Grass Pollens: Are They as Cross- Reactive as We Think?

Allergens of different grass pollens are thought to have strong cross-reactivity, such that immunotherapy with one species—particularly timothy grass—is sufficient to cover IgE-mediated allergy to other species. This study assessed patterns of T-cell cross-reactivity among patients with diagnosed IgE reactivity to timothy grass.

The study included 6 patients with diagnosed grass pollen allergy, based on an ImmunoCAP score for timothy grass pollen extract of 3 or higher. Basophil activation tests were performed using pollen extract from not only timothy grass but also velvet, canary, barley, rye, orchard, and Kentucky grasses. Dual tetramer staining studies were performed to assess cross-reactivity among allergen-specific CD4+ T cells. In addition, T-cell phenotypes were assessed using intracellular cytokine staining assays.

All patients with diagnosed timothy grass allergy also showed reactivity to the other five grass species tested. However, the study also identified grass pollen-specific CD4+ T cells with varying degrees of cross-reactivity. Allergens with high sequence homology were not necessarily highly cross-reactive.

Ex vivo tetramer staining assays demonstrated the presence of minimally cross-reactive T-cell epitopes. On functional assays, these minimally cross-reactive T cells appeared to be memory Th2 cells.

The findings indicate that not all grass species are cross-reactive—even those with high sequence homology. Patients with timothy grass pollen allergy have non-cross-reactive T cells, with frequency, phenotype, and functionality similar to those of timothy grass-specific T cells. The authors discuss the implications for...
Dust mite (HDM) is an important cause of allergic rhinitis (AR) and a trigger of asthma. Early research has suggested that sublingual immunotherapy (SLIT) using HDM extracts may be beneficial in adult patients with AR. This randomized trial assessed the safety and efficacy of two doses of HDM sublingual tablets in adults with AR.

The European multicenter study included 509 adults with HDM-associated AR. In double-blind fashion, they were assigned to receive HDM sublingual tablets at a once-daily dose of 300 or 500 index of reactivity (IR), or placebo. Patients were followed up over one year of treatment as well as the subsequent immunotherapy-free year.

The main efficacy outcome was Average Adjusted Symptom Score during the 1-year treatment period. Secondary outcomes—including symptom and rescue medication scores, onset of action, patient-reported outcomes, and safety variables—were assessed during treatment as well as over the subsequent year.

At both doses, active HDM SLIT was associated with significant reduction in Average Adjusted Symptom Scores. Mean reductions compared to placebo were -20.2% with the 500IR HDM tablets and -17.9% with the 300IR tablets. In both groups, the benefits of treatment were maintained through the symptom-free year. Evidence of efficacy was seen after 4 months. Both doses of active SLIT were associated with higher patient global evaluations of treatment success, compared to placebo. Most adverse effects were application-site reactions, with no cases of anaphylaxis.

The results demonstrate the safety and efficacy of 1-year treatment with HDM sublingual tablets in adult patients with AR. Similar benefits are achieved with 300IR and 500IR doses, and persist through a subsequent year without immunotherapy.

**COMMENT:** This is the largest study of HDM sublingual tablets for AR. There were minimal differences between the two doses in either efficacy or adverse events during 12 months of treatment. The fact that statistically significant improvement was seen within 4 months and that the benefit was sustained even after discontinuing treatment was impressive, particularly since half of the patients were polysensitized. The 25% to 30% inci-
Ragweed Pollen SLIT: Safety and Tolerability

Ragweed is a very common inhalant allergen and an important cause of rhinoconjunctivitis. Sublingual immunotherapy (SLIT) for ragweed allergy could have important advantages over conventional subcutaneous immunotherapy. A new ragweed sublingual tablet was evaluated for safety and tolerability.

The authors report on four randomized, double-blind placebo-controlled trials of the ragweed sublingual tablet MK-3641. The studies included 757, 198, 454, and 1,053 patients, respectively, with ragweed-induced allergic rhinoconjunctivitis, with or without asthma. Short-term safety outcomes were evaluated over 28 days of treatment and long-term safety over 52 weeks.

At doses of 6 and 12 Amb a 1-U, the MK-3641 tablets were associated with higher rates of adverse events, compared to placebo. However, most events were local application-site reactions, occurring especially during the first few days of treatment. No patient had loss of asthma control or worsening asthma related to ragweed SLIT. There were no cases of treatment-related anaphylaxis or serious or life-threatening adverse events at any dose of MK-3641.

In a total of 1,707 patients treated with MK-3641, there was one systemic reaction: a rate of 0.06%. Safety outcomes at 52 weeks generally supported the favorable safety profile seen at 28 days.

The results show good safety and tolerability with the MK-3641 tablet for ragweed SLIT. Systemic reactions or adverse events requiring epinephrine appear rare. After observed administration of the first dose in a medical setting, self-administration of MK-3641 at home appears safe.

COMMENT: Ragweed pollen is one of the most common inhalant allergens, with an estimated 10% to 15% of the US population sensitized as indicated by skin testing. Subcutaneous ragweed immunotherapy is associated with systemic reactions and requires close monitoring. This trial demonstrates the safety of short ragweed protein Amb a 1 in the form of the FDA-approved sublingual tablet MK-3641, commercially labeled as Ragwitek (Merck). Treatment is well-tolerated, with only local throat and ear pruritus and mild mouth edema not resulting in airway obstruction. Epinephrine is needed only rarely. The first dose is administered in a medical facility under observation with subsequent dosing at home. The study includes more than 3,841 patients, including up to 20% with mild controlled asthma and 80% with polysensitization.

C.C.R.


SLIT Effect Size Varies with Pollen Levels

Variations in pollen level from year to year, and even within-season, may influence assessments of the efficacy of allergy immunotherapy. This study evaluated the relationship between grass pollen exposure, allergy symptoms, and treatment effect size in clinical trials of grass pollen sublingual immunotherapy (SLIT).

The researchers performed a post hoc analysis of data from six clinical trials of grass pollen SLIT. The studies, performed over seven grass pollen seasons in North America and Europe, included a total of 2,363 patients with grass allergy and rhinoconjunctivitis. Daily pollen counts were analyzed for association with the total combined rhinoconjunctivitis symptom and medication score (TCS), including the effects of active SLIT versus placebo treatment. Linear regression modeling was performed to assess the impact of differences in pollen count on the treatment effect of SLIT.

Based on TCS, the magnitude of the treatment effect with SLIT was greater when pollen counts were higher. In each trial, the effect of SLIT on TCS was correlated with the average grass pollen exposure during the first period of the season. An increase in average daily pollen exposure of 10 grains/m³ during the first 20 days of pollen season was associated with an expected 3.5% increase in TCS (TCS = 12% + 0.35% × pollen count). There were similarly strong correlations with the overall and peak grass pollen season, but not with pollen exposure toward the end of the season.

Levels of pollen exposure can have a major impact on the observed treatment effect in clinical trials of grass pollen SLIT. The higher the pollen counts, the greater the magnitude of the SLIT effect. Pollen exposure is an important consideration in evaluating the results of SLIT trials.

COMMENT: Proving the efficacy of a treatment for seasonal pollen-induced symptoms typically requires following patients through their natural pollen seasons, in order to document symptoms while patients are taking the study drug or placebo. Unfortunately, Mother Nature does not always cooperate predictably. In addition to its relevance for drug development, this study reminds us of the complexity of translating clinical study findings into clinical practice. Sometimes excellent treatments are not initially appreciated in clinical practice, and others enjoy great initial enthusiasm before prescriptions subsequently fizzle. It remains to be seen where grass SLIT will fit on this spectrum.

S.A.T.

**Alpha-gal-Specific IgE Crosses the Pond**

The mammalian carbohydrate alpha-gal protein has been reported in many animal proteins, including red meats and cat dander. Cases of delayed anaphylaxis related to alpha-gal have been reported in the United States, occurring after red meat ingestion and related to previous tick bites. This study analyzed the prevalence of alpha-gal-specific IgE in two European countries, along with associated factors.

The study included a random sample of adults from one northern and one southern European country: 2,297 from Denmark and 444 from Spain. All were tested for alpha-gal-specific IgE using ImmunoCAP to bovine thyroglobulin. They also underwent skin prick testing (SPT) with a panel of common aeroallergens, along with assessment of epidemiologic factors. In the Danish subjects, additional assessments included history of tick bites.

Alpha-gal-specific IgE levels of 0.1 kU/L were present in 5.5% of Danish and 8.1% of Spanish subjects. Levels of 0.35 kU/L were present in 1.8% and 2.2% of participants, respectively. In both groups, positive results for alpha-gal-specific IgE were associated with the presence of atopy, based on SPT results, and pet ownership. An association with cat ownership was present for the Danish series, in which this information was available.

The presence of alpha-gal-specific IgE was unrelated to SPT results for cat or dog dander. There was a strong association between alpha-gal-specific IgE positivity and history of tick bites. No subject reported red meat as a possible cause of allergy.

This study finds a low prevalence of alpha-gal-specific IgE antibodies in the general adult population of Denmark and Spain. The presence of these antibodies appears related to atopy and cat ownership, as well as to previous tick bites. The possible mechanisms of these associations and the implications for testing in patients with clinically suspected red meat allergy are discussed.

**COMMENT:** Alpha-gal-specific IgE and delayed red meat allergy is a recently described entity, with most previous cases being reported from Virginia. Subsequently, patients with red meat allergy linked to alpha-gal-specific IgE have been reported in Australia and Europe. This study evaluated the prevalence of alpha-gal-specific IgE in a general population from Denmark and Spain, reporting prevalences of 2.2% and 1.8%, respectively. As in previous studies, alpha-gal specific IgE was associated with a history of tick bites, as well as cat ownership.

D.A.K.


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**Gut Microbiome in First Month of Life Predicts Asthma at Age 7**

Previous studies have shown that infants with lower diversity of the gut microbiota are at higher risk of eczema and sensitization. However, there have been no follow-up studies assessing the impact of gut microbial diversity on asthma risk later in childhood. The relationship between gut microbiota diversity in early infancy and the risk of asthma and other allergic diseases at school age was assessed in a cohort of Swedish children.

The study included 47 children from a larger study of allergy prevention in infants at risk. Stool samples obtained at 1 week, 1 month, and 1 year of age were analyzed for microbial diversity and composition. At follow-up to age 7 years, 8 of the children had asthma, 13 had allergic rhinoconjunctivitis, and 12 had eczema.

Diversity of the total gut microbiota at age 1 week and 1 month was significantly lower for children who went on to develop asthma. No significant association was noted with allergic rhinoconjunctivitis, eczema, or skin prick test reactivity. Gut microbiota diversity at 12 months was unrelated to asthma at school age.

Microbial diversity was also reduced for children who had IgE-associated eczema in infancy and went on to develop asthma. No differences in the relative abundance of different types of bacteria, at the level of phylum or genus, were found in children with versus without allergic disease.

Infants with lower total gut microbiota diversity during the first year of life may be more likely to develop asthma by age 7 years. The results raise the possibility of interventions to influence microbial colonization in early infancy, with the goal of reducing childhood asthma risk. Rates of other allergic diseases outcomes, including allergic rhinoconjunctivitis, show no such association in this small study.

**COMMENT:** In recent years the hygiene hypothesis has evolved to pinpoint gut biodiversity in the first year of life as a predictor of subsequent allergic disease. This would help explain why allergies and asthma are more common among affluent populations. A more limited diversity of gut bacterial species has been previously shown to be associated with allergic diseases in infancy, but little is known about the effects later in life. In this study from southeastern Sweden, lower gut biodiversity at age 1 week and 1 month of age strongly correlated with asthma at age 7. The story is to be continued—but if immunologic phenotype is established in the first month of life, we may need to alter our definition of "good parenting" of newborns.

S.A.T.


Cluster Analysis of Asthma Phenotypes--New Findings

Recent studies have used cluster analysis and other statistical techniques to identify asthma phenotypes, with the aim of better understanding pathogenesis and targeting treatment. Cluster analysis was used to evaluate clinical phenotypes in patients with severe or difficult-to-treat asthma.

The post hoc analysis included 518 children (aged 6 to 11 years) and 3,612 adults (aged 12 years or older) with severe or difficult-to-treat asthma. Patients were drawn from Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. A hierarchical clustering algorithm including a wide range of variables was used to identify groups of patients with distinguishing features. Multivariable analyses were performed to examine associations among clusters and asthma-related outcomes, with adjustment for socioeconomic status, environmental exposures, and treatment intensity.

In both age groups, five patient clusters were identified, with sex, atopic status, and nonwhite race as the distinguishing characteristics. Additional distinguishing variables were passive smoke exposure in children and aspirin sensitivity in adolescents and adults.

The clusters in children were unrelated to health outcomes. However, poorer quality of life was found to be associated with adult and adolescent clusters based on nonwhite race and aspirin sensitivity. Patients in the aspirin-sensitive cluster also had more frequent asthma exacerbations.

The analysis identifies some clinical phenotypes of severe or difficult-to-treat asthma based on specific distinguishing variables. Certain clusters are associated with a worse clinical prognosis, suggesting the possibility that intensified surveillance and treatment might lead to improved outcomes. Further studies are needed to assess the generalizability of the phenotypes, their relationship to inflammatory and other markers, and treatment implications.

A previous cluster analysis study from the Severe Asthma Research Program (SARP) identified five asthma subphenotypes representing an increasingly severe spectrum of early-onset allergic asthma, late-onset severe asthma, and severe asthma with chronic obstructive pulmonary disease characteristics. Since then, data on blood and sputum inflammatory cell counts have become available from a large subgroup of SARP participants. An updated cluster analysis was performed to integrate the inflammatory cellular measures with the clinical variables.

The study included 423 SARP participants who underwent sputum induction at three study centers. Unsupervised cluster analysis was performed using 15 variables, comprising clinical characteristics and blood and sputum inflammatory cell assessments.

The analysis identified four phenotypic clusters, with baseline FEV1 percent predicted and sputum neutrophil percentage being the most influential variables. Cluster A included 132 patients and cluster B 127 patients having mild to moderate early-onset allergic asthma with paucigranulocytic or eosinophilic sputum inflammatory cell patterns.

These same sputum inflammatory findings were present in just 7% of the 117 patients in cluster C and 47 patients in cluster D. These groups were characterized by moderate to severe asthma with frequent health care use, despite high doses of inhaled or oral corticosteroids. Cluster D patients had reduced lung function in addition. Sputum neutrophilia was present in 97% of subjects in cluster C and 83% in cluster D, with or without concurrent sputum eosinophilia.

Cluster analysis incorporating clinical phenotypes and inflammatory cellular findings identifies four new asthma subphenotypes. These clusters reflect a spectrum of severity ranging from mild to moderate allergic asthma with minimal or eosinophil-predominant sputum inflammation, to moderate to severe asthma with neutrophil-predominant or mixed granulocytic inflammation. Newer biologic approaches addressing both inflammatory cell types might be useful for patients with both neutrophilic and eosinophilic airway inflammation.

COMMENT: These two reports both used cluster analysis to evaluate phenotypes of asthma. The first was from the large, noninterventional prospective TENOR study, which included both children and adults with difficult to treat persistent asthma. Five distinct clusters were identified, with discrete phenotypes found in the adolescents and adults—particularly in aspirin-sensitive and nonwhite patients. However, there were no distinctive phenotypes in children. A major limitation was that many of the variables were self-reported.

The second study included data on 423 adult patients from the SARP. Four distinct asthma subphenotypes were identified using a variety of variables, including induced sputum cytology. Of interest, sputum neutrophilia with or without eosinophilia was associated with severe asthma, although no single biomarker or cell type identified any specific cluster group. The take-home message is that identification of various asthma phenotypes is complex but should be useful in the future, particularly when targeting therapeutic interventions.


Differences in Antibodies to HRV Species in Asthmatic Children

Human rhinovirus (HRV) is an important cause of childhood asthma exacerbations. Recent studies have reported that the newly recognized species HRV-C causes more severe asthma attacks, compared to HRV-A and HRV-B. The authors previously found low HRV-C-specific antibody responses in health adult sera, with most of the antibody to HRV-C being cross-reactive with HRV-A. The current study compared antibody...
responses to each HRV species in children with and without asthma.

The study included plasma specimens from 96 children presenting to the emergency department (ED) with asthma exacerbations, as well as from 47 nonasthmatic control children. Seventy-two percent of the asthma patients had HRV at the time of their exacerbation; molecular typing was performed to identify the HRV species. Patient and control plasma were tested for total and specific IgG1 binding to HRV viral capsid protein antigens of HRV-A, HRV-B, and HRV-C.

Antibody responses to HRV were higher in asthmatic children than controls. The asthma patients also had higher titers specific to HRV-A and, less so, to HRV-B. In both groups of plasma samples, HRV-C induced substantially lower antibody responses than HRV-A or HRV-B. In asthmatic children, the HRV genotype detected during the exacerbation was unrelated to antibody titers in both acute and convalescent plasma samples.

The results suggest that children presenting to the ED with asthma exacerbations have a heightened immune response against HRV, evidenced by higher total anti-HRV titers and higher titers of antibodies against HRV-A and HRV-B. Both asthmatic and nonasthmatic children show low species-specific HRV-C titers, even when HRV-C is present. Although both groups have high titers to HRV-C antigens, most of these antibodies are cross-reactive with other HRV species.

**COMMENT:** The newly recognized HRV-C species reportedly accounts for most asthma attacks in children, and is associated with even more severe attacks than HRV-A or HRV-B infections. This study of children presenting to the ED with asthma showed a heightened immune response to viral capsid proteins for patients with both HRV-A and HRV-C, compared to nonasthmatic controls. However, there was non-specificity and cross-reacting antibodies with HRV-C to other HRV species, particularly HRV-A. The bottom line is that asthmatic children have a less-than-optimal immune response to HRV-C, which tends to be associated with the most severe attacks.

S.M.F.


**Component-Resolved Diagnosis Changes SIT Prescription in Children**

In patients with pollen-related allergic rhinitis (AR) who are sensitized to more than one allergen, specific immunotherapy (SIT) prescriptions might be affected by cross-reacting molecules such as profilin. In this situation, component-resolved diagnosis (CRD) may improve identification of the disease-eliciting pollens, thus influencing the SIT prescription. This study assessed the impact of CRD on SIT prescriptions in a large group of children with hay fever.

The multicenter Italian study included 651 children with moderate-to-severe pollen-related AR. All underwent skin prick testing (SPT) to grass, cypress, olive, mugwort, pollitory, and/or Betulaceae pollen. Reactions were deemed clinically relevant if the child had symptoms during the peak season for that pollen. ImmunoCAP studies were performed to assess IgE sensitization to Phl p 1, Phl p 5, Bet v 1, Cup a 1, Art v 1, Ole e 1, Par j 2, and Phl p 12, ie, profilin.

Prescriptions for SIT were initially modeled according to the SPT responses and then using CRD. The latter prescriptions were based on GA(2)LEN-European Academy of Allergology and Clinical Immunology guidelines, as well as the opinions of 14 pediatric allergists.

In many cases, no IgE to corresponding major allergens was found in children deemed to have clinically relevant sensitization to various pollens. This was so for 60% of children "sensitized" to mugwort, 60% to Betulaceae, 30% to pollitory, 28% to olive, 15% to cypress, and 10% to grass.

Overall, 37% of SPT reactions to these pollens could be explained by IgE to profilin and/or polyclines. For many children, the SIT prescriptions were altered in response to the information provided on CRD: 42% using the European approach, 48% using the American approach, and 47% based on the opinions of pediatric allergists.

Component-resolved diagnosis can have a major impact on SIT prescriptions in children with hay fever, compared to the clinical history and SPT results. The results suggest that a higher cutoff for positive SPT responses might be considered in countries with high and prolonged exposure to many different pollens. Clinical trials will be needed to assess the effects of CRD-guided prescription on the outcomes of SIT.

**COMMENT:** The ingredients in the prescription formula for allergen extract are based on positive SPTs and clinical correlation with symptoms. These Italian allergists not only used SPT but also serologic component sIgE testing--ie, CRD--to analyze SIT prescriptions in children with AR. The most compelling finding is that the formula was different in over 40% of the cases when CRD was used. The authors suggest that panallergens, such as profilin, were responsible for this discrepancy. They also reported that when the AST was considered positive at 5 mm instead of the usual 3 mm, the discordance rate in the SCIT formula was reduced in half. Should we consider changing our AST cutoff point to 5 mm?

S.M.F.


**How Does Fixed Airflow Obstruction Affect Asthma?**

Some patients with asthma have persistent airflow limitation that is not fully reversible. The optimal definition of such fixed airflow obstruction (FAO) in asthma, and its association with other patient char-
acteristics and treatment responses, remains unclear. Data from previous asthma clinical trials were analyzed to assess the impact of FAO.

The post hoc analysis included data from two pivotal trials of budesonide/formoterol, and the two drugs individually, in 487 patients with mild to moderate asthma and 559 patients with moderate to severe asthma. Based on a screening post-albuterol FEV1/FVC of less than the lower limit of normal, FAO was considered present in 24% of patients with mild to moderate asthma and 40% of those with moderate to severe asthma. Patients with FAO were more likely to be male and had a longer duration of asthma and worse pulmonary function at baseline.

On placebo treatment, patients with FAO generally had poorer lung function and asthma control, compared to asthma patients without FAO. In both studies, patients with FAO did not respond to treatment with formoterol alone. However—as in patients without FAO—the addition of budesonide led to greater improvement in most study outcomes, including worsening asthma based on lung function or clinical symptoms. In patients with FAO, the effects of budesonide/formoterol on lung function were "generally greater than additive."

This analysis of clinical trial data suggests that asthma patients with FAO have greater impairment and are at higher risk of asthma events, compared to those without FAO. Patients with FAO do not respond to formoterol monotherapy, but still respond to budesonide. Their lung function and asthma control responses to budesonide/formoterol are at least as good as those seen in patients of similar asthma severity without FAO.

**COMMENT**: The impact of FAO on asthma and asthma therapy is not established. The authors report two 12-week randomized, placebo-controlled investigations of budesonide/formoterol in combination or separately. Patients with FAO tended to be male, with longer duration of asthma and worse pulmonary function—and therefore at higher risk for asthma exacerbation. However, they did not respond to formoterol but maintained response to budesonide. In patients with FAO, the greatest pulmonary function response to combination therapy was equal to or greater than that in the non-obstructed population.

C.C.R.


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**Is Penicillin G Skin Testing Adequate for Penicillin Allergy in Children?**

For nearly a decade, penicilloyl-polysine (PPL) skin test reagent has been unavailable in North America, greatly hindering diagnostic evaluation of suspected penicillin allergy. Several alternatives to PPL skin testing have been proposed. A new approach consisting of penicillin G skin testing followed by graded penicillin challenge was evaluated in children with a history of penicillin allergy.

The study included 563 patients with a history of reaction to any penicillin class antibiotic, seen at a Canadian pediatric hospital between 2006 and 2009. The study included 25 patients with anaphylactic reactions and 538 with nonanaphylactic reactions; mean age 5.9 and 5.3 years, respectively. All patients underwent skin testing using penicillin G only. Those with negative skin test results were offered a three-dose graded challenge to the implicated penicillin.

Penicillin G skin tests were positive in 33% of patients. Patients with positive skin tests had a shorter time from initial reaction and skin testing than those with negative skin tests. Of 375 patients undergoing graded penicillin challenges, 4.8% had a positive reaction. Negative predictive value (NPV) was 95.2% overall, and 82.4% in patients with a history of anaphylactic reactions. Responses to graded challenge were mild and promptly responded to treatment.

Penicillin G skin testing followed by graded challenge may be useful for evaluation of children with a history of penicillin allergy. The new approach, which is safe and yields a high NPV, provides a diagnostic alternative where PPL skin test reagent is unavailable.

**COMMENT**: The lack of commercially available PPL has impaired the practice of penicillin allergy assessment. Without PPL, skin testing has an NPV as low as 80%. The authors demonstrate that skin testing with penicillin G alone, followed by a three-dose graded challenge to the penicillin incriminated by history, is safe in children with a history of penicillin allergy. This approach provides an acceptable NPV of 95%, with an NPV of 82% in children with a history of anaphylaxis. However, delayed reactions were ruled out using only the three-dose regimen.

C.C.R.


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**How Does Lung Function Change after Bariatric Surgery?**

The mechanism underlying the association between obesity and asthma remains unclear. Involvement of airway reactivity induced by breathing at low lung volumes has been suggested. This study assessed the effects of major weight loss after bariatric surgery on lung function in patients with late-onset, nonallergic asthma.

The study included two groups of severely obese women being evaluated for bariatric surgery: 10 with late-onset, nonallergic asthma and 13 nonasthmatic controls. Both groups underwent evaluation of lung function by conventional clinical tests and by impulse oscillometry before and 1 year after bariatric surgery. In the asthmatic group, body mass index decreased from 47.8 before to 38.6 after bariatric surgery.

At baseline, FEV1 was 79.8% in the asthmatic women compared to 95.5% in controls. Forced vital capacity was 82.4% versus 93.7%, respectively, with no sig-
Significant differences in functional residual capacity or total lung capacity. One year after bariatric surgery, the nonasthmatic controls had significant increases in all four lung function parameters. In contrast, the asthmatic patients showed improvement only in FEV1: to 87.2%.

The two groups showed differing patterns of change in respiratory system resistance after weight loss. Whereas controls had a uniform decrease in resistance at all frequencies, asthmatic patients showed a decrease in frequency dependence of resistance. Mathematical modeling suggested that obesity was associated with greater collapse at the lung periphery in asthma patients versus controls.

In severely obese women with or without asthma, massive weight loss leads to decompression of the lung. However, the greater effects of weight loss on lung elastance indicate that the distal lung may be "inherently more collapsible" in asthma patients. The authors suggest that treatments aimed at lung recruitment could play a role in management of obese patients with late-onset nonallergic asthma.

**COMMENT:** Differences in lung volume do not predictably distinguish between obese patients with versus without asthma. However, mechanical effects of increased weight appear to cause early small airway closure in patients with asthma, resulting in increased airway closure at lower lung volumes. Some of these individuals may not exhibit symptoms of asthma at a normal weight, but may manifest asthma symptoms and then become obese. It is possible that a subset of obese asthmatics with late-onset disease may be curable without drugs, simply through a medically supervised weight loss program.

B.E.C.


**Blood Plus Sputum Eosinophilia Linked to Poor Asthma Control**

Eosinophilia is a key feature of asthma, but its role in asthma severity is debated. Although sputum and blood eosinophil counts in asthma are correlated with each other, some patients have discordance between these measures of local and systemic eosinophilia. This study assessed the prevalence and characteristics of discordant sputum and blood eosinophilia among asthma patients.

The study included retrospective data on 508 patients seen at a European university asthma clinic between 2005 and 2011. Concordance and discordance between local and systemic eosinophilia were assessed, based on a blood eosinophil count of 400 cells/mm³ or higher and sputum eosinophil percentage of 3% or higher. Associations between eosinophil measurements and asthma control (on the Asthma Control Questionnaire) and asthma exacerbation rate were prospectively re-examined in a new cohort of 250 matched asthma patients.

Forty-nine percent of patients in the retrospective cohort did not have eosinophilic inflammation in either sputum or blood. Twenty-five percent had isolated sputum eosinophilia. This group had significant reductions in FEV1 and FEV1/FVC and significant increases in bronchial hyperresponsiveness and exhaled nitric oxide (eNO), compared to patients with noneosinophilic asthma.

Seven percent of patients had systemic but not local eosinophilia; for this group, clinical characteristics were similar to those of patients with noneosinophilic asthma. The remaining 19% of patients had concordant systemic and airway eosinophilia. Fifty-three percent of these patients were male. Compared to the other groups, patients with concordant eosinophilia had the lowest airway caliber, asthma control, and quality of life; and the highest bronchial hyperresponsiveness, eNO, and exacerbation rate. The proportions of patients in the different concordance groups and the associations with asthma control and exacerbation rates were confirmed in the prospective cohort.

The study finds discordance between systemic and bronchial eosinophilic inflammation in about 30% of patients with asthma. About 20% of patients have concomitant systemic and local eosinophilia, which is associated with poor asthma control. The authors suggest studies of treatment interventions targeting either the airways or blood compartment, depending on the patient's individual profile.

**COMMENT:** This study extends observations by the SARP group, previously reported in AllergyWatch, that over 50% of patients with uncontrolled asthma do not have eosinophilic disease (Am J Respir Crit Care Med. 2012;185:612-619). The observation is made that concomitant measurement of peripheral blood eosinophilia and a marker of airway eosinophilia (eNO or sputum eosinophils) defines a group of patients who have more aggressive disease, often requiring higher doses of inhaled steroid. The patients with both blood and sputum eosinophilia have lower lung function, poor asthma control, and significantly more impaired quality of life. It is important these data be considered in creating the appropriate database to manage such patients.

B.E.C.


**Can Children with Food Allergy Have Reactions by Inhalation?**

Patients with food allergies can have reactions to inhaled aerosolized food particles. The authors reviewed the literature on allergic reactions to foods induced by inhalation in children.

There are few reports on the epidemiology of reactions to food particle inhalation in children. One clinic reports that about five percent of children with food allergies and asthma have bronchial symptoms related to inhaling food allergen. Ocular rhinitis and skin
manifestations are reported as well, along with rare cases of anaphylaxis. Challenge testing may be needed to confirm the diagnosis, but can be difficult to perform. Treatment consists of strict avoidance of exposure to aerosolized food proteins.

Aerosolized food particles have been found in a wide range of settings; the primary route of sensitization is unclear. Any food has the potential to induce clinical symptoms in response to inhalation. The authors review reports of specific inhaled food allergens in children—the most commonly reported are seafood, legumes, peanut and tree nuts, and cow’s milk. Children with asthma may account for most severe reactions to food inhalation.

The limited data on allergic reactions to foods induced by inhalation in children are reviewed. The authors call for large studies to assess the frequency and natural history of such reactions, as well as the accuracy of diagnostic tests. In clinical practice, reactions to airborne food proteins are potentially severe, and should be suspected and promptly recognized.

COMMENT: Few studies have investigated the frequency of reactions to food by inhalation. Confirmation by inhalation challenge can be difficult. The authors performed a literature search for articles published over the last 10 years that reported reactions to foods via inhalation. Inhalation reactions usually occur in patients with food allergy after they have had a reaction to that food after ingestion. Some patients have more severe reactions after inhalation, compared to those seen after oral consumption—for example, to fish, shellfish, or nuts. In other children, some foods that cause reactions by inhalation are tolerated when consumed orally. Inhalation rarely provokes first reactions for patients with peanut allergy. Almost two-thirds of patients with reported reactions via inhalation have asthma. The authors comment on the need for large studies to determine the true incidence and best diagnostic tests for these patients.

V.H.-T.

Filaggrin Predicts Severity of Chronic Idiopathic Urticaria

LIKE atopic dermatitis (AD), chronic idiopathic urticaria (CIU) is a common allergic skin disease causing severe pruritus, perivascular inflammatory infiltration, and epidermal involvement. Filaggrin deficiency, leading to epidermal barrier defects, plays an important role in the pathogenesis of AD. This study evaluated filaggrin expression in patients with CIU, including its association with severity of urticaria.

The researchers analyzed skin biopsy specimens from 16 patients with CIU and 11 with AD, as well as 14 healthy controls. Real-time reverse transcriptase polymerase chain reaction and immunostaining were performed to measure filaggrin expression. Associations between epidermal filaggrin and urticaria activity score, transepidermal water loss, and skin pH were assessed.

Specimens of CIU lesional skin showed higher expression FLG compared to lesional AD skin. Specimens of CIU lesions also showed increased staining intensity of filaggrin compared to normal controls or lesional AD skin. Within the CIU group, filaggrin staining intensity was correlated with urticaria activity score. Lesional CIU skin also showed increased transepidermal water loss and decreased pH, compared to either lesional AD skin or normal skin.

Lesions of CIU show increased filaggrin exposure, which is correlated with urticaria severity. The results suggest that changes in filaggrin expression in CIU affect epidermal physiologic function, with increased barrier function compared to skin from AD patients. The findings raise the possibility of treatments aimed at modulating filaggrin expression in patients with severe CIU.

COMMENT: Filaggrin deficiency plays an important role in atopic dermatitis. The authors found increased filaggrin gene expression in lesions of patients with CIU, compared to atopic dermatitis. Filaggrin also appears to play a role in the severity of CIU lesions, as intensity of filaggrin staining correlated with urticarial activity score. Skin pH was also lower in patients with CIU lesions, likely due to increased filaggrin breakdown products. This reminds the clinician about the importance of filaggrin expression in multiple atopic skin diseases—where deficiency may result in one disease and overexpression in another—supporting the saying that too much of a good thing is not necessarily good.


Do Stress and Anxiety Affect Skin Test Results?

ANXIETY has been shown to have an influence on symptoms of allergic diseases, as well as on allergy-related immune function. However, it is unclear how anxiety and stress may affect clinical evaluation of allergen patients. The authors designed a laboratory study to evaluate the effects of anxiety and stress exposure on responses to skin prick testing (SPT).

The study included 28 young adults with a history of allergic rhinitis. In a hospital research unit, they underwent SPT for common allergens on two separate occasions: with or without acute stress induced by the Trier Social Stress Test, a validated laboratory stressor. Wheal responses were compared in the stress and non-stress conditions, including the development of positive responses to allergens that tested negative on multiple baseline examinations.

Under the stressful condition, patients with higher baseline anxiety had an increased rate of positive SPT reaction to allergens to which they had previously tested negative. In contrast, without the stress-inducing laboratory tests, anxiety was unrelated to the rate of…
positive SPT results. The stressful condition was associated with enhanced SPT wheal response for allergens previously testing negative, but not for histamine as a positive control or saline as a negative control.

Stress induced in the laboratory affects SPT responses to common allergens in young adults with allergic rhinitis. A patient’s recent stress level may affect whether SPT results are positive or negative in the clinic. The authors suggest assessing anxiety level and current stress at the time of SPT, in addition to the clinical history.

**COMMENT:** Stress and anxiety are reported at high rates in patients with allergic conditions, including allergic rhinitis. In this study, a stress-inducing laboratory test significantly affected the results of allergen SPT. Results converted from negative to positive largely in a false negative setting--more anxious subjects had a history of reactivity. Allergists should assess anxiety and stress at the time of skin prick testing, as this may provide valuable insight into the patient’s allergic status and assist in clinical decisions. An accompanying editorial by Wright and Berin (Ann Allergy Asthma Immunol. 2014;113:1-2) reflects current knowledge of the neurologic circuit connecting anxiety or stress to the allergic response.

C.C.R.


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**Empiric or 'Testing-Directed' Food Elimination for EoE?**

**Patients** with eosinophilic esophagitis (EoE) have esophageal dysfunction and eosinophilic inflammation caused by food allergens. An empiric six-food elimination diet (SFED) has proven effective in both adults and children with EoE. Targeted elimination diets, based on the results of allergy testing, have been shown effective in children but not in adults.

These two management approaches were compared in a prospective series of 43 adult patients with EoE. All underwent specific IgE measurement, skin prick testing, and atopy patch testing for the six foods included in the SFED. Those with one or more positive specific IgE tests underwent targeted elimination of the implicated foods for 6 weeks.

Those with no positive specific IgE results underwent the SFED. Patients who responded to dietary elimination (less than 15 eosinophils/hpf) underwent gradual food reintroduction, followed by histologic assessment.

Specific IgE-directed food elimination was performed in 26 patients and SFED in 17. In the testing-directed elimination group, the mean number of foods eliminated was 3.81; wheat was eliminated in 85% of patients, nuts in 73%, and cow’s milk in 61%. Histologic response rates were similar between groups: 73% with specific IgE-directed elimination and 53% with SFED.

The most common cause identified on food challenge was cow’s milk, 64%; followed by wheat in 28% of patients, egg in 21%, and legumes in 7%. Seventy-one percent of patients had a single food trigger. In IgE-sensitized patients, specific IgE testing was more accurate in identifying the causative foods, with sensitivity of 87.5% and specificity of 68%. All atopy patch test results were negative.

In adults with EoE, specific IgE-targeted food elimination may produce a better histologic remission rate than SFED, with fewer food restrictions and endoscopies. Specific IgE testing may be especially useful in identifying cow’s milk allergy as the triggering food in EoE.

**COMMENT:** What to do with adult and pediatric EoE patients has become an increasingly common and challenging question in recent years. The results of this study from Spain suggest that specific IgE testing does have a role in EoE treatment decisions for adults. Although treatment assignment was not randomized, the subjects in whom testing directed their elimination diet actually did better than those who eliminated all six foods. On the other hand those undergoing SFED had negative test results and therefore may represent a different EoE phenotype. Stay tuned; but skin testing and/or ImmunoCAP testing appears to be justified in these patients.

S.A.T.


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**Promising New Option for Adult Atopic Dermatitis**

The type 2 helper T-cell cytokines interleukin (IL)-4 and IL-13 are believed to contribute to the pathogenesis of atopic dermatitis. Anti-IL-4/IL-13 therapy with dupilumab has demonstrated efficacy in patients with moderate to severe asthma and elevated eosinophil levels. Four randomized, placebo-controlled trials of dupilumab for adults with atopic dermatitis are reported.

All trials enrolled adult patients who had moderate to severe atopic dermatitis that did not respond to topical glucocorticoid and calcineurin inhibitor therapy. The studies were two 4-week trials of dupilumab monotherapy, including a total of 77 patients; a 12-week trial of dupilumab monotherapy, including 108 patients; and a 4-week trial of dupilumab and topical glucocorticoids, including 31 patients.

Four weeks of dupilumab monotherapy yielded prompt, dose-related improvements in clinical outcomes, biomarkers, and the disease transcriptome. Twelve weeks of dupilumab produced similar results: at least a 50% improvement in the Eczema Area and Severity score (EASI-5) was achieved by 85% of patients receiving dupilumab versus 35% with placebo. On investigator global assessment, 40% of patients in the dupilumab group had clearing or near-clearing of skin lesions, compared to 7% in the placebo group. Reductions in pruritus score were 55.7% and 15.1%, respectively.

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In the combination trial, the EASI-50 endpoint was reached by all patients receiving dupilumab plus topical glucocorticoid versus 50% with placebo plus topical glucocorticoid. This was even though patients in the dupilumab group used less than half as much topical medication as in the placebo group. The most common adverse events were headache and nasopharyngitis with dupilumab, and skin infection with placebo.

Treatment with dupilumab produces "marked and rapid improvement" in adults with moderate to severe atopic dermatitis. Side effects are overall similar with dupilumab versus placebo. The authors suggest that dupilumab might be useful in other conditions driven by the Th2 cytokines IL-4 and IL-13.

**COMMENT:** Dupilumab is a human monoclonal anti-IL-4 and anti IL-13 antibody with demonstrated efficacy in patients with asthma and eosinophilia. The authors report four separate randomized controlled trials in adults with moderate-to-severe atopic dermatitis despite standard treatment: dupilumab monotherapy in three trials and combined with topical glucocorticoids in one. Dupilumab yielded conspicuous and quick improvement in all assessed measures of atopic dermatitis disease activity. These findings stoutly reiterate the pathogenetic significance of Th2 cytokines in atopic dermatitis.


**First-Rate Transplantation Outcomes in SCID**

ALLOGENEIC hematopoietic stem cell transplantation has improved outcomes for children with severe combined immunodeficiency (SCID) and other primary immunodeficiencies. With newborn screening and data showing improved outcomes for children transplanted in the first few months of life, information on factors affecting the results of transplantations needed. A decade's experience with transplantation for children with SCID is presented.

The report included 240 infants with SCID undergoing transplantation at 25 member institutions of the Primary Immune Deficiency Treatment Consortium (PIDTC) from 2000 through 2009. Transplantation from matched sibling donors was associated with higher 5-year survival, freedom from immunoglobulin substitution, and CD3+ T-cell and IgA recovery, compared to those with other types of transplant donors.

However, regardless of graft type, survival was 94% for infants transplanted at 3.5 months or younger. Survival was 90% for older infants without previous infection, and 82% for those with infection that had resolved. For infants with active infection and no matched sibling donor, survival was best with haploidentical T-cell-depleted transplantation without any pretransplant conditioning.

For surviving infants, the chances of a CD3+ T-cell count greater than 1,000 mm$^3$, freedom from immunoglobulin substitution, and IgA recovery were better with reduced-intensity or myeloablative pretransplant conditioning. However, conditioning did not affect CD4+ T-cell recovery or recovery of phytohemagglutinin-induced T-cell proliferation. Although the quality of CD3+ T-cell recovery was affected by SCID genetic subtype, patient survival was not.

For infants with SCID, transplantation from donors other than matched siblings can still produce high survival rates, if performed before the onset of infection. The high success rate of early transplantation supports the survival benefits of newborn screening for SCID and early transplantation.

**COMMENT:** Members of the PIDTC performed a retrospective analysis of 240 transplanted infants with SCID at 25 centers between 2000 through 2009. The survival rate was high, regardless of donor type, among infants who received transplants at or before 3.5 months of age, and even in older infants without prior infection or whose infection had resolved. The genetic subtype of SCID affected the quality of CD3+ T-cell recovery but not survival. These heartening findings suggest that all available graft sources can be anticipated to lead to excellent survival among asymptomatic infants.


**CLINICAL TIDBITS**

**Allergy to Electronics?**

**ALLERGIC** contact dermatitis (ACD) is increasingly common among children, with nickel being the most frequently identified allergen. A case of ACD related to nickel exposure from an iPad is reported.

The patient was an 11-year old boy with generalized dermatitis present for several months. He had a history of atopic dermatitis, but the new rash was different from his typical dermatitis and did not improve with topical corticosteroid therapy. Allergic contact dermatitis was suspected, and the patient had a positive reaction to nickel on patch testing.

On avoidance counseling, the family reported that the child had been using a first-generation iPad increasingly often in recent months. The device tested positive for nickel. The patient was advised to avoid nickel, and to use a case that covered the back of the iPad. His dermatitis improved with a nickel avoidance regimen.

Nickel in tablet computers and other electronic devices is a potential cause of ACD. This may be an important consideration with the rising prevalence of nickel sensitization in children. Using a case or other barriers may help to reduce skin contact with the implicated device.
COMMENT: Ah finally, here is a perfectly legitimate reason for technophobia! This interesting case report describes an 11-year-old with a history of atopic dermatitis, who presented with a new-onset rash that was evaluated and diagnosed as nickel contact dermatitis. The source of exposure was traced to his recent increasing use of a first-generation iPad that tested positive for nickel. The authors note that significant nickel release has also been associated with laptop computers, cell phones, razors, wind-up toys, and videogame controllers.

C.D.


Depressive Symptoms--the Link between Obesity and Asthma?

OBESITY is linked to poor asthma control, and depression is more common among both patients with obesity and asthma. This study sought to clarify the possible role of depression in the relationship between obesity and asthma.

The study included 798 patients with physician-diagnosed asthma, who completed assessments including the Beck Depression Inventory (BDI)-II and Asthma Control Questionnaire (ACQ). The association between obesity and asthma was assessed, along with the potential mediating role of depressive symptoms.

Significant associations were noted between BMI and ACQ score, BMI and BDI-II score, and ACQ and BDI-II scores, after adjustment for age, sex, education, cohabitation, and inhaled corticosteroid use. In a model including both BDI-II and BMI, the association between BMI and ACQ remained significant, but the association between BMI and ACQ did not. The model suggested that obesity is related to increased depressive symptoms, which in turn are related to poorer asthma control.

The results find that depression and obesity are both associated with worse asthma control, but that depressive symptoms mediate the relationship between BMI and asthma control. The study suggests the possibility of interventions to prevent weight gain and associated asthma morbidity in asthma patients identified as having depressive symptoms.

COMMENT: Numerous studies have suggested that obesity may contribute to worse asthma outcomes. Similarly, depressive disorders have been associated with worse asthma control and quality of life. This Canadian study found that both obesity and depressive symptoms are associated with worse asthma control. Obesity was also associated with depressive symptoms. Using statistical models, the researchers found that depressive symptoms, not obesity per se, was the factor associated with poor asthma control. This study adds to the growing literature on the importance of depressive symptoms and disorders in asthma control.

D.A.K.


REVIEWS OF NOTE

COMMENT: The committees on infectious diseases and bronchiolitis of the American Academy of Pediatrics provide updated recommendations regarding the use of palivizumab to reduce serious lower respiratory tract infection caused by respiratory syncytial virus in at-risk infants and young children. This policy statement updates and replaces the 2012 Red Book recommendations.

C.D.

Committee on Infectious Diseases and Bronchiolitis Guidelines Committee: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014 134:e620-e630.

COMMENT: With the advent of global warming, some of us residing in temperate climates may need to become familiar with more than just the "northern grasses." This review focuses on the differences between subtropical grasses and their contribution to allergic disease worldwide.

S.A.T.


COMMENT: This is an excellent review of eosinophilic esophagitis pathophysiology, diagnosis, and management. The authors advocate evaluation with both in vitro IgE and skin testing for food and inhalant allergens to help guide treatment.

S.A.T.


COMMENT: This is a review of new research on asthma published in 2013 by the American Journal of Respiratory and Critical Care Medicine.

B.E.C.


COMMENT: Here's an excellent review of the physiologic effects of underwater diving. It also gives recommendations to guide patients with pulmonary disease regarding the safety of diving.

B.E.C.