AllergyWatch®

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

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New Therapy for Eosinophilic, Severe Asthma

MORE effective treatments for moderate to severe asthma are needed. Dupilumab is an investigational monoclonal antibody that inhibits signaling of the Th2-associated cytokines interleukin (IL)-13 and IL-4. This randomized trial evaluated dupilumab for treatment of adults with moderate to severe asthma and elevated eosinophil levels.

The phase 2A multicenter trial included 104 patients with moderate to severe asthma plus a blood eosinophil count of 300 cells/μL or greater or sputum eosinophil level of 3% or higher. At baseline, all patients were treated with medium- to high-dose inhaled corticosteroids (ICS) and long-acting beta-agonists (LABAs).

One group received dupilumab 300 mg sc once weekly, while the other group received placebo. Patients were to stop taking LABAs at 4 weeks and to taper and stop using ICS between 6 and 9 weeks. Treatment continued through 12 weeks, or until an asthma exacerbation occurred.

The asthma exacerbation rate during treatment was 6% in the dupilumab group versus 44% with placebo: odds ratio 0.08 for this primary endpoint. Several secondary endpoints were also improved with dupilumab, including change in FEV_1, morning and evening asthma symptom scores, and albuterol use. Dupilumab was also associated with reductions in exhaled nitric oxide and Th2-associated biomarkers. The dupilumab group had higher rates of injection-site reactions, nasopharyngitis, nausea, and headache.

In adults with moderate to severe asthma and elevated eosinophils, dupilumab is associated with a lower risk of exacerbations during withdrawal of ICS and LABAs, compared to placebo. The results also show improved lung function and reduction in Th2-associated inflammatory markers. Further studies of dupilumab under "real-world" conditions are needed.

COMMENT: *There is promise that a new anti-Th2 therapy may change the way we treat asthma. The efficacy and safety of dupilumab--a monoclonal antibody to the interleukin-4 receptor α subunit that inhibits* ➤➤

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The American College of Allergy, Asthma & Immunology expresses its appreciation to MERCK for its grant in support of the publication of *AllergyWatch*®.

The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

- 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
- 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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both IL-4 and IL-13 signaling--were evaluated in a randomized controlled trial of adults with persistent, moderate to severe asthma and elevated eosinophil levels. The response to dupilumab was very impressive, with an 87% reduction in the proportion of patients with asthma exacerbation and significant improvement in lung function, even while ICS and LABAs were being withdrawn. Concerns that may need to be addressed in future studies include dupilumab's utility in patients without eosinophilia and whether this approach has added value over treatment with ICS and LABAs. Of note, the degree of reduction in exhaled NO corresponded to the improvement in FEV_1, suggesting clinical relevance of Th2 inhibition. Since the sample was small, a larger study is warranted to assure safety and clinical role of this promising therapy. (See also the accompanying editorial by Wechsler: N Engl J Med. 2013;368:2511-2513.)
C.D.
Wenzel S, Ford L, Pearlman D, et al: Dupilumab in persistent asthma with elevated eosinophil levels.
N Engl J Med. 2013;368:2455-2466. ♦♦

Immunotherapy Reduces Costs in Children and Adults with AR

ALLERGEN-specific immunotherapy (AIT) is the only treatment that alters the clinical course of allergic rhinitis (AR), reducing the risk of asthma and new allergen sensitizations. A recent Florida Medicaid claims study found that AIT reduced costs in children with AR. A further study was performed to evaluate the cost impact of AIT for adult as well as pediatric AR patients.

Through a review of Florida Medicaid claims from 1997 to 2009, the researchers identified 1,319 adults and 3,648 children receiving de novo AIT for recently diagnosed AR. They were matched to 4,815 adult and 14,463 pediatric patients with a recent diagnosis of AR who were not treated with AIT. Eighteen-month health care costs were compared between groups, including separate analyses of adults and children.

For the total sample, 18-month total health care costs were $6,637 for AR patients receiving AIT versus $10,644 without AIT --a 38% reduction. The cost savings were realized within 3 months after the start of AIT. The cost reductions were similar and significant for adults and children, with savings of 30% and 42% ($4,397 and $3,965), respectively.

In adults as in children, AIT reduces health care costs among patients with newly diagnosed AR. Cost benefits appear within 3 months and are sustained through 18 months' follow-up. The authors call for "coordinated efforts to remediate modifiable barriers to AIT access, adoption, and adherence."

COMMENT: *This report uses Florida Medicaid data to document substantial health care cost savings for children and adults receiving AIT for AR. The cohorts were matched carefully, with up to 5 controls for each AIT patient. The main savings were from both inpatient and outpatient expenses. Interestingly, the AIT-treated children had a three times greater savings for outpatient visits, compared to adults. Although the study showed impressive cost savings over an 18-month period, it did not address overall health care outcomes. As health care changes, allergists will need more studies like this to demonstrate the beneficial outcomes resulting from our treatments.*
S.M.F.
Hankin CS, Cox L, Bronstone A, Wang Z: Allergy immunotherapy: reduced health care costs in adults and children with allergic rhinitis.
J Allergy Clin Immunol 2013;131:1084-1091. ♦♦

One Year Later, Benefits of SLIT Persist

SUBLINGUAL immunotherapy (SLIT) using the five-grass 300IR tablet is safe and effective for the treatment of grass-pollen induced seasonal allergic rhinoconjunctivitis. A previous study found sustained efficacy after 3 years of treatment with grass-pollen SLIT. The current report describes outcomes during the subsequent pollen season, after the end of SLIT.

The analysis included 435 adults with grass pollen sensitization and moderate to severe allergic rhinoconjunctivitis, who had been randomly assigned to 3 years of 300IR or placebo SLIT. Treatment began either 4 or 2 months before the beginning of each pollen season, and continued through the end of the season. The current study examined outcomes in the subsequent pollen season, during which patients received no SLIT.

During the fourth year, the active SLIT groups had significant reductions in the Average Adjusted Symptom score. Relative least-squares mean differences compared to placebo were -22.9% in patients starting 300IR SLIT 4 months before pollen season and -25.8% for those starting 2 months before the season. Other efficacy outcomes were also better with 300IR SLIT, including measures of rhinoconjunctivitis symptoms, rescue medication use, and rhinoconjunctivitis-specific quality of life. There were no safety risks in the year after the end of SLIT.

This follow-up study shows continued benefits of grass pollen SLIT in the year after 3 years of discontinuous treatment with the 300IR five-grass pollen tablet. The observed benefits are meaningful from the patient's perspective. The findings add to the evidence for the safety and efficacy of grass pollen SLIT for patients with moderate to severe allergic rhinoconjunctivitis.

COMMENT: *Although SLIT as an alternative to subcutaneous immunotherapy is gaining favor in the United States, the jury is still out on whether SLIT alters the natural history of allergic rhinitis. In this study the efficacy of SLIT persisted for the year following discontinuation of therapy. This is a promising finding, especially given that FDA approval of grass SLIT is likely in the near future.*
S.A.T.

Didier A, Malling H-J, Worm M, et al: Post-treatment efficacy of discontinuous treatment with 300IR 5-grass pollen sublingual tablet in adults with grass pollen-induced allergic rhinoconjunctivitis.
Clin Exp Allergy. 2013;43:568-577. ♦♦

Three Biomarkers Predict Response to Omalizumab

RESPONSES to asthma treatment are variable, highlighting the need for markers to assess the effectiveness of specific medications. Airway inflammation is primarily an allergic, Th2-weighted process in many asthma patients, but variable inflammatory findings suggest phenotypic differences. Data from a trial of anti-IgE therapy with omalizumab were used to evaluate inflammatory biomarkers as predictors of treatment effectiveness.

The Study of Xolair in Subjects with Moderate to Severe Persistent Asthma (EXTRA) included 850 patients, aged 12 to 75 years, with uncontrolled, severe persistent asthma. Data on baseline exhaled nitric oxide (eNO), blood eosinophils, and serum periostin were available in 46.4%, 93.8%, and 62.8% of patients, respectively. Safety and efficacy outcomes with omalizumab were evaluated for patients with low versus high levels of each biomarker. The primary endpoint was the number of protocol-defined asthma exacerbations over 48 weeks of treatment.

For all three biomarkers, patients with higher baseline levels had greater reductions in asthma exacerbations after 48 weeks on omalizumab. Exacerbations decreased by 53% in patients with high baseline eNO versus 16% for those with low eNO. The reductions were 32% versus 9% for patients with high and low baseline eosinophils and 30% versus 3% for those with high versus low periostin, respectively. In contrast, for patients with low baseline biomarker levels, there was no significant difference with omalizumab versus placebo.

In patients with severe persistent asthma, the effects of omalizumab on exacerbation risk are greater for those with higher levels of three inflammatory biomarkers. This finding likely reflects the increased exacerbation risk among patients with higher levels of eNO, peripheral blood eosinophils, and serum periostin. Further studies will be needed to evaluate the clinical utility of these biomarkers.

COMMENT: *This study helps expand our understanding of predictors for response to omalizumab. All three markers, when elevated, were associated with a significant reduction in exacerbations. The strongest signal was seen with exhaled nitric oxide greater than 19.5 ppb. Also of interest was the easily obtainable absolute eosinophil count, with values greater than 260/μL predicting response and decreased exacerbation risk. A prospective study to explore the value of these biomarkers is now in progress.*
B.E.C.

Hanania NA, Wenzel S, Rosén K, et al: Exploring the effects of omalizumab in allergic asthma: An analysis of biomarkers in the EXTRA study.
Am J Respir Crit Care Med. 2013;187:804-811. ♦♦

Hand in Glove: Rhinovirus and 17q21 Asthma Locus

GENE variants at the 17q21 locus may interact with viral wheezing in the development of asthma. Data from two large cohorts of children were used to evaluate associations among genotypes at the 17q21 locus, viral causes of wheezing, and childhood asthma risk.

The study included genotype data on variations at 17q21 in children from the Childhood Origins of Asthma and the Copenhagen Prospective Study on Asthma in Childhood birth cohorts. The analysis sought evidence ➤➤

of interactions between 17q21 variants and wheezing illness caused by human respiratory virus (HRV) and respiratory syncytial virus (RSV) for the outcome of childhood asthma.

Five single-nucleotide polymorphisms at 17q21 were associated with early-life wheezing illness caused by HRV, but not RSV. These variants showed a significant interaction effect with the development of childhood asthma only in cohort members who had had HRV-related wheezing illness.

An in vitro study evaluated genotype-specific expression of 17q21 genes in peripheral blood mononuclear cells (PBMCs), in the presence and absence of HRV. Two genes, *ORMDL3* and *GSDMB*, showed increased expression in response to HRV stimulation. Expression of these genes was associated with the presence of 17q21 variants under both conditions; the increase with HRV exposure was not genotype-specific.

Building on previous studies linking childhood asthma risk to gene variants at 17q21 and viral respiratory wheezing illness, the new results show a specific interaction between 17q21 and wheezing illness caused by HRV, but not RSV. Two genes at 17q21, *ORMDL3* and *GSDMB*, show increased expression in the presence of HRV, independent of 17q21 genotype. The authors call for additional research to evaluate the mechanisms behind the observed interaction.

COMMENT: *These researchers sought to further clarify the effect of the genotype at the 17q21 asthma locus and respiratory viral illnesses in early life on the risk of childhood-onset asthma. They evaluated data from two large cohorts of children and adult volunteers for genotype associations, interactions, and expression of the 17q21 locus with asthma, HRV, RSV, and wheezing illnesses. The 17q21 variants were associated with HRV wheezing illness in early life, but not with RSV wheezing illness. The effects of the 17q21 genotype on susceptibility to asthma were seen mainly among children who experienced HRV wheezing illness during early childhood. It is possible that the study was underpowered to detect an association with RSV and that a causal association with HRV could not be established because of the study design. However, the findings illustrate the importance of exploring gene-environment interactions as a unit in asthma pathogenesis.*
C.D.

Çalişkan M, Bochkov YA, Kreiner-Møller E, et al: Rhinovirus wheezing illness and genetic risk of childhood-onset asthma.
N Engl J Med. 2013;368:1398-1407. ♦♦

Prevent RSV and Reduce Wheezing in Infants

RESPIRATORY syncytial virus (RSV) infection during infancy is associated with a high prevalence of wheezing. The nature of this relationship is unclear: RSV could play a causal role, or may simply be the "earliest stimulus" in infants predisposed to wheezing. This trial evaluated the effects of palivizumab treatment to prevent RSV infection on later recurrent wheezing in preterm infants.

The trial included 429 healthy preterm infants, born at 33 to 35 weeks' gestation. They were randomly assigned to RSV-preventive therapy with palivizumab or placebo treatment during RSV season. The main outcome of interest was days of wheezing during the first year of life, as reported by parents. The study included virologic analysis of nasal swabs obtained during episodes of respiratory illness.

Babies receiving palivizumab had wheezing on 1.8% of days during the first year, compared to 4.5% in the placebo group. The percentage of infants with recurrent wheezing was 11% with palivizumab versus 21% with placebo. Palivizumab lowered recurrent wheezing risk regardless of family history of atopy or asthma. Rates of RSV-related hospitalization were 0.9% in the palivizumab group versus 5.1% with placebo.

Giving palivizumab to prevent RSV infections reduces the risk of recurrent wheezing in healthy preterm infants. The reduction in wheezing is still apparent in the months after the end of RSV season, providing "evidence that RSV infection is an important mechanism in the pathogenesis of wheezing during the first year of life among late preterm infants."

COMMENT: *While it is established that the monoclonal antibody palivizumab can reduce RSV-related healthcare utilization in premature infants, the impact on prevention of viral = induced wheezing was not known. This large-scale randomized controlled trial showed a significant (61%) reduction in total number of wheezing days in the first year of life, even after therapy had ended and outside the RSV season. The findings add to our suspicion that RSV infection is a key catalyst of recurrent wheeze during the first year of life in such infants. Notably, RSV prevention reduced wheezing, but did not eliminate it. As astutely pointed out by Lemanske in an accompanying editorial (N Engl J Med. 2013;368:1839-1841), a genetic background of atopy (parental history of atopy) did not influence wheezing frequency. This hints that palivizumab treatment may have a lesser influence on some of the asthma risk pathways, perhaps those relating to allergic sensitization.*
C.D.

Blanken MO, Rovers MM, Molenaar JM, et al: Respiratory syncytial virus and recurrent wheeze in healthy preterm infants.
N Engl J Med. 2013;368:1791-1799. ♦♦

Lone Star Tick Region: Eat Red Meat with Caution

SOME children have recurrent symptoms of allergic reactions for which no cause is identified, despite thorough evaluation and testing. An IgE antibody specific for galactose-α-1,3 galactose (α-Gal) has recently been identified as a cause of delayed urticaria and anaphylaxis occurring a few to several hours after eating beef, pork, or lamb. The presence of this antibody was evaluated in a group of children with idiopathic urticaria or anaphylaxis.

The study included 51 children and adolescents with a clinical history of recurrent urticaria, idiopathic anaphylaxis, or angioedema consistent with a delayed ➤➤

response to ingesting mammalian meat. The patients were recruited from allergy clinics in central Virginia. Serum specimens underwent ImmunoCAP testing for total IgE and specific IgE to α-Gal, beef, pork, cat epithelium and dander, Fel d 1, dog dander, and milk.

Forty-five of the children tested positive for IgE antibody to α-Gal. Many had a history of frequent emergency visits for allergic reactions; some had been diagnosed with chronic urticaria. All children with α-Gal antibodies had a clear history of tick bites, with itching, redness, and swelling for several weeks thereafter. As in previous studies in adults, the children had positive immunoassays to mammalian meat products, including beef and pork. In almost every case, allergic symptoms were delayed 3 to 6 hours after meat ingestion.

The α-Gal syndrome is a relatively common cause of delayed anaphylaxis and urticaria after ingestion of mammalian meat among children in the study area. The new study along with previous findings suggest a causal relationship between bites from the Lone Star tick and sensitization to α-Gal. The level of α-Gal-specific IgE tends to decrease over time, if the patient is able to avoid subsequent tick bites.

COMMENT: *Delayed anaphylaxis, urticaria, and angioedema to mammalian meat products were first described in the adult population in 2009. This report describes 45 pediatric patients, aged 4 to 17, with a clinical history suggestive of delayed urticaria, angioedema, or anaphylaxis to mammalian meat products who had IgE antibodies to the carbohydrate α-Gal. Most of these children had a history of tick bites within the past year, which itched and persisted. This study suggests that specific serologic testing should be considered for children living in the area where the Lone Star tick is common and who present with the symptoms described above after eating "red meat."*
C.D.
Kennedy JL, Stallings AP, Platts-Mills TAE, et al: Galactose-α-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children.
Pediatrics. 2013;131:e1545-e1552. ♦♦

Could Antacids Be Contributing to Increased Food Allergy in Children?

MORE information is needed on factors involved in the development of pediatric food allergy. Treatment with antacid medications has been linked to an increased risk of food sensitization in adults. Antacid exposure was evaluated for association with the risk of food allergies in children.

A questionnaire was sent to parents of 104 children with atopic diseases, mean age 7 years, seen at a university allergy clinic. The questionnaire included items related to the child's history of treatment with antacid medications and food allergies. Information on food-specific IgE levels and/or skin-prick test results was obtained from independent chart review. Food allergy was defined as reactions to foods consistent with the anaphylaxis consensus statement, plus an elevated food-specific IgE level or positive food skin-prick test.

A history of antacid medication use was reported for 45% of children. The prevalence of food allergy was 57% for children who had taken antacid medications verses 32% in those who had not: adjusted prevalence ratio (PR) 1.7. Food allergy prevalence was also increased for children with atopic dermatitis, PR 2.4; and age 5 years or younger, PR 1.5. Mean peanut-specific IgE level was 11.0 in children with a history of antacid exposure versus 2.0 in unexposed children.

Treatment with antacid medications may be linked to an increased risk of food allergy among children with atopic diseases. The authors call for prospective studies to assess the clinical impact of antacid treatment on the development of food allergy and the underlying mechanism of the association. The findings may have important implications for the treatment of gastroesophageal reflux (GER) in children.

COMMENT: *Prior studies have shown the possibility that increased pH may contribute to higher prevalence of food allergy. This cross-sectional study used a questionnaire to further investigate the possible link between the two. The authors found that patients who had ever used an antacid had increased prevalence of food allergy. The findings support the likelihood that changes in pH could lead to changes in the conformation of food epitomes, affecting allergenicity. The authors discuss the need for further studies to investigate whether family or personal history of atopy plays an important role, and the need to consider whether treatment for GER in children may affect the development of food allergy.*
V.H.-T.
Demuth K, Stecenko A, Sullivan K, Fitzpatrick A, et al: Relationship between treatment with antacid medication and the prevalence of food allergy in children.
Allergy Asthma Proc. 2013;34:227-232. ♦♦

Milk Allergy in the US: Is It as Common as We Think?

FOOD allergy in children is a very common problem, and strict dietary avoidance is the only approved treatment. However, there are important gaps in knowledge regarding the distribution and diagnosis of this condition. This nationally representative survey study sought to clarify the epidemiology of milk allergy in U.S. children.

The analysis included survey responses from 38,420 parents, including data on demographic characteristics, children's allergic symptoms associated with ingestion of foods, and the methods used in diagnosis of food allergy. Multiple logistic regression models were used to assess child characteristics and reaction history associated with the odds of having allergy to milk, compared to other food allergens.

A total of 3,218 children with food allergies were identified. Of these, 19.9% had parent-reported milk allergy. Rates of milk allergy were significantly lower for Asian and black children, compared to white children: odds ratio (OR) 0.5 and 0.4, respectively. By age group, the percentage of children with milk allergy ranged ➤➤

from 23.8% from age 6 to 10 versus 15.0% from age 11 to 15. Although food allergy was more prevalent in children younger than 2 years, severe reactions were more common in children aged 3 to 5 years and 14 to 17 years.

Children with milk allergy were more likely to have a doctor's diagnosis of allergy and more likely to outgrow their allergy, compared to children with other food allergies: OR 1.7 and 2.1, respectively. Some type of diagnostic test was performed in 43.5% of children with physician-diagnosed food allergy.

The study is the first comprehensive survey of the prevalence, distribution, symptoms, severity, and diagnosis of milk allergy in U.S. children. Milk allergy accounts for one-fifth of all food allergy and is severe in nearly one-third of cases. Although physician diagnosis is more common than for other types of food allergy, confirmatory tests are performed in less than half of children.

COMMENT: *While milk allergy is common, more information regarding its diagnosis in children is needed. This cross-sectional survey found that almost 20% of children with food allergy were allergic to milk. The reactions were less severe than in children with other food allergies; in almost half of patients, the most commonly reported symptom was vomiting. While the patients' mean age at the time of their first reaction was 2 years, the mean age at tolerance was 4 years. Less than half of patients had confirmatory testing: skin prick test, specific IgE levels or oral food challenge. This survey reminds us that confirming the diagnosis is important, since patients will otherwise be subjected to a restricted diet due to avoidance measures.*
V.H.-T.

Warren CM, Jhaveri S, Warrier MR, et al: The epidemiology of milk allergy in US children.
Ann Allergy Asthma Immunol. 2013;110:370-374. ♦♦

Should We Consider *Mycoplasma* in Pediatric Asthma Exacerbations?

MYCOPLASMA pneumoniae has been linked to worsening of asthma in children. A newly developed assay can sensitively detect *M. pneumoniae* derived community-acquired respiratory distress syndrome (CARD) toxin. This test was used to assess the frequency and persistence of *M. pneumoniae* in children with acute and refractory asthma versus healthy controls.

The study included 143 children, age range 5 to 17 years: 53 with acute and 26 with refractory asthma, along with 64 healthy controls. Over a 20-month period with two to five follow-up visits, the children were tested for *M. pneumoniae* by CARDS toxin antigen capture and polymerase chain reaction and P1 adhesin polymerase chain reaction. Levels of IgG and IgM antibodies against CARDS toxin and P1 adhesin were measured. Other assessments included pH in exhaled breath condensates, asthma control, and asthma quality of life.

Rates of *M. pneumoniae* detection were 64% in children with acute asthma, 65% in those with refractory asthma, and 56% in healthy controls. The two asthmatic groups had lower levels of *M. pneumoniae* antibodies compared to the control group. Among the children with asthma, exhaled breath condensate pH, asthma control, and quality of life were significantly lower in those testing positive for *M. pneumoniae*. Rates of poor asthma control were 70% for children who were positive for *M. pneumoniae* versus 30% for those who tested negative.

A sensitive assay detects *M. pneumoniae* in a high percentage of children, with or without asthma. Among asthmatic children, *M. pneumoniae* is associated with worsening asthma. Follow-up studies are needed to assess the impact of *M. pneumoniae* on asthma control and morbidity over time.

COMMENT: *Infections are a common cause of asthma exacerbations.* M. pneumoniae *has been reported to lead to asthma exacerbations and new-onset asthma. These authors found that* M. pneumoniae *is common among asthmatic children. In the study, some children with* Mycoplasma *infections had poor antibody responses, making them more susceptible to asthma exacerbations. Asthmatic children had infections that tended to be persistent or recurrent, and were associated with lower quality of life scores. For allergists, who play an integral role in the care of such patients, these are important factors to consider in asthmatic children with recurrent exacerbations.*
V.H.-T.

Wood PR, Hill VL, Burks ML, et al: Mycoplasma pneumoniae *in children with acute and refractory asthma .*
Ann Allergy Asthma Immunol. 2013;110:328-334. ♦♦

What's the Best Way to Diagnose Atopy to Aeroallergens in Young Children?

AMONG young children with recurrent wheezing, aeroallergen sensitization before age 4 is a risk factor for persistent asthma. Skin pricking testing (SPT) or serum IgE testing may be performed, but there are possible discrepancies in sensitivity between the two tests. Concordance between SPT and specific IgE testing for common aeroallergens was assessed in children aged 4 years or younger.

The study included 40 inner-city children with atopy and a history of wheezing, drawn from a randomized trial of subcutaneous immunotherapy. The children were 18 to 48 months old, with recurrent wheezing and a family history of asthma, eczema, or both. The children underwent SPT and specific IgE measurement for seven common aeroallergens. Correlations between the results of the two tests were assessed.

For each allergen, there were discordant results between tests. There was moderate agreement for mouse allergen; for all others (dog, grass, roach, cat, dust mite, and ragweed), agreement was rated poor or fair. At least one sensitization would have been missed in 80% of children if SPT had been the only test performed, and in 38% if specific IgE measurement had been the only test. Positive specific IgE results were more likely for children with high total specific IgE, 300 kU/L or greater; with negative corresponding SPT results. ➤➤

In this population of highly atopic young children, there is significant discordance between the results of SPT and specific IgE testing for common aeroallergens. The results suggest that, in children under 5 at high risk of asthma, both forms of testing should be performed.

COMMENT: *This study looked at children enrolled in a prospective clinical trial investigating the use of subcutaneous immunotherapy in asthma. The authors compared the use of SPT and specific IgE testing in the diagnosis of allergy to aeroallergens among children younger than 4 years with a history of wheezing. For all allergens tested, differences existed in the results of SPT versus specific IgE tests. Less than 10%--only 3 patients--had identical results on both tests. Parents frequently state that they are waiting for allergy testing until the child is 5. As a pediatric allergist, I have always questioned this statement. The authors remind us that we may consider using both SPT and specific IgE to aeroallergens in young children at risk for asthma, since many patients with sensitization to aeroallergens would be missed with use of only one test.*
V.H.-T.

de Vos G, Nazari R, Ferastraoaru D, et al: Discordance between aeroallergen specific serum IgE and skin testing in children younger than 4 years.
Ann Allergy Asthma Immunol. 2013;110:438-443. ♦♦

Indoor Pollutants Have Greater Impact in Overweight Children with Asthma

OVERWEIGHT and indoor air pollutant exposure are both linked to worse health status in patients with asthma, and are both common among inner-city minority populations. The combination of the two risk factors might contribute to the disproportionately high asthma morbidity in this population. This study looked at how weight influences susceptibility to harmful effects of indoor pollutants among asthmatic inner-city youth.

The study included 148 children and adolescents with persistent asthma in Baltimore. The subjects were 5 to 17 years old; 91% were African American and 85% were on public health insurance. Every 3 months, assessments were made of asthma symptoms, health care use, lung function, pulmonary inflammation, and indoor pollutant levels. Asthma health outcomes were compared for children in different weight categories, based on body mass index.

Weight category was underweight for 4% of children, normal-weight for 52%, overweight for 16%, and obese for 28%. Asthma symptoms associated with exposure to fine particulates measuring less than 2.5 μm in diameter ($PM_{2.5}$) were significantly increased for children in the overweight and obese groups, compared to normal-weight children. Overweight and obesity were also linked to increased symptoms in association with exposure to nitrogen dioxide (NO_2), although this was not consistent across all symptoms.

Weight did not seem to influence asthma symptoms related to coarse particulates (2.5 to 10 μm). The effects of indoor pollutant exposure on health care use, lung function measures, or pulmonary inflammation were not significantly different between weight categories.

Among inner-city minority children with asthma, overweight and obesity are associated with increased asthma symptoms related to indoor $PM_{2.5}$ and NO_2 exposure. Together with weight loss, interventions to reduce indoor pollutant exposure could be especially helpful for overweight children with asthma.

COMMENT: *It is well known that obesity and second-hand smoke are risk factors for increasing severity of childhood asthma. This study of inner-city, lower socioeconomic status, predominantly African-American children found that exposure to indoor air pollution--especially fine particulates, smoke and nitrogen dioxide--were significant risk factors for worsening asthma symptoms in obese children. The authors suggest that interventions aimed at encouraging weight loss and reducing indoor air pollutant levels, particularly environmental smoke exposure, may benefit overweight children with asthma.*
S.M.F.

Lu KD, Breysse PN, Diette GB, et al: Being overweight increases susceptibility to indoor pollutants among urban children with asthma.
J Allergy Clin Immunol. 2013;131:1017-1023. ♦♦

Blood Pressure Drugs May Affect Anaphylaxis Severity

LITTLE is known about factors that may affect anaphylaxis severity, with conflicting data on the effects of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. Emergency department (ED) data were analyzed to assess the relationship between antihypertensive medications and the severity of anaphylaxis.

The study included data on 302 adult patients with anaphylaxis seen at one ED over a 3-year period. Multiple logistic regression analyses were performed to determine whether various classes of antihypertensive drugs--not only ACE inhibitors and beta-blockers but also calcium channel blockers, angiotensin-receptor blockers, and diuretics--were related to markers of anaphylaxis severity.

Criteria for severe anaphylaxis included syncope, hypotension, or hypoxia, present in 18% of patients; involvement of three or more organ systems, 46%; and hospitalization, 19%. With adjustment for age, sex, suspected anaphylaxis trigger, and pre-existing lung disease, multi-organ system involvement and hospitalization were more likely for patients taking ACE inhibitors, beta-blockers, or diuretics.

The same associations were significant for antihypertensive medication use in aggregate. For overall antihypertensive use, adjusted odds ratios were 2.8 for anaphylaxis involving 3 or more organ systems and 4.0 for hospitalization.

Among adult patients with anaphylaxis seen in the ED, use of antihypertensive medications may be linked to an increased rate of multi-organ system involvement and hospitalization. The associations could reflect ➤➤

the use of multiple antihypertensive drugs, cardiovascular comorbidities, or a combination of these. Further studies are needed to assess the impact of blood pressure drugs on specific anaphylaxis symptoms or triggers.

COMMENT: *This retrospective analysis of emergency room data found that patients with anaphylaxis on antihypertensive medications had more severe clinical manifestations. It is not surprising that patients on ACE inhibitors and beta-blockers had increased rates of multi-organ system involvement and hospitalization, but patients on diuretics were also at increased risk as well. Larger studies are needed before firm recommendations can be made, but we should be extra-cautious with patients at risk for anaphylaxis who are also receiving antihypertensive drugs.*
S.M.F.

Lee S, Hess EP, Nestler DM, et al: Antihypertensive medication use is associated with increased organ system involvement and hospitalization in emergency department patients with anaphylaxis.
J Allergy Clin Immunol 2013;131:1103-1108. ♦♦

Maternal Asthma Outcomes Linked to Perinatal Outcomes

ASTHMA may affect pregnancy outcomes, and vice-versa. However, there are conflicting data regarding the impact of maternal asthma on pregnancy and neonatal complications. This issue was addressed in a systematic review and meta-analysis.

The literature review identified nine cohort studies of the effects of maternal asthma severity, asthma exacerbations, and oral corticosteroid use on perinatal outcomes. The perinatal outcomes of interest were birthweight less than 2,500 g; preterm birth, ie, before 37 weeks' gestation; and small for gestational age, ie, below the 10th percentile for gestational age and sex.

On meta-analysis, maternal asthma exacerbations were associated with an increased risk of low birth weight, relative risk (RR) 3.02; and preterm delivery, RR 1.54. The same two risks were increased with oral corticosteroid use: RR 1.41 for low birth weight and 1.51 for preterm delivery. Moderate to severe asthma during pregnancy was associated with an increased risk of small for gestational age and low birthweight infants: RR 1.24 and 1.15, respectively.

Available evidence suggests that maternal asthma severity, exacerbations, and oral corticosteroid treatment are associated with increased rates of adverse perinatal outcomes. Acute asthma events appear to be linked to an increased risk of preterm delivery, while increased asthma severity may affect the risk of intrauterine growth restriction. Improving asthma control during pregnancy to reduce the risk of exacerbations may reduce adverse perinatal outcomes.

COMMENT: *This meta-analysis implicates asthma exacerbations in the risk of adverse perinatal outcomes. Clearly, whatever it takes to ensure asthma control is the tack we should follow. The concept that our obstetric colleagues have to minimize medications during pregnancy should be countered by the justifiable use of appropriate medications to achieve asthma control.*
S.F.W.

Namazy JA, Murphy VE, Powell H, et al: Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes.
Eur Respir J. 2013;41:1082-1090. ♦♦

What Practices Modify the Risk of Systemic Reactions?

SERIOUS or life-threatening reactions are rare but do occur in patients undergoing subcutaneous immunotherapy (SCIT), and may be a limiting factor on its use. In 2008, a surveillance program was set up to monitor the occurrence of SCIT-related systemic reactions (SRs) reported by members of the American Academy of Allergy, Asthma & Immunology (AAAI) and American College of Allergy, Asthma & Immunology (ACAAI). This monitoring system was used to survey allergists regarding what practices they use to reduce the risk of SRs.

In the first 3 years of the surveillance system, from 2008 to 2011, approximately 18.9 million injection visits were reported. In year 3, participants were asked for information about SCIT-related procedures potentially affecting the risk of SRs, such as screening of patients with asthma, dose adjustments during peak pollen season, buildup regimens, and premedication.

Through the first 3 years, no fatal reactions were reported. Systemic reactions occurred at a rate of 0.1% of injection visits in all 3 years, and were reported by 83% of participating practices. By severity grade, SR rates per 10,000 injection visits were 7.1 for grade 1 reactions, 2.6 for grade 2 reactions, and 0.4 for grade 3 reactions.

Eighty-six percent of practices said they always screened for worsening asthma symptoms during SCIT visits. Practices that reported always using reduced SCIT doses during peak pollen season had a lower rate of reported grade 2 or 3 SRs: 44%, compared to 65% for practices that did not always follow this step. Systemic reaction rates were higher with cluster and buildup SCIT regimens. Rates of grade 2 or 3 SRs were also lower for practices reporting premedication.

These surveillance data suggest a declining rate of fatal reactions to SCIT, perhaps reflecting the near-universal practice of screening for worsening asthma. Dose adjustments during pollen season may lead to a reduced rate of severe SRs. Premedication does not appear to affect risk; this step may be influenced by the severity of previous SRs.

COMMENT: *The authors of this survey of SCIT practices of ACAAI and AAAAI membership conclude that almost-universal screening of patients with asthma and decreased doses during pollen season are associated with a lower risk of SRs. Cluster and rush immunotherapy are linked to an increased risk. The take-home message for the practicing allergist is that specific* ➤➤

practices--particularly screening of asthmatics and decreasing doses of pollens seasonally--may lead to diminished mortality and severity of systemic reactions.
C.C.R.
Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI: AAAAI and ACAAI surveillance study of subcutaneous immunotherapy, year 3: What practices modify the risk of systemic reactions?
Ann Allergy Asthma Immunol. 2013;110:274-278. ♦♦

Peptide-Based Peanut Immunotherapy Appears to Be on the Way

BECAUSE of the risk of severe reactions, whole-allergen extracts are not used for specific immunotherapy for peanut allergy. Immunotherapy approaches using epitope-based peptides of the major peanut allergen, Ara h 1, may allow a new approach to targeting allergen-specific T cells without producing IgE-mediated inflammatory cell activation. This study reports the development of a set of short, HLA-degenerate T cell-reactive Ara h 1 peptides for peanut allergy immunotherapy.

The researchers generated Ara h 1-specific CD4+ T-cell lines using peripheral blood mononuclear cells (PBMCs) from patients with peanut allergy, with T-cell epitopes identified by means of CFSE- and thymidine-based proliferation assays. Blocking antibodies, HLA genotyping, and epitope prediction algorithms were used to characterize epitope HLA-restriction. Basophil activation assays were used to assess functional peanut-specific IgE reactivity to the new peptides.

Using PBMCs from 18 HLA-diverse patients with peanut allergy, the researchers generated 145 Ara h 1-specifc T-cells lines, which recognized 20-mer peptides throughout the major peanut allergen. Further studies confirmed that nine 20-mers containing the most commonly recognized epitopes were recognized in 18 additional peanut-allergic patients. Within these 20-mers, 10 core HLA-DQ and/or HLA-DR epitopes were mapped, each of which presented on two or more different HLA molecules. Donor PBMC T-cell assays were used to validate seven short non-basophil-reactive peptides including all core epitopes.

The development and validation of a set of short CD4+ T-cell epitope-based Ara h 1 peptides is reported. The authors plan further studies evaluating these peptides--in combination with previously described Ara h 2 peptides--as candidates for T-cell-targeted peanut-specific immunotherapy in HLA-diverse patients.

COMMENT: *After decades of increases in the prevalence of food allergy, a number of new treatment strategies are finally under development. Oral immunotherapy studies using whole-allergen extracts have shown promising efficacy, although patients occasionally have anaphylactic reactions. Short peptide extracts have the potential to desensitize without a significant risk of anaphylaxis; this strategy has been applied successfully with a variety of aeroallergens. The authors of the present study characterized overlapping peptide epitopes of Ara h1, which can be combined with previously characterized Ara h2 peptides for use in future peptide immunotherapy studies.*
S.A.T.
Prickett SR, Voskamp AL, Phan T, et al: Ara h 1 CD4+ T cell epitope-based peptides: candidates for a peanut allergy therapeutic.
Clin Exp Allergy. 2013;43:684-697. ♦♦

In Asthmatic Adults, Asthma Is Leading Cause of Death

ASTHMA has been linked to increased mortality in adults, but there are few long-term follow-up data on patients with well-characterized asthma. This study assessed 25-year outcomes, including cause-specific mortality, in a large group of patients with asthma.

The study included data on 1,075 adult asthma patients seen at a Danish allergy clinic from 1974 to 1990, with follow-up through 2011. Based on history and test results, patients were classified as having allergic or nonallergic asthma. Danish registries were used to obtain information on vital status and cause of death. All-cause mortality was compared with that in a group of age- and sex-matched patients without asthma.

The risk of death from any cause was twice as high in asthma patients versus controls: relative risk 2.1. The excess mortality was mainly attributable to obstructive lung disease, which accounted for 95 out of 261 deaths in asthma patients. Factors associated with an increased risk of death in asthma patients included older age, percentage of predicted FEV_1, bronchodilator reversibility, peripheral blood eosinophil count, and history of acute hospital contacts for asthma. Smoking and self-reported symptom severity were not significantly associated with mortality. With adjustment for age and percentage of predicted FEV_1, patients with nonallergic asthma were at higher risk of death from asthma: RR 1.9.

Long-term follow-up of asthma patients evaluated at an allergy clinic shows increased mortality, compared to nonasthmatic controls. Obstructive lung disease appears to be the major reason for excess deaths among asthma patients. This group of patients likely has more severe asthma that is more difficult to control.

COMMENT: *A number of studies have evaluated risk factors for fatalities from asthma. Few studies have evaluated all-cause mortality among asthmatics. This study evaluated causes of death (using ICD-10) among 1,075 Danish asthma patients evaluated an average of 25 years earlier in a specialty clinic. All-cause mortality was higher in asthma subjects (who were also older) than nonasthmatic patients evaluated for other allergic diseases. Obstructive lung disease was the most common cause of death in asthmatics--however, the majority (65%) were never-smokers. The authors suggest that these patients died from asthma, not chronic obstructive pulmonary disease. Older age, severity of obstruction, larger bronchodilator responses, hospitalizations for asthma, and peripheral eosinophilia were all associated with higher risk of death from asthma. Patients with nonallergic asthma had almost a twofold high-*➤➤

er risk of asthma death than allergic asthmatics. These sobering results indicate that death from asthma is not a rare event, but in fact the leading cause of mortality in adults with asthma.
D.A.K.
Ali Z. Dirks CG, Ulrik CS: Long-term mortality among adults with asthma: A 25-year follow-up of 1,075 outpatients with asthma.
Chest. 2013;143:1649-1655. ♦♦

Glucocorticoids May Increase Pulmonary Embolism Risk

CHRONIC endogenous glucocorticoid excess has recently been linked to an increased risk of venous thromboembolism. It's unclear whether exogenous glucocorticoid use may carry a similar increase in risk. This study evaluated corticosteroid treatment as a potential risk factor for pulmonary embolism (PE).

A Dutch pharmacy registry, linked to hospital admissions data, was used to identify 4,495 patients with initial hospitalization for PE between 1998 and 2008. These cases were matched for age and sex to 16,802 controls with no history of PE. The association between PE risk and oral glucocorticoid use was assessed, with consideration of underlying medical conditions.

The largest increase in PE risk was noted within the first 30 days of glucocorticoid exposure: adjusted odds ratio (OR) 5.9. Risk of PE gradually decreased with increasing duration of glucocorticoid use, but remained elevated beyond 1 year, OR 1.8. The risk of PE was even higher, OR 9.6, among patients receiving the highest glucocorticoid dose: equivalent to greater than prednisolone 30 mg/d. On analysis stratified for glucocorticoid dose and duration, the increase in PE risk was greater for patients who recently started taking glucocorticoids versus long-term users, regardless of dose.

Oral glucocorticoid treatment is associated with an increased risk of pulmonary embolism. The risk is greatest during the first month of glucocorticoid exposure, but remains significant with long-term use. Further studies are needed to confirm this association and explore the underlying mechanisms.

COMMENT: *Venous thromboembolic disease has been shown to be increased in patients with Cushing syndrome. This study using a large Dutch database compared cases of PE with matched controls, examining corticosteroid use as a risk factor. Risk of PE was highest for patients who were treated with glucocorticoids in the previous month. There was a dose-response effect, with high daily doses (over 30 mg prednisolone) having a tenfold increased risk; however, even low doses (less than 5 mg) had a twofold increased risk. Whether this risk was causal or associated with underlying disease is not clear, but several underlying diseases were controlled for. While we await further studies to clarify the risk, allergists should be aware of this association.*
D.A.K.
Stuijver DJF, Majoor CJ, van Zaane B, et al: Use of oral glucocorticoids and the risk of pulmonary embolism: A population-based case-control study.
Chest. 2013;143:1337-1342. ♦♦

IgE-Mediated Acute Infusion Reactions to Infliximab Are Not Rare

PREVIOUS reports have described IgE-mediated reactions to infusions of biologic agents. Although in vitro and in vivo tests can detect anti-drug antibodies (ADAs), the clinical value of skin testing in patients receiving biologic agents is undefined. This study evaluated the use of skin testing in patients with hypersensitivity reactions to infliximab.

The study included 30 patients with previous immediate hypersensitivity reactions to infliximab, along with 20 disease-matched, nonexposed patients; 15 disease-matched patients who did not react to infliximab; and 15 patients who did not have a clinical response to infliximab. A double-capture enzyme-linked immunosorbent assay was used to measure non-isotype-specific ADAs, while an ImmunoCAP assay was used to detect IgE antidrug antibodies. Skin-prick and intradermal tests were performed using serial dilutions of infliximab.

Skin tests were performed in 23 of the 30 patients who reacted to infliximab, with positive results in 7 patients-a rate of 30.4%. There were no positive skin tests in the comparison groups. Of the 30 reactors, 76.6% had non-isotype-specific ADAs while 26% had IgE antibodies to infliximab. All 6 patients with IgE antibodies had positive skin tests. One patient with positive ADAs but no detectable IgE antibodies had a positive skin test result. Positive skin tests were associated with severe reactions occurring by the third dose of infliximab. There were no unexpected adverse reactions to infliximab skin testing.

About 30% of patients with hypersensitivity reactions to infliximab have positive results on skin testing. This group of patients tends to have severe reactions, especially in response to the first few infliximab infusions. The results support the specificity and safety of infliximab skin testing, when indicated.

COMMENT: *Acute infusion reactions have been reported with many biologics, especially tumor necrosis factor inhibitors such as infliximab. Reports of IgE-mediated reactions to biologics have predominantly been case reports. This study from Italy evaluated 30 patients with immediate infliximab reactions, using both skin tests and in vitro specific IgE tests. With use of a non-irritating concentration for intradermal testing (1 mg/ml or 1:10 dilution), 30% of acute reactors had positive skin tests compared to only 3% of infliximab-treated controls. Positive skin tests were more common in patients with severe reactions (5/7), and all developed reactions within the first three doses of infliximab. In vitro testing was less sensitive than skin testing. Interestingly, all patients became skin-test-negative when tested 8 months later, but none were rechallenged to determine tolerance. Prospective studies are needed to determine the true specificity, sensitivity and predictive value of skin testing. Nevertheless, this report suggests that skin testing does have a role in evaluating infliximab patients, particularly those with severe reactions.*
D.A.K.
Matucci A, Pratesi S, Petroni G, et al: Allergological in vitro and in vivo evaluation of patients with hypersensitivity reactions to infliximab.
Clin Exp Allergy. 2013;43:659-664. ➤➤

Fluoroquinolone Allergy Is on the Rise

As the use of fluoroquinolones increases, so do reports of hypersensitivity reactions--especially immediate-type reactions--to these antibiotics. A large series of patients with hypersensitivity reactions to fluoroquinolones is analyzed, focusing on factors contributing to the development of reactions.

The retrospective study included 218 patients with reactions associated with fluoroquinolones, seen at a Spanish allergy department from 2005 through 2010. Diagnostic evaluation included basophil activation or drug provocation tests. The study looked at potential contributing factors including patient age and sex, type and timing of reactions, type of symptoms, the specific fluoroquinolone involved, and history of confirmed hypersensitivity to betalactams or other medications.

Sixty-nine patients were confirmed as having hypersensitivity reactions to fluoroquinolones. Of these, 66 had immediate-type reactions; moxifloxacin was the most frequently implicated drug. On logistic regression analysis, factors associated with diagnosed fluoroquinolone hypersensitivity were previous confirmed hypersensitivity to betalactams, immediate reactions, and moxifloxacin as the inducing drug. Adjusted odds ratios were 23.65, 52.49, and 13.6, respectively.

In this experience, diagnostic testing confirms hypersensitivity reactions to fluoroquinolones in about one-third of cases. Such reactions are usually immediate, most often associated with moxifloxacin, and often occur in patients with hypersensitivity to betalactams. Larger, prospective studies are needed to confirm these findings.

COMMENT: *The frequency of fluoroquinolone reactions appears to be increasing. In this retrospective study from Spain, the authors report on their experience with basophil activation tests and drug provocation tests in evaluating 215 patients with histories of fluoroquinolone allergic reactions. The number of patients evaluated for quinolone allergy has increased in recent years. Most (68%) did not have confirmed hypersensitivity. Of those with confirmed hypersensitivity, most had immediate reactions and symptoms of anaphylaxis. Basophil activation tests had poor sensitivity. Moxifloxacin and ciprofloxacin were the culprit agents in 93% of immediate reactions. Whether this is representative of the U.S. experience requires further study.*
D.A.K.

Blanca-López N, Ariza A, Doña I, et al: Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved.
Clin Exp Allergy. 2013;43:560-567. ♦♦

Early Recurrent Wheezing: What's the Long-Term Prognosis?

Up to half of children with recurrent wheezing during early childhood may go into remission. However, these children are at increased risk of adult asthma. Long-term follow-up data from a birth cohort study were analyzed to assess the prognosis of early-life recurrent bronchial obstruction (rBO) into adolescence.

The analysis included 2-, 10-, and 16-year follow-up data from a population-based Norwegian birth cohort study. Of 550 children included at age 16 years, 143 (26.0%) had rBO at age 2. Recurrent bronchial obstruction during the first 2 years of life was defined as two or more episodes of physician-diagnosed wheezing. Follow-up focused on the presence of asthma, based on physician diagnosis, symptoms, and medication use.

Of the 143 children with rBO at age 2 years, 34% had asthma at 10 to 16 years. Lung function measures were significantly reduced in the overall group of children with rBO, compared to those who never had asthma. Of children with rBO in remission, 48.4% had asthma symptoms, were using asthma medications, or had bronchial hyperresponsiveness, compared to 26.7% of those who never had asthma.

Most children with rBO at age 2 do not have asthma at age 16. However, two-thirds of these children have asthma symptoms, medication use, or bronchial hyperresponsiveness when followed up to adolescence. Thus recurrent wheezing in early childhood may be associated with an increased risk of respiratory disease in adulthood.

COMMENT: *This study reinforces previous reports that the prognosis for recurrent wheezing in the first 2 years of life is good. At age 16, only one-third of children in the study had asthma at sixteen years of age. The association of an allergic diathesis and recurrent wheezing only held until age 10. Children with early-onset wheezing also had reduced lung function and were more likely to have bronchial hyperreactivity and use of asthma medication. Thus they may in fact have risk for recurrent respiratory disease later in life.*
B.E.C.

Hovland V, Rüser A, Mowinckel P, et al: The significance of early recurrent wheeze for asthma outcomes in late childhood.
Eur Respir J. 2013;41:838-845. ♦♦

CLINICAL TIDBITS

Parental Generosity: Gift of Germs

In infants, stimulation of the immune system by commensal microbes may reduce allergy risk. Pacifier cleaning practices were evaluated for their influence on the risk of allergy development.

The birth cohort study included 184 infants followed up to age 36 months for the occurrence of clinical allergies and sensitization. When the babies were 6 months old, parents were asked about pacifier use and pacifier cleaning practices. Sixty-five parents said they "cleaned" their baby's pacifier by sucking it. At age 18 months, these infants were significantly less likely to have asthma, eczema, or sensitization to food and airborne allergens: odds ratios 0.12, 0.37, and 0.37, respectively.

Vaginal delivery also had an independent protective effect against eczema. The oral microbiota differed ➤➤

for infants whose parents did versus did not suck their baby's pacifier.

Stimulation of the infants' immune system by parental microbes could explain the lower risk of allergies associated with parents sucking their baby's pacifier. The authors call for further studies to see if this could be a "simple and safe" method of reducing allergy risk in infants and young children.

COMMENT: *A provocative study of pacifier cleaning practices investigated whether immune stimulation through exposure to commensal microbes--as when parents suck their infants' pacifiers to clean them--may protect against allergy development. The results showed that children whose parents "cleaned" their pacifier by sucking it were less likely to have asthma, eczema, and allergic sensitization at 18 months of age. Vaginal delivery and parental pacifier sucking provided independent and additive protective effects against eczema development. While the findings of this small study need replication, it is nevertheless heartening to harried parents that their unwitting gift of germs may indeed be beneficial!*
C.D.
Hesselmar B, Sjöberg F, Saalman R, Pacifier cleaning practices and risk of allergy development.
Pediatrics. 2013;131:1-6. ♦♦

Is 'Stepping-Down' Asthma Drug Therapy Successful in Children?

CURRENT National Asthma Education and Prevention Program (NAEPP) 3 guidelines call for stepping-down asthma medications when the patient's condition remains stable for 3 months. The use and effectiveness of this approach was evaluated among children with asthma.

The retrospective analysis included 4,777 children, aged 5 to 18 years, enrolled in a pediatric asthma management program at an integrated U.S. primary care practice. Based on NAEPP 3 guidelines, 55.4% of children were eligible for stepping-down their asthma medications.

However, step-down was attempted in only 33.7% of eligible patients. Overall, stepping-down of asthma medications was attempted in 34.8% of children, including those who were not eligible by NAEPP 3 criteria. The step-down attempt was successful in 71.6% of cases with available follow-up.

Step-down was more likely to be successful if attempted during any season except fall: odds ratio 3.81 on univariate and multivariate analysis. Meeting guidelines for step-down was associated with a higher success rate on univariate analysis, odds ratio 2.51; but not multivariate analysis.

For children with asthma, stepping-down of asthma medications based on NAEPP 3 guidelines is successful in most cases. Currently, step-down is not attempted on two-thirds of occasions when the child is eligible.

COMMENT: *Fifty-five percent of children participating in an asthma management program through the Mayo Clinic were candidates for stepping-down therapy, based on NAEPP 3 guidelines. However, only 33% did so. The NAEPP 3 guidelines were successful 72% of the time in stepping-down, while step-down without guidelines was successful 62% of the time. The take home message for allergists is that NAEPP 3 guidelines for stepping-down asthma medications in children are underused, but are frequently successful when used.*
C.C.R.
Rank MA, Branda ME, McWilliams DB, et al: Outcomes of stepping down asthma medications in a guideline-based pediatric asthma management program.
Ann Allergy Asthma Immunol. 2013;110:354-358 ♦♦

REVIEWS OF NOTE

COMMENT: *This is an excellent meta-analysis and review of the role of intranasal corticosteroids in asthma. While stopping short of endorsing intranasal steroids as an asthma treatment, the review concludes that their use is associated with improved asthma outcomes.*
S.A.T.
Lohia S, Schlosser RJ, Soler ZM, et al: Impact of intranasal corticosteroids on asthma outcomes in allergic rhinitis: a meta-analysis.
Allergy. 2103;68:569-579. ♦♦

COMMENT: *This study was a comprehensive review of clinical trials of sublingual immunotherapy (SLIT) in pediatric patients with respiratory and food allergies. Grass pollen SLIT was effective in the treatment of seasonal allergic rhinitis in children 5 years and older. Grass or house dust mite SLIT was effective for children with allergic rhinitis and asthma as well. Oral immunotherapy for food had better results than SLIT to milk.*

At this time, the use of SLIT for Alternaria *allergy needs further evidence. As allergists, we use SLIT in pediatric patients with allergic rhinitis. However, these authors remind us that there is low-to-moderate evidence for the use of SLIT for prevention of asthma in children. Further randomized trials in pediatric patients are needed.*
V.H.-T.
Larenas-Linnemann D, Blaiss M, Van Bever HP, et al: Pediatric sublingual immunotherapy efficacy: evidence analysis, 2009-2012.
Ann Allergy Asthma Immunol. 2013;110:402-415. ♦♦

COMMENT: *Here's a thoughtful review of the mechanism of action and dosing strategies for inhaled corticosteroids in patients with lung disease.*
B.E.C.
Raissy HH, Kelly HW, Harkins M, Szefler SJ: Inhaled corticosteroids in lung diseases.
Am J Respir Crit Care Med. 2013;187:798-803. ♦♦

COMMENT: *This is a comprehensive review of beta-agonist therapy in lung disease.*
B.E.C.
Cazzola M, Page CP, Rogliani P, Matera MG: β_2-Agonist therapy in lung disease.
Am J Respir Crit Care Med. 2013;187:690-696. ♦♦

COMMENT: *This is an excellent review and position statement by a European drug allergy interest group that specifically focuses on appropriate skin test extract concentrations for evaluating drug allergy.*
S.A.T.
Brockow K, Garvey LH, Aberer W, et al: Skin test concentrations for systemically administered drugs--an ENDA/EAACI Drug Allergy Interest Group position paper.
Allergy. 2013;68:702-712. ♦♦