preventing Food Allergy May Be Harder Than We Thought

Observational data suggest that early introduction of peanut, egg, and cow's milk may help to prevent allergy to these foods. While the LEAP study has confirmed this benefit for peanut, the effects of early introduction of other foods remain unclear. The EAT ("Enquiring about Tolerance") trial evaluated the effects of early introduction of common dietary allergens in a general population.

The single-center UK trial included 1,303 infants who were exclusively breast-fed when enrolled at age 3 months. One group was randomly assigned to early introduction of six common food allergens: peanut, cooked egg, cow's milk, sesame, whitefish, and wheat. Control infants continued on exclusive breast-feeding to about age 6 months, following UK guidelines. Rates of food allergy were compared between groups when the children were 1 to 3 years old.

On intention-to-treat analysis, at least one type of food allergy developed in 5.6% of children in the early introduction group and 7.1% in the control group—the difference was not significant. Per-protocol analysis suggested that early introduction reduced the risk of any food allergy: 2.4% versus 7.3%. There were also significant reductions in peanut allergy, zero versus 2.5%; and egg allergy, 1.4% versus 5.5%.

The prevalence of peanut or egg allergy was significantly reduced for children who consumed 2 g per week of peanut or egg-white protein, respectively, compared to lower amounts. Early introduction of the six study foods was difficult to achieve but was safe, with no episodes of anaphylaxis and no problems related to breast-feeding or growth.

Analyzed by intention to treat, the EAT study shows no significant reduction in food allergies with early introduction of multiple potentially allergenic foods. Some findings suggest that the protective effect of early introduction may depend on dose and adherence. Per-protocol analysis suggests possible reduction in peanut and egg allergy with early introduction of these foods.

**COMMENT:** With the landmark LEAP study suggesting that early introduction of peanut prevents peanut allergy, there has been great

enthusiasm for seeing if even earlier introduction of multiple allergenic foods might prevent other food allergies. The EAT study's per-protocol analysis results were impressive—but of course, they were biased by exclusion of subjects who did not complete the study. Intention-to-treat analysis did not show a significant protective effect, and in the absence of such data it is hard to conclude that this primary prevention strategy works. Darn it! Stay tuned for further data...in the meantime, it appears allergists will remain busy taking care of young children with food allergies.

S.A.T.

Perkin MR, Logan K, Tseng A, et al: Randomized trial of introduction of allergenic foods in breast-fed infants.
N Engl J Med. March 4, 2016; DOI: 10.1056/NEJMoa1514210SAT.

Keywords: early introduction, egg allergy, food allergy, peanut allergy

## Wheezy Bronchitis in Childhood Linked to COPD 50 Years Later

Childhood asthma is associated with chronic obstructive pulmonary disease (COPD) later in life. It is unclear whether wheezy bronchitis and virus-associated wheezing—common conditions in early childhood—are also related to later COPD. This question was addressed using follow-up data from a 50-year cohort study.

The analysis included children in Aberdeen, Scotland, who were 10 to 15 years old when recruited in 1964. Of the initial sample of 2,511 children, 121 were classified as having childhood asthma and 167 as having wheezy bronchitis—wheezing only in the presence of upper respiratory tract infection. Participants were followed up in 1989, 1995, 2001, and 2014. Evaluation included pulmonary function testing, with COPD defined as a postbronchodilator $FEV_1$/FVC of less than 0.7.

The 2014 follow-up data included 330 participants, mean age 61 years. Of these, 38 had childhood asthma and 53 had wheezy bronchitis. Of 239 controls without childhood wheezing, 57 developed adult-onset wheezing between age 16 and 46 years.

On multivariate analysis, risk of COPD was increased not only for participants with childhood asthma, odds ratio 6.37; but also for those with wheezy bronchitis, odds ratio 1.81. The increase in COPD risk with childhood asthma and wheezy bronchitis was associated with reductions in $FEV_1$ developing by age 50. A faster rate of decline in $FEV_1$ was apparent only in the cohort members with adult-onset wheezing.

These very long-term follow-up data suggest that children with wheezy bronchitis or virus-associated wheezing are at increased risk of COPD and reduced ventilator function as older adults. These children have reduced $FEV_1$ early in life, as do those with childhood asthma, whereas adult-onset wheezing is associated with a more rapid decline in $FEV_1$. The findings have important implications for long-term follow-up of children with wheezy bronchitis.

**COMMENT:** This very important study links the burden of airflow obstruction in the immediate postnatal period to poor outcomes in later life, including COPD. Attention must be given to exposure to active and passive smoking and air pollution. It is possible that decreasing allergen exposure and sensitization early in life may have added benefit.

B.E.C.

Tagiyeva N, Devereux G, Fielding S, et al: Outcomes of childhood asthma and wheezy bronchitis: a 50-year cohort study.
Am J Respir Crit Care Med. 2016;193:23-30.

Keywords: asthma (child), wheezing, COPD

## Epigenetic Signature for IL-13 Important in Asthma Pathophysiology

Epigenetic effects on airway cells may modulate the effects of environmental factors on airway diseases. Interleukin-13 (IL-13), an important mediator of asthma and other allergic airway diseases, is upregulated in response to exposures including air pollution, viruses, and airborne allergens. This study compared IL-13-induced epigenetic changes in airway epithelial cells (AECs) from asthmatic and nonasthmatic subjects.

The researchers performed genome-wide DNA methylation and gene expression studies in 58 primary AEC cultures, exposed or unexposed to IL-13. Interleukin-13 induced changes in genome-wide DNA methylation levels, with significant enrichment near asthma-related genes. The IL-13 epigenetic signature observed in cultured AECs was largely validated in freshly isolated cells from individuals with and without asthma.

Weighted gene coexpression network analysis identified two distinct comethylation networks associated with asthma phenotype: one module related to asthma severity and lung function and another with eosinophilia. Analysis of these networks identified pathways and molecules implicated in IL-13-mediated pathophysiologic changes.

Exposure to IL-13 may induce persistent DNA methylation changes in airway cells from asthma subjects. The IL-13-induced epigenetic signature affects specific AEC pathways involved in asthma clinical phenotypes. Epigenetic changes in airway cells may be an important contributor to individual variations in asthma susceptibility or severity.

**COMMENT:** This important study of cultured AECs gives us insight that more than genetic variation is operative in the phenotypic expression of asthma. The finding that IL-13-mediated epigenetic signature is highly correlated with nearby gene expression in individuals with asthma may have implications for the onset of clinical asthma. New insights on DNA methylation and disease-specific gene expression may provide significant breakthroughs for the application • • •

of precision medicine.

B.E.C.

Nicodemus-Johnson J, Naughton KA, Sudi J, et al: Genome-wide methylation study identifies an IL-13-induced epigenetic signature in asthmatic airways. Am J Respir Crit Care Med. 2016; 193: 376-385.

Keywords: asthma phenotypes, epigenetics, risk factors

## Controlling Asthma Reduces Costs: Further Evidence

Disease control has become an important endpoint in asthma clinical trials. Although several studies have examined the costs of asthma, few have addressed the potential for reducing costs related to uncontrolled asthma. The authors estimated the cost savings achieved by following a guideline-based approach to asthma symptom control.

Five hundred seventeen Canadian adults and adolescents with asthma, mostly mild to moderate, were recruited by random digit dialing. Average age at baseline was about 49 years; nearly two-thirds of patients were female. In three-monthly visits up to 1 year, the Global Initiative for Asthma (GINA) 2014 management strategy was followed to achieve asthma symptom control. The association between costs (expressed in 2012 Canadian dollars) and symptom control was assessed, with adjustment for potential confounders.

In 2,033 follow-up visits, asthma was considered controlled in 29.4% of visits, partially controlled in 39.8%, and uncontrolled in 30.8%. Three-month asthma costs averaged CA$134.50. Of the total, 47.8% was attributed to outpatient care, 31.5% to medications, and 20.5% to inpatient care. Adjusted 3-month costs were CA$81.17 higher for uncontrolled versus controlled asthma. Partially controlled asthma was associated with a nonsignificant CA$9.50 increase in costs.

The study estimates the savings in direct healthcare costs achievable with asthma symptom control. The findings will be useful in evaluating the cost-effectiveness of asthma treatments. The researchers note that, even with guideline-based management, asthma was uncontrolled in more than 30% of patient visits.

**COMMENT:** Unlike most studies that examine the goal of achieving asthma control, this study evaluated the impact of control and health care utilization. Even though the majority of subjects in the study had mild to moderate asthma, a substantial fraction did not have symptom control. Achieving symptom control was associated with a reduction in direct costs. In light of the changes in our health care system—with the new mantra of pay for performance—the study reinforces that asthma control is of great importance and translates to cost savings to the system.

J.J.O.

Sadatsafavi M, Chen W, Tavakoli H, et al: Saving in medical costs by achieving guideline-based asthma symptom control: a population-based study. Allergy. 2016:71:371-377.

Keywords: asthma (adult), asthma control, costs

## Grass SCIT plus Anti-IL-4 Yields Unclear Clinical Benefit

More effective control of Th2 memory cells might further improve the outcomes of allergen immunotherapy. Previous studies have demonstrated that induction of forkhead box P3-positive T-regulatory (Treg) cells is dependent on interleukin-4 (IL-4). This trial evaluated the effect of adding anti-IL-4 treatment to a suboptimal course of subcutaneous immunotherapy (SCIT) on sustained tolerance to allergen.

The randomized, double-blind, placebo-controlled trial included 37 patients with seasonal allergic rhinitis and a positive skin-prick test to grass pollen. Two groups received suboptimal grass pollen SCIT, 30,000 standardized quality units, with or without anti-IL-4 treatment with VAK694. A third group received double placebo; all treatments were given in the 13 weeks before grass pollen season.

At 12 months, both active treatment groups had significant and sustained reduction of the allergen-induced skin late-phase response (LPR), evaluated as a surrogate for clinical response to SCIT. The improvement in LPR was similar with or without the addition of anti-IL-4 therapy. Exploratory analysis of immune markers suggested that the combination treatment led to sustained reduction in allergen-specific IL-4-producing cell counts. With or without anti-IL-4 treatment, suboptimal SCIT resulted in induction of dual IL-4/IL10-producing cells during grass pollen season. Both SCIT groups reported significant reduction in global seasonal symptom scores.

Combining anti-IL-4 treatment with suboptimal SCIT does not produce additional suppression of the allergen-induced skin LPT, compared to SCIT alone. However, secondary analyses suggest that adding VAK694 is associated with ex vivo downregulation of Th2 responses. The potential clinical benefit of deletion of peripheral antigen-specific Th2 cells warrants further study.

**COMMENT:** Allergen immunotherapy induces Treg cells and alters Th2 cytokine responses, but we need optimal doses to induce clinically significant impact. These researchers hypothesized that adding anti-IL-4 to suboptimal doses of SCIT could be effective in suppressing the Th2 response, as measured by late-phase skin reaction. Although they were not able to show additional benefit in reduction in LPR on skin testing, there was a substantial reduction of allergen-specific memory Th2 responses. Larger studies will need to be completed to show clinical benefit, but the concept of enhancing the immunologic responses to SCIT using various biologics is fascinating.

S.M.F.

Chaker AM, Shamji MH, Dumitru, et al: Short-term subcutaneous grass pollen immunotherapy under the umbrella of anti-IL-4: a randomized controlled trial. J Allergy Clin Immunol. 2016;137:452-461.

Keywords: allergic rhinitis, biologics, SCIT

## Can Component Testing Optimize Peanut SLIT?

Responses to sublingual immunotherapy (SLIT) for peanut allergy are highly variable. With the availability of ImmunoCAP tests specific for peanut component allergens, there is increased interest in component-resolved diagnosis of peanut allergy. This trial evaluated whether component analysis can predict the outcomes of peanut SLIT.

The researchers analyzed the results of double-blind placebo-controlled food challenges in 33 patients who had completed 12 months of peanut SLIT. Plasma samples collected before and after SLIT were assayed using ImmunoCAP tests for IgE and IgG4 for whole peanut and for the component allergens Ara h 1, Ara h 2, Ara h 3, Ara h 8, and Ara h 9.

Thirty percent of patients were considered desensitized, with no symptoms in response to challenge with 2,500 mg of peanut protein. For those who failed challenge, the amount of peanut protein tolerated varied widely, with a median of 460 mg. Compared to patients who tolerated the full challenge dose, those who were not desensitized had lower median levels of IgE against peanut, 40.8 vs 231 kUA /L; Ara h 2, 17.0 vs 113 kUA /L; and Ara h 3, 0.3 vs. 8.5 kUA. On receiver operating characteristic curve analysis, baseline results for whole peanut and Ara h 2 were equally effective at predicting response to peanut SLIT.

On component testing, patients with lower baseline levels of IgE against whole peanut, Ara h 2, and Ara h 3 are more likely to be completely desensitized after a year of peanut SLIT. The results suggest the possible value of performing SLIT in younger children with lower peanut-specific IgE levels. Further studies of immunotherapy-related biomarkers are needed.

**COMMENT:** Although peanut SLIT is very safe, studies have demonstrated great variability in efficacy. Only a small group of subjects have a complete response; in others, SLIT works no better than placebo. Understanding this profound heterogeneity in treatment response, the authors explored potential predictors of response to peanut SLIT. As noted by Burk and colleagues, it would be a great advance to optimize selection of patients most likely to benefit from SLIT to peanut. They examined baseline ImmunoCAP levels to IgE and IgG4 against whole peanut as well as Ara h 1 to 3, 8, and 9. They found that patients with successful outcomes had low IgE levels to whole peanut, as well as Ara h 1 and 2, with whole peanut and Ara h 2 being the best discriminators. The findings are consistent with other studies that have shown immunodominance of Ara h 2 in American patients with peanut allergy and an inverse relationship between immunotherapy treatment outcomes and the strength of allergic priming. Although the results are exciting, the authors reinforce that further study is needed to confirm these findings, as well as to explore other potential biomarkers for peanut SLIT.

J.J.O.

Burk CM, Kulis M, Leung N, et al: Utility of component analyses in subjects undergoing sublingual immunotherapy for peanut allergy.
Clin Exp Allergy. 2016;46:347-353.

Keywords: component testing, peanut allergy, SLIT

## FDA Warnings on LABAs Had an Impact

Safety concerns regarding the use of long-acting $\beta_2$-agonists (LABAs) have led to a series of US Food and Drug Administration (FDA) warnings about this class of medications. This study sought to analyze the effects of the 2005 and 2010 FDA regulatory activities on the use of LABA-containing products as well as other types of medications by asthma patients.

The study used "rolling cohorts" of pediatric and adult patients with asthma from 2005 to 2011, drawn from the Mini-Sentinel Distributed Database—a national system for monitoring the safety of medical products. Trends in prevalent asthma medications were assessed to determine the proportion of patients using single-agent and combination LABA products, as well as other controller medications and bronchodilators.

After the 2005 FDA regulatory activity, used of fixed-dose inhaled corticosteroid (ICS)/LABA combinations decreased by 0.98 percentage points in children and 1.24 percentage points in adults. Soon afterward, both age groups had significant increases in the use of ICS and leukotriene receptor antagonists (LTRAs). Smaller but significant changes occurred after the 2010 regulatory activity. Neither warning had an immediate effect on single-agent LABA use, but both were followed by changes in slope among children.

The results provide evidence that recent FDA regulatory activities on LABAs led to reductions in the use of these medications, as intended. Changes in other classes of asthma medications are observed as well. The authors note that their study cannot determine the effects of the regulatory activities independent of other factors.

**COMMENT:** This is an interesting report using rolling cohorts of both pediatric and adult asthmatics in a nationwide database to investigate the impact of the FDA warnings about the use of LABAs between 2005 and 2010. The boxed warning of 2005 had a greater impact in reducing the use of LABA medications, particularly in children. However, other potential variables may have contributed to the change in LABA use between those years. Postmarketing studies, other published asthma guidelines, and widespread drug formulary recommendations could also have been influential in the shift from the use of LABA to the overall increase in use of ICS, LTRAs, and other therapies in asthma patients.

S.M.F.

Butler MG, Zhou EH, Zhang F, et al: Changing patterns of asthma medication use related to US Food and Drug Administration long-acting β-agonist

regulation from 2005-2011.
J Allergy Clin Immunol. 2016;137:710-717.
Keywords: asthma (adult), asthma (child), LABAs,

## Time to Revisit the ICS-LABA Black Box Warning Label?

Two large clinical trials have linked long-acting beta-agonists (LABAs) to increased rates of serious asthma-related events. This prompted the FDA to request further prospective trials comparing safety outcomes with LABA plus inhaled corticosteroid (ICS) versus ICS alone. This large, international trial assessed serious adverse events with fluticasone plus salmeterol compared to fluticasone alone.

The study included 11,679 adolescent and adult patients with persistent asthma and a history of severe exacerbation within the previous year (but not the previous month). Patients were enrolled at 710 centers in 33 countries. They were randomly assigned to 26 weeks of treatment with fixed-dose fluticasone plus salmeterol or with fluticasone alone. Serious asthma-related events—death, endotracheal intubation, or hospitalization—were the main outcome of interest. The study also assessed severe asthma exacerbations and other efficacy outcomes.

Rates of serious asthma-related events were similar between groups: 36 events in 34 patients with fluticasone-salmeterol and 38 events in 33 patients with fluticasone only. Nearly all serious events were hospitalizations. There were no deaths and just two asthma-related intubations, both in the fluticasone-only group.

One or more severe asthma exacerbations occurred in 8% of the fluticasone-salmeterol group versus 10% in the fluticasone-only group. The difference was significant, with a 0.79 hazard ratio for patients assigned to combination therapy. The reduction in severe exacerbation risk with combination therapy was 35% for adolescents and 24% for patients whose asthma was previously well-controlled with a previous ICS-LABA regimen.

For patients with persistent asthma, treatment with a fixed-dose combination of salmeterol and fluticasone does not increase the risk of serious asthma-related events, compared to fluticasone alone. As a secondary outcome, the study also finds a reduction in severe asthma exacerbations with ICS-LABA therapy.

**COMMENT:** The results of this fluticasone-salmeterol trial suggest that serious asthma-related events with this combination were no different than with inhaled fluticasone alone. Daily use of fluticasone-salmeterol therefore can provide safe levels of asthma control in most patients. In fact, the study showed a significant clinical benefit to using fluticasone-salmeterol over fluticasone alone, with a 21% lower risk of severe asthma exacerbation. Even more interestingly, adolescents showed the greatest difference in severe exacerbations. However, as pointed out in the accompanying editorial by Martinez (N Engl J Med. DOI: 10.1056/NEJMe1601040), adherence was unusually high: over 95%. That's in contrast to the patients we typically follow, who have widely varying adherence rates. The study did not evaluate patients with life-threatening episodes/unstable asthma. The safety of this regimen in that group, and in children less than 12 years, remains to be determined.

C.D.

Stempel DA, Raphiou IH, Kral KM, et al: Serious asthma events with fluticasone plus salmeterol versus fluticasone alone.
N Engl J Med. March 6, 2016; DOI: 10.1056/NEJMoa1511049.
Keywords: asthma (adult), LABAs

# FOCUS ON EFFECTS OF SMOKING

## Protect Older Kids from Secondhand Smoke!

Despite laws against smoking in public, many children continue to be exposed to secondhand smoke (SHS) in private settings, such as homes and vehicles. This study assessed rates of SHS exposure in a nationally representative sample of older children and adolescents.

The school-based survey assessed the prevalence and determinants of SHS exposure in a sample of 18,406 middle- and high-school students (sixth through twelfth grade). The survey included questions about the presence of and compliance with smoke-free rules at home and in vehicles.

Of respondents who had never used tobacco, 48.0% said they were exposed to SHS in at least one location. Exposure was more common in indoor/outdoor public areas, 35.2%; followed by 27.1% at work, 16.8% at school, 15.5% at home, and 14.7% in vehicles.

Rates of SHS exposure at home were 79.4% among students reporting no home smoke-free rules, 55.3% with partial smoke-free rules, and 8.5% with complete smoke-free rules. Rates by smoke-free rules in vehicles were 70.2%, 44.8%, and 7.1%, respectively. Exposure to SHS was greater for respondents with current tobacco use, truant behavior, and friends or household members who used tobacco. Adolescent girls were more likely to report any SHS exposure compared to boys.

Nearly half of middle- and high-school students who have never smoked still report exposure to SHS. Complete smoke-free rules in homes and vehicles are associated with substantially lower rates of SHS exposure. The authors call for additional efforts to educate children and teens to avoid SHS, especially targeting former tobacco users.

**COMMENT:** It is a shame that almost half of US middle- and high-school students who never used tobacco are exposed to SHS, according to data from over 18,000 respondents in the 2013 National Youth Tobacco Survey. It is also disconcerting

that public areas—possibly through drifting of smoke from designated smoking areas in restaurants, airports, and sports venues—are the most common location of SHS exposure. The good news is that children in homes and vehicles with smoke-free rules have much less exposure. It is imperative that healthcare providers counsel smoking parents and caretakers to ensure smoke-free homes and vehicles, in addition to engaging them in smoking cessation counseling.

C.D.

Agaku IT, Singh T, Rolle I, et al: Prevalence and determinants of secondhand smoke exposure among middle and high school students.
Pediatrics. 2016;137:1-9.

Keywords: secondhand smoke, smoking, risk factors

## More Evidence That E-Cigarettes May Not Be Efficacious

Quitting smoking is commonly cited as a reason for using e-cigarettes. Previous meta-analyses of the efficacy of e-cigarettes for tobacco cessation have had conflicting results—perhaps related to the way these devices are used in the "real world" versus clinical trials. Meta-analyses of clinical trials and observational studies were performed to analyze the association between e-cigarette use and tobacco cessation, whether or not the users were interested in quitting smoking.

A systematic review identified 38 studies evaluating the relationship between e-cigarette use and cigarette smoking cessation in adults. Twenty studies including control groups—15 cohort studies, three cross-sectional studies, and two clinical trials—were included in a meta-analysis.

The results suggested a significant reduction in smoking cessation among participants who used e-cigarettes: odds ratio (OR) 0.72, compared to smokers who didn't use e-cigarettes. There was no significant difference on analysis of studies including only smokers interested in quitting, compared to all smokers regardless of intention to quit. The effect size was unaffected by other study-related factors; the one randomized trial found a nonsignificant increase in smoking cessation among e-cigarette users.

Analysis of "real world" data suggests that cigarette smokers who use e-cigarettes are actually less likely to quit smoking. This is in contrast to marketing claims that e-cigarettes aid tobacco cessation. The authors discuss possible reasons why e-cigarette users may be less likely to stop smoking cigarettes.

**COMMENT:** In 2015, the US Preventive Services Task Force concluded that the evidence was insufficient to make recommendations regarding the utility of e-cigarettes for smoking cessation. The new meta-analysis found that the odds of quitting cigarettes were 28% lower in smokers who used e-cigarettes compared to those who did not. There are several possible reasons for this outcome. Prior studies examining the effectiveness of nicotine patches in smoking cessation showed that subjects who required a prescription to receive their patch were more likely to quit than those who were able to obtain patches over the counter. Another potential explanation is that e-cigarettes are sometimes used to circumvent smoking avoidance in smoke-free environments.

J.J.O.

Kalkhoran S, Glantz SA: E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis.
Lancet Respir Med. 2016;4:116-128.

Keywords: e-cigarettes, smoking

## Does Secondhand Smoke Facilitate IgE Sensitization?

Exposure to secondhand smoke (SHS) during gestation and childhood is associated with increased rates of respiratory and allergic disease. However, the effect on risk of IgE-mediated sensitization to food or inhalant allergens remains uncertain. This study evaluated SHS exposure as a risk factor for allergic sensitization from childhood to adolescence.

The study included 3,316 children from a Swedish birth cohort study, followed up for 16 years. Parents provided information on SHS exposure and allergic disease symptoms in response to questionnaires. At age 4, 8, and 16 years, the children underwent ImmunoCAP testing for eight inhalant and six food allergens. Exposure to maternal smoking during pregnancy and to SHS during childhood were assessed as risk factors for allergic sensitization.

For children not exposed during gestation, exposure to SHS during infancy was associated with an increased risk of sensitization to food allergens: the odds ratio (OR) was 1.47 at age 4 and remained similar at later assessments. An increased risk of sensitization to indoor allergens was apparent at 4 years, but was no longer significant at longer follow-up. Longitudinal analysis showed a significant overall association between SHS in infancy and food sensitization up to 16 years: OR 1.24.

There was also a dose-dependent association with number of cigarettes smoked by the father during infancy. Exposure to maternal smoking during pregnancy was unrelated to sensitization. Infants exposed to SHS also had a higher overall risk of eczema with sensitization: OR 1.62.

Infants exposed to parental smoking appear to be at increased risk of sensitization to food allergens, and this risk may persist into adolescence. Maternal smoking during pregnancy does not affect the risk of any type of sensitization. The finding that SHS exposure during infancy increases the risk of sensitization coupled with eczema is consistent with previous studies in preschool-aged children.

**COMMENT:** Although there is plenty of evidence linking secondhand smoke exposure to respiratory and allergic disease, its impact on IgE-mediated sensitization is less clear. This study by Thacher and colleagues demonstrates an • • •

increased risk of sensitization to food for up to age 16 years. The authors acknowledge that the potential mechanism(s) responsible for this finding is not fully understood. However, it might be a manifestation of the "mucosal concept of atopy," which suggests that sensitization occurs mainly through the mucosal surfaces of the airways. Secondhand smoke may result in mucosal insult and inflammation, facilitating antigen penetration with subsequent sensitization. One thing is for sure—this is one more reason to reinforce smoking cessation to parents.

J.J.O.

Thacher JD, Gruzieva O, Pershagen G, et al: Parental smoking and development of allergic sensitization from birth to adolescence. Allergy. 2016;71:239-248.

Keywords: atopy, risk factors, smoking, secondhand smoke

## Why Do Some Sensitized Children Have No Allergy Symptoms?

Most children with aeroallergen sensitization do not develop symptoms of asthma or allergic rhinitis. Previous studies suggest that asthma risk may be related to levels of allergen-specific IgE, and that this association might be modified by allergen-specific IgG. This study sought to clarify the endogenous control mechanisms influencing IgE-related responses to aeroallergens in children.

The study used three samples of Australian and British children: two population-based birth cohorts and a group of children at high risk of atopy. Associations between house dust mite- and grass-specific IgE and IgG levels were assessed. The effects on immunophenotypes in atopic children and susceptibility to childhood asthma and rhinitis were assessed.

In all cohorts and age groups, house dust mite-sensitized children with asthma had significantly lower mite-specific IgG/IgE ratios than nonasthmatic children. Children with severe asthma had the lowest specific IgG/IgE ratios; there was no significant difference in $IgG_4$/IgE ratios. Similar associations were noted for the presence of rhinitis, and for specific antibodies to grass.

Twenty to forty percent of children with allergen-specific IgE levels of 0.35 kU/L or higher had negative skin test results, depending on age and allergen specificity. This group of skin test-negative children also had a high specific IgG/IgE immunophenotype. In mechanistic studies, specific $IgG_1$ from these children with high specific IgG/IgE inhibited allergen-induced, IgE-dependent basophil activation in a dose-dependent fashion. On analysis of allergen-specific Th2 memory responses, specific IgG/IgE ratios were positively related to interleukin-10 (IL-10)-dependent gene signatures. Asymptomatic children also had increased IL-10/Th2 cytokine ratios.

High specific IgE/IgG ratios, with high coproduction of specific $IgG_1$, may help to explain why many children sensitized to aeroallergens experience no symptoms. In vitro findings suggest specific $IgG_1$-mediated inhibition of basophil activation and allergen-specific CD4+ Th2 memory responses involving a strong IL-10-dependent gene signature. The authors discuss the potential implications for improving desensitization approaches.

**COMMENT:** This well-designed study analyzed the relationship between allergen-specific IgE and allergen-specific IgG with associated immunophenotypes, focusing on sensitivity to dust mite and grass. Children with negative skin tests but positive specific IgE had a strong IL-10 dependent basophil activation and gene signatures within the aeroallergen-specific CD4+ Th2 memory responses. The authors suggest that allergen exposure in asymptomatic, sensitized children could trigger a signaling network that involves IL-10, which acts to attenuate potential pathologic Th2 responses. As we learn more about the intricate immunologic mechanisms controlling allergic symptoms, there may be potential for novel therapies; is there an anti-IL-10 in the future?

S.M.F.

Holt PG, Strickland D, Bosco A, et al: Distinguishing benign from pathological $T_H2$ immunity in atopic children. J Allergy Clin Immunol. 2016;137:379-387.

Keywords: asthma (child), atopy, immunotherapy

## Antiviral Interferon Responses Differ by Asthma Inflammatory Subtype

At least some people with asthma appear to have abnormal antiviral host defenses. Deficient production of interferon (IFN) in response to viruses may occur in certain groups, possibly including patients with difficult-to-treat asthma. This study compared systemic antiviral IFN production across inflammatory phenotypes in patients with exacerbation-prone asthma.

The study included 86 adults with stable but poorly controlled asthma: mean asthma control questionnaire score of 6. The patients were 54 men and 32 women; mean age was 59 years and 76% had atopy. Based on sputum cell counts, the inflammatory phenotype was classified as eosinophilic in 35 patients, paucigranulocytic in 35, neutrophilic in 12, and mixed in 4. Release of IFN-α and IFN-β was assessed in peripheral blood mononuclear cells exposed to human rhinovirus (HRV) serotype 1b.

In response to HRV, production of both IFN-α and IFN-β was significantly lower in patients with the neutrophilic subtype compared to the eosinophilic or paucigranulocytic subtype. On adjusted analysis, the only independent predictors of IFN-α release were sputum neutrophil proportion and inhaled corticosteroid dose.

Among patients with poorly controlled asthma, the neutrophilic inflammatory subtype is associated with impaired production of IFN in response to HRV. The association with

higher inhaled corticosteroid dose might reflect the refractory nature of asthma in patients with noneosinophilic inflammation. The findings might have implications for identifying patients most likely to benefit from inhaled IFN treatment for exacerbations.

**COMMENT:** Abnormal viral defenses in asthma have not been a consistent finding in studies of asthma patients. This study evaluated a well-characterized, poorly controlled asthma population classified by sputum inflammatory subtypes. Subjects with neutrophilic asthma had lower capacity to produce interferons in response to rhinovirus, compared to those with the eosinophilic or paucigranulocytic subtypes. Inhaled IFN therapy for asthma is being developed, and potentially the group with neutrophilic asthma may respond best.

D.A.K.

Simpson JL, Carroll M, Yang I, et al: Reduced antiviral interferon production in poorly controlled asthma is associated with neutrophilic inflammation and high-dose inhaled corticosteroids. Chest. 2016;149:704-713.

Keywords: asthma (adult), asthma phenotypes, interferon, rhinovirus

## How Accurate is Exhaled Nitric Oxide for Asthma Diagnosis?

Exhaled nitric oxide is commonly used as a noninvasive marker of airway inflammation in asthma. A growing number of studies have evaluated the use of exhaled NO for asthma diagnosis, with conflicting results. The authors performed a review and meta-analysis of the diagnostic accuracy of exhaled NO in different groups of asthma patients.

A systematic review identified 25 prospective studies evaluating the use of exhaled NO for asthma diagnosis. On pooled analysis of the entire population of 3,983 patients, sensitivity was 72% and specificity 78%. Diagnostic odds ratio (DOR) was 15.92 with an area under the receiver-operating characteristic curve of 0.88. Subgroup analysis showed that exhaled NO was more accurate in patients with certain characteristics: DOR was 4.47 in patients using corticosteroids, 21.40 in steroid-naive patients, 19.84 in nonsmokers versus 5.41 in smokers, and 35.36 in patients with chronic cough versus 2.99 in those with allergic rhinitis.

The growing evidence on exhaled NO supports its use for asthma diagnosis, but suggests significant differences in accuracy between patient subgroups. The authors call for standardized methods and equipment for measuring exhaled NO and verification of optimal cutoff points.

**COMMENT:** Exhaled NO is widely used as a biomarker for eosinophilic inflammation, particularly in asthma. This systematic review and meta-analysis of prospective studies demonstrates that exhaled NO is accurate for diagnosis of asthma in steroid-naive patients and nonsmokers, and particularly in individuals with chronic cough.

C.C.R.

Guo Z, Wang Y, Xing G, Wang X: Diagnostic accuracy of fractional exhaled nitric oxide in asthma: a systematic review and meta-analysis of prospective studies. J Asthma. 2016;53:404-12 .

Keywords: asthma (adult), asthma (child), diagnosis, exhaled nitric oxide

## In Obese Patients, Dyspnea May Look Like Asthma

Some obese patients have been diagnosed with asthma but do not have confirmed airflow limitation, reversible obstruction, or hyperresponsiveness. These cases of misdiagnosed asthma might be related to other obesity-related mechanisms causing dyspnea. This study evaluated factors contributing to asthma-like symptoms in obese patients.

The study included three groups of obese patients: 25 who met diagnostic criteria for asthma, 23 with misdiagnosed asthma, and 27 controls with no asthma or respiratory symptoms. All underwent bronchial challenge studies and exercise testing; perceptions of dyspnea were compared between groups.

The Borg-$FEV_1$ slope during bronchial challenge was significantly higher in patients with diagnosed or misdiagnosed asthma, compared to the asymptomatic controls. The two symptomatic groups also had higher maximal dyspnea and a greater Borg-oxygen uptake slope. On bronchial challenge studies, maximal dyspnea level was correlated with systemic interleukin (IL)-1β levels. Independent predictors of the Borg-oxygen uptake slope were peak respiratory frequency, ventilator equivalent for carbon dioxide, and levels of IL-6 and IL-1β. A model comprising these four factors accounted for 85% of explained variance in perceived dyspnea during exercise.

Obese patients with misdiagnosed asthma have elevated perceptions of dyspnea, approaching those in patients with asthma. Exercise dyspnea in obesity appears to be related to excessive ventilation for metabolic demands along with systemic inflammatory measures. Interleukin-1β might contribute to the changes in respiratory patterns as well as perceptions of breathing-related discomfort.

**COMMENT:** It is often difficult to make an accurate diagnosis of asthma in obese patients because they frequently present with dyspnea, particularly on exertion. This study showed a higher perception of dyspnea, particularly with exercise, in obese subjects with misdiagnosed asthma compared to asymptomatic controls. Interestingly, there were increases in inflammatory cytokines that could impact neuroinflammation contributing to the increase in respiratory frequency. The bottom line is that the diagnosis of asthma in obese patients should not be based on symptoms alone—although inflammatory factors might contribute to the dyspnea symptoms experienced by these patients.

S.M.F.

Carpio C, Villasante C, Galera R, et al: Systemic inflammation and

higher perception of dyspnea mimicking asthma in obese subjects.
J Allergy Clin Immunol. 2016;137:718-726.

Keywords: asthma (adult), diagnosis, obesity

## FOCUS ON TECHNOLOGY AND EDUCATION

### Can Chip Technology Identify Allergic Sensitization in Children?

Patterns of sensitization to a wide range of allergens can provide useful information on the risk and prognosis of allergic disease. With recent advances in microarray chip technology, IgE against dozens of component allergens can be identified from a small serum sample. This study used latent class analysis (LCA) to assess patterns of sensitization in children and their association with asthma and allergic disease risk.

The study included 7- to 8-year-old children, 196 with and 136 without asthma, from New York City neighborhoods with low and high asthma prevalence. The ISAC multiplex array panel was used to assess IgE against a panel of 112 antigens. Data on the 26 most common allergens with measurable specific IgE levels were analyzed using a four-class LCA model. Patterns of allergic sensitization were analyzed for association with morbidity from asthma, allergic rhinitis, and eczema.

Four patterns of allergic sensitization in asthma were identified on LCA. A low risk of sensitization was found in 53% of children with and 76% without asthma, while sensitization to indoor allergens was found in 23% of asthmatic and 15% of nonasthmatic children. Two patterns of sensitization to pollen and indoor allergens were identified: group 1 prevalence was 16% in children with and 5% in children without asthma, while group 2 prevalence was 9% and 4%, respectively.

Asthma risk was significantly higher for children with any of the three patterns of sensitization, compared to those at low risk of sensitization. This was so both at age 7 to 8 and at 3 years' follow-up. Children with the pollen and indoor group 1 pattern, associated with a high probability of sensitization to all allergens, were at highest risk of asthma.

Latent class analysis of data from microarray chip testing of IgE levels can provide useful information on patterns of allergic sensitization. This method will provide a better understanding of the relationship between asthma and sensitization to multiple allergens. Future studies will enable identification of addition patterns of sensitization and the associations with geographic, ethnic, and other factors.

**COMMENT:** The use of technology to improve identification of patients with atopy is increasing. Risk factors associated with sensitization include history of food allergic reactions, maternal history of asthma, and any worsening wheezing from pollen, animal, or smoke exposure, among others. The authors note that the microarray chip technology is beneficial as it requires small amounts of blood. Latent class analysis helps separate children with low sensitization from those with multiple sensitivities. It also separates children who are sensitized to indoor allergens only from those sensitized to both indoor allergens and pollen. Further studies of the use of LCA would be helpful in comparing larger populations of patients by ethnic group and geographic location.

V.H.-T.

Chen Q, Zhong X, Acosta L, et al: Allergic sensitization patterns identified through latent class analysis among children with and without asthma.
Allergy. 2016;71:239-248.

Keywords: atopy, component testing, microarray testing, prognosis

### Smart Devices Assist Home Management

Recent developments in technology show promise for meeting the complex challenges of improving asthma self-management. Researchers with the University of Buffalo's Home-BASE Center (Center for Excellence in Home Health and Well-Being through Adaptive Smart Environments) review some efforts to develop new approaches to home management of asthma.

Taking advantage of the ubiquity of smart devices, researchers are developing new approaches to help patients monitor and control their asthma. These include several types of devices to monitor breathing patterns and sounds, and possibly even to analyze common lung function measures. Smartphone games are being developed to provide asthma patients with training and guidance in breathing exercises. Following a "transdisciplinary and transcommunity" approach will help to ensure that that these technologies are relevant and clinically meaningful. The researchers also describe their efforts to engage researchers, clinicians, and industry in their efforts. These include the use of patent searches to identify technological advances that would not be identified by a conventional search of the scientific literature.

The authors highlight the importance of collaborative efforts to maximize the potential of new "smart" technologies for improving asthma monitoring and management. They conclude, "By crossing borders between disciplines and in our respected lay and health industry partners, smarter solutions will result in healthier people."

**COMMENT:** This is an interesting brief report highlighting several "smart" innovations that may revolutionize the home evaluation of respiratory disease. These include smart shirts (a wearable breath measurement device), smart necklaces (which can sense breath sounds), as well as the MobiSpiro (a microphone-based spirometry device for unmodified smartphones). One can only say that the future is here. The next question is how to best utilize these tools in our care of patients.

J.J.O.

Castner J, Klingman K, Sullivan S, et al: Hitting home with technology development for asthma. Lancet Respir Med. 2016;4:102-103.

Keywords: asthma (adult), asthma (child), self-management, smartphones

## Handbook Helps Teach Parents about Food Allergy

Education is a critical part of management of food allergy, yet many parents feel they don't receive enough information. They also have difficulty identifying reliable sources of information on the Internet. A handbook for parents of food-allergic children was evaluated in terms of parental knowledge, confidence, and quality of life.

The randomized trial included parents of 153 children diagnosed with food allergies over the past year, identified from hospital-based allergy clinics and food allergy organizations. After a baseline survey, one group of parents received a handbook providing accurate, understandable information and practical strategies for managing and coping with childhood food allergies. Control parents received the handbook at the end of the study. Both groups completed online surveys at 2 weeks and 2 months.

At both follow-up times, parents receiving the handbook had greater improvement in food allergy knowledge and confidence in allergy management skills. Improvement in food allergy-specific quality of life became significant at 2 months. Parents were satisfied with the information provided by the handbook, with a modal score of 3 on a 0- to 4-point scale.

The handbook evaluated in this study appears to be a useful supplement to physician management for parents of food-allergic children. The *Living Confidently with Food Allergy* handbook is available online in English and Spanish at www.allergyhome.org/handbook/

**COMMENT:** Education is important for all patients with chronic disease. As practicing clinicians, we know that proper education is a time-consuming process. This study supports others that have shown the need for educational resources for parents of food-allergic children. Quality of life, as well as knowledge regarding food allergy, improved in the parents who received the handbook. This study reminds us that good resources, along with education by the medical provider, are useful tools for parents of children with food allergies. Further studies looking at outcomes of the patients would be interesting.

V.H.-T.

LeBovidge JS, Michaud A, Deleon A, et al: Evaluating a handbook for parents of children with food allergy: a randomized clinical trial. Ann Allergy Asthma Immunol. 2016;116:230-236.

Keywords: asthma (child), education, self-management

## Can Cytokine Responses to Egg Predict Egg Allergy?

Early dysregulation of T-cell responses may contribute to the development of egg allergy, especially in infants with eczema. However, questions remain about the allergen-specific T-cell responses occurring before the first symptoms of egg allergy appear, and whether they can be influenced by early egg exposure. This study evaluated egg-specific T-cell cytokine responses as a predictor of egg allergy in high-risk children.

The study included infants from a randomized, placebo-controlled trial of early egg introduction, all with moderate to severe eczema and no known egg ingestion when enrolled at age 4 months. At that time, the infants underwent measurement of egg-specific T-cell cytokine responses—interleukin (IL)-5, IL-13, IL-10, interferon-γ, and tumor necrosis factor- α—to ovomucoid, ovalbumin, conalbumin, and lysozyme. They were then assigned to early, regular egg consumption or placebo. At age 12 months, skin prick testing and food challenge were performed to assess IgE-mediated egg allergy.

Infants who developed egg allergy had greater Th2 cytokine responses to multiple egg allergens—especially IL-13 and IL-5 responses to ovalbumin, ovomucoid, and lysozyme and IL-13 responses to ovalbumin and lysozyme. Among the egg-allergic infants, all responses declined with age, unaffected by early egg introduction.

Many high-risk infants have strong Th2 responses to multiple egg proteins by age 4 months, before introduction of egg in solid foods. The IL-5 and IL-13 responses in particular are predictors of later development of egg allergy. Early egg exposure does not appear to modify Th2 cytokine responses to egg.

**COMMENT:** Up to one-third of infants with eczema may develop egg allergy. This study evaluated infants who were part of a trial evaluating the effects of early egg consumption on development of tolerance. At 4 months of age, egg-specific cytokine responses to egg proteins were higher in the 5 infants who reacted to egg compared to the 17 who tolerated egg. These responses waned at 12 months. Interestingly, egg consumption did not affect cytokine responses to egg, suggesting a different pattern of tolerance than in oral immunotherapy. While the authors suggest that these Th2 responses could be used as a biomarker to select infants for early prevention and management strategies, the sample size was too small and the confidence intervals overlapped. Larger studies will need to be performed to determine if this could be a predictive biomarker.

D.A.K.

Metcalfe JR, D'Vaz N, Makrides M, et al: Elevated IL-5 and IL-13 responses to egg proteins predate the introduction of egg in solid foods in infants with eczema. Clin Exp Allergy. 2016:46;308-316.

Keywords; egg allergy, early introduction, food allergy

## Do Antihistamines Help Kids with Atopic Dermatitis?

Antihistamines are commonly prescribed to reduce pruritus in atopic dermatitis (AD). Recent guidelines emphasize intermittent use of first-generation antihistamines in certain situations. Parents of children with AD were asked about the usefulness of antihistamines to relieve itching.

A questionnaire was mailed to parents of children with AD seen in a pediatric allergy clinic. The survey included 12 questions regarding the use and effectiveness of antihistamines for pruritus. One hundred twenty-four responses were received, most from parents of children between age 2 and 10 with IgE-mediated AD that had been present for more than a year.

Sixty-three percent of parents believed that antihistamines were useful in management of itching; only 5% said antihistamines weren't effective at all. More than two-thirds of parents perceived that itching did not disrupt their child's sleep. Of this group roughly equal numbers were using first- or second-generation antihistamines. Parents who believed antihistamines were more effective against itching used them more often and believed they provided greater relief than other treatments. Some parents rated antihistamines as effective as corticosteroids.

Most parents of children with AD believe that antihistamines are an effective medication for itching. In light of current guidelines suggesting more intermittent use, further studies of the value of antihistamines for AD-associated pruritus are needed.

**COMMENT:** Parents of children with AD report that antihistamines are useful in controlling itch. While treatment guidelines recommend the use of antihistamines intermittently and for aiding in sleep, in this survey almost 50% of parents report using antihistamines consistently. Of those who used antihistamines intermittently, more than two-thirds felt the medications were helpful. The authors postulate that the difference between acute and chronic inflammation seen in the young versus older patients may account for the utility of antihistamines reported by parents in this study. The patients were also more atopic than in most studies of AD. I agree that further controlled studies of pediatric patients with AD are needed to determine the effectiveness of antihistamines in control of itch, and feel that the verdict is still out!

V.H.-T.

Chawla V, Hogan MB, Moonie S, et al: Parental perception of efficacy of antihistamines for pruritus in pediatric atopic dermatitis.
Allergy Asthma Proc. 2016;37:157-163.

Keywords: antihistamines, atopic dermatitis, pruritus

## REVIEWS OF NOTE

**COMMENT:** This review presented by the Pediatric Endocrine Society Drugs and Therapeutics Committee is an excellent update of the potential risks of using inhaled corticosteroids in children. These risks include hypothalamic-pituitary-adrenal axis suppression and effects on growth, bone mineral density, and glucose metabolism. The authors' categorization of daily doses and recommendations for appropriate step-down therapy can be helpful for all of us who treat children with asthma.

S.M.F.

Kapadia C, Nebesio TD, Myers SE, et al: Endocrine effects of inhaled corticosteroids in children. JAMA Pediatr. 2016;170:163-170.

**COMMENT:** This panel report from the National Heart, Lung, and Blood Institute gives recommendations for asthma research.

B.E.C.

Levy BD, Noel PJ, Freemer MM, et al: Future research directions in asthma: an NHLBI working group report. Am J Respir Crit Care Med. 2016;192:1366-1372.

**COMMENT:** This is an excellent review of asthma phenotypes and the role of IgE in various presentations of asthma.

B.E.C.

Froidure A, Mouthuy J, Durham SR, et al: Asthma phenotypes and IgE responses. Eur Respir J. 2016;47:304-319.