AllergyWatch®

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

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Omalizumab for Non-Allergic Asthma?

ANTI-IgE therapy with omalizumab provides a therapeutic alternative for patients with continued allergic asthma symptoms on optimal treatment. No previous studies have reported on the use of omalizumab in patients with nonallergic asthma. A beneficial response to anti-IgE therapy in a patient with severe asthma but no evidence of sensitization is reported.

The patient was a 60-year-old woman with a history of surgical resection for Barrett's esophagus, but no history of asthma or allergy. She was seen in the emergency department with dyspnea and wheezing. After successful hospital treatment, the patient was discharged on appropriate inhaled medications, yet continued to have asthmatic symptoms with recurrent severe exacerbations. Skin tests for a wide range of airborne and food allergens were negative; bronchoscopic biopsy findings were consistent with asthma.

Despite the negative skin tests, the patient had relatively high serum total IgE, prompting a trial of omalizumab: 300 mg sc every 2 weeks. This led to a dramatic reduction in symptoms, allowing discontinuation of oral steroids. Lung function also improved, with FEV_1 increasing from 47% to 93% predicted. Over 2.5 years' follow-up on omalizumab, the patient had no further exacerbations. Asthma symptoms returned about 1 month after a trial of omalizumab discontinuation. Omalizumab treatment was restarted, with return of benefit.

Based on this case report, omalizumab is potentially beneficial for patients with severe nonatopic asthma who do not respond to other treatments. The authors suggest that previous high health care use is a helpful parameter for judging the success of anti-IgE therapy. They emphasize the need for randomized trial data to confirm this finding.

COMMENT: *Although case reports are looked at askance in scientific discourse, they may pose questions that deserve further inquiry. This report of a woman with severe, uncontrolled asthma without demonstrable skin sensitization to aeroallergens who was successfully treated with omalizumab is one such case. It gener-*➤➤

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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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ated an accompanying editorial (Chest. 2011;139;8-10), focusing on whether guidelines for this innovative, useful, but expensive treatment are too narrow. Unfortunately, double-blind placebo controlled trials--the gold standard for determining increased use--are unlikely to be performed. We are left in limbo. Many allergists have used omalizumab not according to guidelines. Compiling a series of cases of anecdotal reports is a step to help elucidate this finding, but hardly scientific.
S.F.W.
van den Berge M, Pauw RG, de Monchy JGR, et al: Beneficial effects of treatment with anti-IgE antibodies (omalizumab) in a patient with severe asthma and negative skin-prick test results.
Chest. 2011;139:190-193. ♦♦

Data Support Safety of Add-on Omalizumab

OMALIZUMAB is a monoclonal anti-IgE antibody approved for treatment of moderate to severe allergic asthma. Because of its mechanism of action, there is special interest in safety monitoring. Published data on the safety and efficacy of omalizumab were reviewed and analyzed.

A systematic review identified eight trials of subcutaneous omalizumab as add-on therapy to corticosteroids in patients with moderate to severe asthma. The studies included a total of 3,429 patients. The main outcomes of interest were reduction of steroid use and asthma exacerbations; other efficacy and safety outcomes were analyzed as well.

Omalizumab was associated with a higher rate of steroid discontinuation, compared to placebo: relative risk (RR) 1.80. Significant reductions in asthma exacerbations were noted at the end of the stable- and adjustable-steroid phases: RR 0.57 and 0.55, respectively. The reduction in exacerbation risk appeared consistent in subgroup and sensitivity analyses.

There was no significant difference in serious adverse events: 3.8% with omalizumab and 5.3% with placebo. Omalizumab was associated with a higher rate of injection site reactions, 19.9% versus 13.2%. Hypersensitivity reactions, cardiovascular effects, and cancers were all similar between the omalizumab and placebo groups.

Based on published data, omalizumab is acceptably safe as add-on therapy to corticosteroids in patients with moderate to severe asthma. Further studies are needed to establish long-term safety and efficacy.

COMMENT: *This is a compilation of eight registration studies previously published. The results are pooled and, as expected, show significant efficacy and safety in multiple asthma measures. However, the studies include add-on omalizumab to inhaled corticosteroid, rather than current guideline-based therapy of adding omalizumab to an inhaled corticosteroid/long-acting beta-agonist combination. In addition, postmarketing data (including possible cardiac risks) are referenced but not included. This article is a source for the basis of use of omalizumab in asthma.*
S.F.W.
Rodrigo GJ, Neffen H, Castro-Rodriguez JA, et el: Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review.
Chest. 2011;139:28-35. ♦♦

Dose Adjustments for LLRs Don't Affect Systemic Reaction Risk

IN patients receiving subcutaneous immunotherapy, the occurrence of large local reactions (LLRs) does not predict an increased risk of systemic reactions. One recent study found an increase in LLRs among patients with systemic reactions in practices that routinely make dose adjustments ➤➤

after LLRs. The relationship between LLRs and systemic reactions was analyzed using data from a practice that does not perform dose adjustments.

The retrospective study included 360 patients receiving immunotherapy at the study clinic over a 12-month period. The association between systemic reactions and LLRs was assessed, controlling for number of injections and patient visits. Reactions larger than the palm of the patient's hand after 30 minutes were considered LLRs.

A total of 38 LLRs occurred in 24 patients, accounting for 6.7% of patients, 0.4% of injections, and 0.6% of visits. There were also 51 systemic reactions in 46 patients: 12.7% of patients, 0.5% of injections, and 0.77% of visits. Both LLRs and systemic reactions occurred in 10 patients, or 2.8%. Thus 78.3% of patients with systemic reactions had no LLRs.

Among the 24 patients with LLRs, systemic reactions occurred in 1.3% of injections and 2.0% of visits. For patients without LLRs, rates of systemic reactions were 0.4% of injections and 0.7% of visits. Systemic reactions occurred in 41.7% of patients with LLRs, compared to 10.7% of those without LLRs. Analysis controlling for number of injections identified a subgroup of LLR patients who were more likely to have a systemic reaction: odds ratio 4.7. The 10 patients with recurrent LLRs were not at increased risk of systemic reactions: 0.4% per injection.

At a clinic that does not dose-adjust for LLRs, the occurrence of LLRs does not predict systemic reactions. However, about 40% of patients with LLRs are at higher risk of systemic reactions sometime during their immunotherapy. These patients appear to be at increased risk whether or not dose adjustment is used.

COMMENT: *Most of us were taught to make dose adjustments for local reactions to subcutaneous immunotherapy because of safety concerns. These investigators are to be congratulated for making a significant contribution to our clinical understanding that dose adjustments in LLRs do not reduce systemic, anaphylactic reactions to immunotherapy. Our group still adjusts doses for patient comfort, but our staff is always nervous with large locals. Old habits die slowly. D.K.L.*

Calabria CW, Stolfi A, Tankersley MS: The REPEAT study: recognizing and evaluating periodic local reactions in allergen immunotherapy and associated systemic reactions.

Ann Allergy Asthma Immunol. 2011;106:49-53. ♦♦

Egg-Allergic Patients May Not Need Skin-Testing for Flu Vaccination

THE influenza A H1N1 pandemic has prompted a re-evaluation of the safety of influenza vaccination for patients with egg allergy. The Joint Task Force on Practice Parameters has issued an updated statement on administration of current influenza vaccines for egg-allergic patients.

Evaluation by an allergist/immunologist is still recommended for patients with diagnosed or suspected egg allergy who have clinical indications for the 2010-11 trivalent influenza vaccine (TIV). However, based on available evidence, the Task Force concludes that routine skin-testing to TIV is no longer necessary. Instead, egg-allergic patients may receive the vaccine in a two-step graded challenge. Patients are first given 10% of the age-appropriate dose, then observed for 30 minutes. If no symptoms occur, the remaining 90% is given, and the patient is observed for another 30 minutes. Alternatively, patients can receive TIV in a single, age-appropriate dose, followed by a 30-minute observation period.

With either approach, booster doses should consist of the same vaccine product; it is not necessary to use the same lot. Influenza vaccine can also be given to patients with a history of anaphylaxis to egg, although studies of this issue have been small. The available data suggest that no more than a two-step protocol is needed.

With specialist evaluation and monitoring, the benefits of influenza vaccination outweigh the risks for most patients with egg allergy, the Task Force concludes. The update includes a statement that vaccine administration should be done by experienced clinicians equipped to deal with potential adverse effects, including anaphylaxis.

COMMENT: *This paper is a useful reference when facing questions from patients and physicians concerning egg allergy and administration of influenza vaccine. Our practice's policy had previously been to perform influenza skin tests in subjects with convincing egg allergy histories, but we will change now to giving the smaller initial dose followed by the remaining vaccine. D.K.L.*

Greenhawt MJ, Li JT: Administering influenza vaccine to egg allergic recipients: a focused practice parameter update.

Ann Allergy Asthma Immunol. 2011;106:11-16. ♦♦

Which Flu Vaccine for Patients with Egg Allergy?

WITH appropriate safeguards, egg allergy should not preclude influenza vaccination. For these patients, it makes sense to select a vaccine with a lower content of egg protein. Some recent data relevant to vaccine selection egg-allergic patients are reviewed.

The author presents information on the ovalbumin content of various influenza vaccine products. Affluria has a low ovalbumin content, but because of concerns about febrile seizure risk, it is not recommended for children younger than 9 years. Fluarix and Fluvirin have similarly low ovalbumin contents, but have demonstrated lower immune responses in children under age 3 or 4. There are no data on FluLaval or Agriflu in pediatric patients. FluMist, a live attenuated vaccine, has a very low ovalbumin content. However, there are no data on its use in egg-allergic patients, or on exposure to egg protein via the respiratory route. FluMist cannot be used in patients with asthma, and there are safety ➤➤

concerns in children under 2. The Fluzone products have the highest ovalbumin content.

Based on these data, Fluarix appears to be the best choice for egg-allergic patients over age 3. For older children and adults, other options become appropriate. The choice is more difficult for children aged 6 to 23 months; the only approved product is Fluzone, which has the highest ovalbumin content. However, the author emphasizes that all of these indications are relative--even with Fluzone, the actual ovalbumin content is lower than that commonly given without allergic reactions.

Any risks can be reduced by performing vaccination in settings where anaphylaxis can be recognized and treated, and by observing patients for at least 30 minutes. Skin-testing before vaccination now appears unnecessary. Divided dosing is another option for patients with a history of severe reactions or when a low-ovalbumin vaccine is unavailable.

COMMENT: *Influenza vaccine and egg-allergic patients: To give or not to give? Almost certainly yes, but the devil is in the details. This is a timely two-page review of the clinical studies, as well as the egg protein content of the different influenza vaccines for the year 2010-11. It does seem settled that preliminary skin testing of the vaccine isn't necessary, and that even a history of egg-anaphylaxis does not preclude giving the vaccine. Some patients might still benefit from a 10%-90% staged dose regimen.*
R.J.M.

Kelso JM: Administration of influenza vaccines to patients with egg allergy: update for the 2010-2011 season (letter).
J Allergy Clin Immunol. 2011;126:1302-1303. ♦♦

In Difficult Asthma Cases, Consider NTM

RATES of infection with nontuberculous mycobacteria (NTM) in non-AIDS patients are increasing worldwide, most frequently causing symptoms in patients with structural lung disease. Few studies have reported on the possible association of these pathogens with asthma. A case-control study evaluated the rate of NTM infection in a cohort of patients with difficult-to-control asthma.

From a larger patient cohort, the investigators identified 22 patients with difficult-to-control or complicated asthma who were found to be infected with NTM at a tertiary referral center. Each NTM case was matched to two controls from the same center. Features associated with NTM infection in difficult-to-control asthma were analyzed.

Among cases, the average time from onset of new or worsening asthma to the diagnosis of NTM infection was over 2 years. Worsening cough was the main symptom, present in 77% of patients. Other common symptoms were sputum production, 41%, and frequent exacerbations, 32%. Sixty-four percent of the NTM infections were with *Mycobacterium avium* complex and the rest with *Mycobacterium xenopi*.

The NTM cases averaged 60 years of age with an FEV_1 of 57%, compared to 43 years with an FEV_1 of 89.5% among controls. Cases had been using inhaled corticosteroids for a longer time, but doses were similar between groups. Six of the NTM cases were taking daily oral steroids, compared to none of the controls. Of 10 NTM-infected patients started on antimycobacterial drugs, 7 showed clinical improvement or symptom resolution.

Some patients referred for evaluation of difficult-to-control asthma are found to be infected with NTM. These patients tend to be older, with more severe airflow obstruction and greater exposure to inhaled or oral corticosteroids. Symptoms include chronic or recurring cough but are nonspecific, with the potential for long delays in diagnosis.

COMMENT: *Difficult-to-control asthma may be related to nontuberculous mycobacteria. The authors matched subjects with positive sputum or BAL cultures and NTM imaging findings (nodules and/or bronchiectasis) with a matched control population. We should consider this organism in our patients with severe asthma who are referred for BAL and imaging studies.*
S.F.W.

Fritscher LG, Marras TK, Bradi AC, et al: Nontuberculous mycobacterial infection as a cause of difficult-to-control asthma: a case-control study.
Chest. 2011;139:23-27. ♦♦

Peanut during Pregnancy May Increase Infants' Sensitization Risk

TO lower the risk of childhood peanut allergy, high-risk mothers are sometimes advised to avoid peanut during pregnancy and breast-feeding. However, the evidence basis for this recommendation is questionable. Factors associated with peanut sensitization were analyzed in a large group of children being evaluated for likely food allergy.

The analysis included 503 infants, mean age 9.4 months, undergoing evaluation for likely allergy to egg or milk but no previous known peanut allergy. A history of immediate allergic reaction to cow's milk, egg, or both was present in 308 infants, while 204 had moderate to severe atopic dermatitis plus a positive allergy test for milk and/or egg. The current study analyzed clinical and immunologic factors associated with peanut sensitization--indicated by a peanut-specific IgE level of 5 kU_A/L or higher.

Peanut IgE levels above that cutoff point were identified in 27.8% of infants. On multivariate analysis, frequent peanut consumption during pregnancy was associated with a threefold increase in the risk of peanut sensitization in infants: odds ratio (OR) 2.9. Other factors associated with a peanut IgE level of 5 kU_A/L or higher were milk and egg IgE levels, male sex, and nonwhite race. Risk was related to frequency of peanut consumption during pregnancy and breast-feeding in dose-response fashion. However, only consumption was a significant predictor. The association with frequent consumption during pregnancy was strongest, OR 4.99, ➤➤

in a subgroup of 71 infants who were never breast-fed.

Among infants evaluated for likely milk or egg allergy, consumption of peanuts by the mother during pregnancy is a strong risk factor for peanut sensitization. Although further study is needed, maternal avoidance of peanut during gestation might be helpful in preventing peanut allergy in children.

COMMENT: *Peanut allergy occurs in more than 1% of American children, and is usually lifelong. Primary prevention would be nice. This paper comes from the Consortium of Food Allergy Research, an "A team" of U.S. researchers. They studied over 500 children enrolled for likely egg or milk allergy, and found that 69% of the children were also sensitized (by in vitro test) to peanut. Maternal ingestion of peanut during pregnancy was correlated in a dose-dependent way with the children's elevated peanut-specific IgE levels. Clinical outcomes are not available yet, but extrapolation suggests that maternal avoidance of peanuts might be advisable.*
R.J.M.

Sicherer SH, Wood RA, Stablein D, et al: Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants.
J Allergy Clin Immunol. 2010;126:1191-1197. ♦♦

Study Defines Three Asthma 'Transcriptional Phenotypes'

CLINICAL or inflammatory phenotypes of asthma have been defined, based on patient characteristics or sputum cell counts. Whole-genome gene expression profiling might be useful in studying the heterogeneous types and mechanisms of asthma. This technology was used to define transcriptional asthma phenotypes.

The study used induced sputum samples from 589 asthma patients: mean age 58 years and FEV_1 76% predicted. Most patients were receiving inhaled corticosteroids. Samples from 13 non-asthma controls were studied as well. In addition to inflammatory cell counts, RNA was extracted for generation of transcriptional profiles. Transcriptional asthma phenotypes were compared with patient and clinical characteristics.

Three distinct groups of gene expression profiles were identified. The first transcriptional phenotype, including 21 patients, was associated with a lower FEV_1% predicted, higher scores on asthma control questionnaires, and higher exhaled nitric oxide and sputum eosinophils. The second transcriptional phenotype, 14 patients, was associated with a lower FEV_1% predicted and forced vital capacity percentage, compared to the third phenotype. That group, consisting of 24 patients, had higher sputum macrophages and was similar to healthy controls.

The differences in gene expression between groups reflected genes involved in inflammatory and immune responses. The samples analyzed showed overexpression of genes in the interleukin-1 and tumor necrosis factor-α/nuclear factor-κβ pathways, which were correlated with clinical characteristics and neutrophilic airway inflammation.

Gene expression profiling identifies distinct transcriptional phenotypes in patients with asthma. This new technique may prove useful in evaluating the molecular heterogeneity of asthma and in classifying asthma phenotypes.

COMMENT: *Many studies have commented on the phenotypic variations of asthma. (Who was the sage who said, "If you've seen one case of asthma, you've seen one case of asthma"?) This study analyzed induced sputum cells for their genome-wide gene expression profiles, and found three distinct correlated phenotypes: one neutrophil-rich, one eosinophil-rich, and one non-granulocytic. If we can put the genetics and the correlated molecules with the clinical expressions, can tailored treatments be far behind?*
R.J.M,

Baines KJ, Simpson JL, Wood LG, et al: Transcriptional phenotypes of asthma defined by gene expression profiling of induced sputum samples.
J Allergy Clin Immunol. 2011;127:153-156. ♦♦

Grass Pollen SLIT Shows Efficacy in North American Adults and Children

In Europe, sublingual immunotherapy is now widely used for the treatment of allergic rhinoconjunctivitis (ARC). Because of differences in sensitization and pollen types, it is unclear whether good results achieved in Europe will translate to North America. A randomized trial of timothy grass SLIT for North American adults with grass pollen-induced ARC is reported.

The randomized controlled trial included 439 adult patients with grass pollen-induced ARC, with or without asthma. One group received active SLIT, consisting of a 75,000 standardized quality *Phleum pratense* tablet, containing about 15 μg of Phl p 5. The other group received placebo; both groups started treatment about 16 weeks before the start of pollen season. The main outcome of interest was a combination of the daily symptom and medication scores.

Grass pollen SLIT was associated with a 20% improvement in average total combined daily symptom and medication scores. Symptom scores improved by 18% and rhinoconjunctivitis-specific quality of life score by 17%. A 26% reduction in daily medication scores trended toward significance. Active SLIT led to significant improvement in Phl p 5-specific IgG4 and IgE-blocking factor levels, compared to placebo.

Adverse events were generally transient, mild, local reactions. No serious adverse events or cases of anaphylaxis were reported. One patient in the active SLIT group was treated with epinephrine for a possible grade 1 systemic reaction.

The results support the safety and efficacy of timothy grass SLIT for North American adults with grass pollen-induced ARC. Improvements in symptoms, medication use, quality of life, and other outcomes are reported, even in a group of patients with a high rate of multiple sensitizations.

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UP to 17% of American children have ARC. Especially in children, the need for subcutaneous injections may be a deterrent to effective allergen immunotherapy. A trial of grass pollen SLIT for U.S. and Canadian children with grass pollen-induced ARC is reported.

The study included 345 children and adolescents, aged 5 years or older, with grass pollen-induced ARC, with or without asthma. One group received a 75,000 standardized quality Phl p 5 tablet, identical to that used in the preceding adult trial. Controls received placebo. Treatment started 16 weeks before pollen season, and continued throughout the season. As in the adult study, most patients had multiple sensitizations.

Children in the active SLIT group had a 26% improvement in average total combined daily symptom and medication scores. Treatment was associated with a 25% reduction in daily symptom score and an 81% reduction in medication score, as well as an 18% improvement in quality of life. Phl p 5-specific IgG4 and IgE-blocking factor levels were higher during peak pollen season, as well as at the end of the season.

As in the adult study, treatment was safe and well-tolerated, with generally mild and transient adverse events. There was one possible systemic reaction in the active SLIT group.

In North American children as in adults, SLIT appears to be a safe and effective treatment for grass pollen-induced ARC. Along with ease of administration, good results, low complication rates, and lack of need for dose buildup, SLIT could offer an important new alternative for the treatment of ARC.

COMMENT: *These reports present data from two relatively large studies using grass pollen SLIT in both children and adults for grass pollen ARC. The same dose of timothy grass tablet was used in both children and adults, and was started approximately 16 weeks prior to the onset of grass pollen season and continued through the season. Interestingly, the total combined symptom improvement in the pediatric patients receiving SLIT was 26%, compared to only 20% in the adult study. The authors suggest that these are similar to the results from the European SLIT studies. Relatively low seasonal grass pollen counts may help explain the mediocre improvement. However, the fact that there was a reasonable safety profile as well as documented immunologic responses suggests that SLIT may soon be legally available to our patients with seasonal allergic rhinitis.*

S.M.F.

Nelson H, Nolte H, Creticos P, et al: Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults.
J Allergy Clin Immunol. 2011;127:72-80.

Blaiss M, Maloney J, Nolte H, et al: Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents.
J Allergy Clin Immunol. 2011;127:64-71. ♦♦

Early Rhinitis Predicts Childhood-Onset Wheezing

EVEN without atopy, rhinitis predicts later onset of asthma. Such interactions between the upper and lower airways have led to the concept of the "united airways." However, it is unclear whether rhinitis in children predicts the development of childhood asthma.

The question was addressed using a birth cohort of 1,314 healthy children enrolled in the German Multicentre Allergy Study. The children underwent regular follow-up from birth to age 13 years, including parental questionnaires and annual measurement of specific IgE levels. Other assessments included measurement of airway hyperresponsiveness at age 7. Symptoms of rhinitis developing in early childhood were evaluated as a predictor of childhood-onset wheezing.

Children with allergic rhinitis before age 5 were significantly more likely to have developed wheezing between age 5 and 13. On adjusted analysis, children with early rhinitis were nearly four times more likely to have childhood-onset wheezing: relative risk 3.82. This risk was independent of atopy during the first 2 years of life, including type and severity of sensitization or atopic dermatitis. Children with early allergic rhinitis accounted for 41.5% of all cases of childhood wheezing.

Allergic rhinitis first appears in the preschool years, and is a predictor of the onset of wheezing later in childhood. In preschool children with rhinitis, assessment of allergic sensitization might help in identifying a group at high risk of wheezing. More study is needed to see if early intervention can modify the course of disease in these children.

COMMENT: *The German Multicentre Allergy Study is a well-defined prospective birth cohort study using standardized questionnaires as well as objective measures in 1,314 children through 13 years of age. The authors found that allergic rhinitis at 5 years was predictive of wheezing illness at 13 years. Interestingly, neither the type or severity of allergic sensitivity nor the presence of atopic dermatitis predicted this association. The authors do confirm that allergic rhinitis is a risk factor for wheezing in preschool children. The findings add to the literature suggesting that early detection of allergic sensitivities and intervention might benefit these children.*

S.M.F.

Rochat MK, Illi S, Ege MJ, et al: Allergic rhinitis as a predictor for wheezing onset in school-aged children.
J Allergy Clin Immunol. 2011;126;1170-1175. ♦♦

Combination Therapy vs Doubling Dose for Step 3 Asthma Treatment in Children

FOR children who continue to have asthma symptoms despite low to moderate doses of inhaled corticosteroids, the next step in treatment is unclear. Some guidelines now recommend adding a long-acting bronchodilator instead of doubling the inhaled corticos-➤➤

teroid dose. This randomized trial compared salmeterol/fluticasone with a doubling dose of fluticasone in children with symptomatic asthma.

The multicenter, noninferiority trial included 158 children, aged 6 to 16 years, who had continued asthma symptoms during a 4-week run-in period on fluticasone propionate, 100 µg twice a day. The children were randomly assigned to 26 weeks of treatment with salmeterol/fluticasone, 50/100 µg twice a day, or fluticasone, 200 µg twice a day, via Diskus inhaler. Asthma control and lung function outcomes were compared between groups.

During the last 10 weeks of treatment, there was no difference in percentage of symptom-free days between the two groups. In both groups, this outcome improved by about 25% on treatment, compared to baseline. Pulmonary function values also improved to a similar extent, with a small effect on maximal expiratory flow in the salmeterol/fluticasone group at 1 week. Asthma exacerbations, adverse events, and growth were not significantly different between groups.

For asthmatic children who remain symptomatic on a moderate dose of inhaled corticosteroid, salmeterol/fluticasone and a doubling dose of fluticasone provide similar results in terms of symptom control and lung function. Thus the combination of a long-acting bronchodilator with an inhaled corticosteroid provides an option for step 3 treatment of childhood asthma. More study is needed to evaluate the effects by asthma phenotype.

COMMENT: *This impressive study addresses step 3 care for children. No adverse event signal was seen in this trial or in the Badger Study* (**Lemanske RF Jr, et al: NEJM**. 2010;362:975-985). *Clinical experience and the recently published data would lead one to suggest that low-dose inhaled corticosteroid/long-acting beta-agonist is a preferable choice. The accompanying editorial* (**Am J Respir Crit Care Med**. 2010;82:1219-1220) *does not agree with this position.*
B.E.C.

Vaessen-Verberne AAPH, van den Berg NJ, van Nierop JC, et al: Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma.
Am J Respir Crit Care Med. 2010;182:1221-1227. ♦♦

Reduced Lung Function in *Aspergillus* - Associated Asthma

THE contribution of *Aspergillus fumigatus* sensitization and colonization to asthma is unclear. Some patients have *A. fumigatus*-associated asthma (AFAA) despite not meeting criteria for allergic bronchopulmonary aspergillosis. Using a focused approach to detecting *A. fumigatus* in sputum, the investigators examined associations between the clinical and laboratory findings of AFAA.

The study included 79 patients with asthma, most GINA 4 or 5. Sputum examination focusing on detection of *A. fumigatus* found that 40 patients were IgE-sensitized only, with immediate skin reactions larger than 3 mm and/or a specific IgE level greater than 0.35 kU/L. Another 13 patients were IgG-sensitized only, with IgG levels above 40 mg/L. The remaining 26 patients were nonsensitized, as were 14 healthy controls.

Lung function was significantly reduced in the asthma patients sensitized to *A. fumigatus*: postbronchodilator FEV_1% predicted was 68%, compared to 88% in nonsensitized patients. Bronchiectasis was present in 68% of sensitized vs 35% of nonsensitized patients; median sputum neutrophil percentage was 80.9% vs 49.5%. On regression analysis, *A. fumigatus* IgE sensitization and sputum neutrophil count were significant predictors of lung function. Sputum culture of *A. fumigatus* and eosinophil count were supporting factors.

In patients with asthma, detection of *A. fumigatus* in sputum is associated with IgE sensitization to this fungus, along with neutrophilic airway inflammation and reduced lung function. Damage to the airways caused by *A. fumigatus* colonization may lead to fixed airflow obstruction. More study is needed to assess the possible benefits of antifungal treatment for patients with AFAA.

COMMENT: *Asthmatics (GINA Step 4 and 5) with* Aspergillus*-specific IgE and* Aspergillus *isolated from the sputum have a more arduous clinical course. These are patients who do not meet the diagnostic criteria for allergic bronchopulmonary aspergillosis. They also have increased sputum neutrophils and peripheral eosinophilia. A randomized, placebo-controlled treatment trial is needed to determine if neutrophil airway inflammation and the clinical course of these patients may be successfully addressed.*
B.E.C.

Fairs A, Agbetile J, Hargadon B, et al: IgE sensitization to Aspergillus fumigatus *is associated with reduced long function in asthma.*
Am J Respir Crit Care Med. 2011;182:1362-1368. ♦♦

Can HEPA Cleaners Reduce Effects of Secondhand Smoke in Asthma?

IN children with asthma, exposure to secondhand smoke (SHS) leads to increased rates of wheezing and exacerbations. Anticipatory guidance has proven ineffective in reducing children's SHS exposure. This study examined the possible benefits of high-efficiency, particle-arresting (HEPA) air cleaners for asthmatic children exposed to SHS.

The randomized, double-blind trial included 225 asthmatic children, aged 6 to 12. All were exposed to SHS, 5 or more cigarettes per day. Children in the intervention group received two active HEPA air cleaners: one installed in the main activity room and one in the child's bedroom. Controls received inactive air cleaners. No attempt was made to reduce exposure to SHS or other potential asthma triggers.

On adjusted analysis, children receiving active HEPA air cleaners had an 18.5% reduction in unscheduled asthma visits over 12 months. Levels of airborne particles larger than 0.3 µM decreased by 25% in the intervention group, compared to 5% in the con-➤➤

trol group. There was no significant difference in asthma symptoms. Exhaled nitric oxide levels, air nicotine levels, and cotinine levels were also similar between groups.

Installing HEPA air cleaners in the home may be a useful part of strategies to reduce morbidity in asthmatic children exposed to SHS. Unscheduled asthma visits and exposure to particles larger than 0.3 µM are significantly reduced, although exposure to the gaseous phase of tobacco smoke is unaffected. Other approaches to reducing SHS exposure are needed.

COMMENT: *It is an intriguing question: can HEPA cleaners really reduce the impact of second hand smoke in the homes of asthmatic children? The answer might well be "It's better than nothing at all," given the lack of effect on nicotine exposure or cotinine levels. While it is too early to recommend this as a strategy, concerns with such an approach might include a reduced motivation to smoke outside the home! Nonetheless, our advice to provide a smoke-free home environment is not always followed.*
K.R.M.
Lanphear BP, Hornung RW, Khoury J: Effects of HEPA air cleaners on unscheduled asthma visits and asthma symptoms for children exposed to secondhand tobacco smoke.
Pediatrics. 2011;127:93-101. ♦♦

Cord Blood Vitamin D Levels and Early Childhood Wheezing, Part II

CHILDREN whose mothers have a higher vitamin D intake during pregnancy are at lower risk of wheezing. Recent studies have suggested that vitamin D may be related to favorable changes in innate immunity, particularly in infants. Associations between cord blood levels of 25-hydroxyvitamin D (25[OH]D) and the risks of respiratory infection, wheezing, and asthma were assessed.

The study included 922 newborns with 25(OH)D measured in cord blood. When the infants were 3 months old, parents were asked about history of respiratory infections. History of wheezing was assessed at age 15 months and annually thereafter. The presence of asthma at age 5 years was assessed by physician diagnosis and/or reported inhaler use or wheezing over the previous year.

Median cord blood 25(OH)D level was 44 nmol/L. With adjustment for season of birth, infants with lower cord blood levels were at higher risk of respiratory infection at 3 months old. Compared to a reference level of 75 nmol/L or higher, odds ratio was 1.39 for a cord blood 25(OH)D level of 25 to 74 nmol/L and 2.16 at a level of less than 25 nmol/L. Inverse associations were also noted for wheezing at age 15 months, 3 years, and 5 years, and were little affected by adjustment for a wide range of potential confounders. Cord blood 25(OH)D levels were not significantly related to incident asthma at age 5.

Infants with lower cord blood 25(OH)D levels have higher rates of respiratory infections in the first 3 months of life. They also have increased rates of wheezing later in childhood, although they are not at increased risk of asthma at age 5. Randomized controlled trials of vitamin D supplementation during pregnancy and early childhood are warranted.

COMMENT: *Do low vitamin D levels contribute to wheezing as a function of increased susceptibility to viral infection versus low vitamin D levels predisposing to asthma per se? The author of the current study first noted the association between low cord vitamin D level and wheezing in 2006* (**J Allergy Clin Immunol**. 2006;117[suppl]:721-722). *In this follow-up study, he teases out the contributory factors. Changes in innate immunity, causing an increase in respiratory infections, could explain this association.*
K.R.M.
Camargo CA Jr, Ingham T, Wickens K, et al: Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma.
Pediatrics. 2011;127:e180-8187. ♦♦

Good Results with C1-INH for Repeated HAE attacks

IN recent years, C1-esterase inhibitor (C1-INH) has become available for the treatment of acute attacks of hereditary angioedema (HAE). A previous study showed the efficacy of C1-INH, at a weight-based dose of 20 U/kg, for treatment of single acute abdominal and facial HAE attacks. A follow-up study was performed to assess the same dose of C1-INH for treatment of successive abdominal and facial attacks.

The prospective, open-label study included patients with HAE attacks at 15 North American centers. A total of 706 attacks in 53 HAE patients were treated: 663 abdominal attacks in 50 patients and 43 facial attacks in 16 patients. Treatment consisted of a single 20 U/kg IV dose of C1-INH. As reported by patients, median time to onset of symptom relief was 19.8 minutes and time to complete resolution 11.0 hours. Time to onset was shorter for abdominal than facial attacks: 19.8 versus 28.2 minutes. Symptom relief was faster in women than men and faster in adults and adolescents than in children.

There were no serious adverse events, including HIV, hepatitis, or parvovirus B19 infection. Treatment was well-tolerated.

At the weight-based dose used in this study, C1-INH concentrate is a "reliable, long-term therapeutic option" for repeated abdominal and facial attacks in patients with HAE. The results appear better than in previous studies using fixed doses of 500 or 1,000 U.

COMMENTS: *I am amazed with the developments in the treatment of HAE that have occurred over the past 5 years--after what seemed to be no advances for the other 25 years of my career. Two things strike me. I am getting older and allergy/immunology is still exciting. I only hope that our patients will have access to these remarkably effective but relatively expensive therapies. Progress, as well as aging, usually comes with a price.*
D.K.L. ➤➤

Wasserman RL, Levy RJ, Bewtra AK: Prospective study of C1 esterase inhibitor in the treatment of successive acute abdominal and facial hereditary angioedema attacks.
Ann Allergy Asthma Immunol. 2011;106:62-68. ♦♦

'Humming Nasal NO' Is Useful for Monitoring Sinus Disease

BLOCKAGE of the paranasal sinus outflow tracts is a key factor in chronic rhinosinusitis with nasal polyposis (CRSNP). Having the patient hum at a certain frequency with the mouth closed induces a sharp rise in nasal nitric oxide levels, if sinus ostial patency is present. The effects of systemic steroid treatment on humming nasal NO in patients with CRSNP were evaluated.

Twelve adult patients with grade 2 or higher CRSNP completed 2 weeks of treatment with oral prednisolone, 25 mg/d. Nasal NO was measured using three techniques: aspiration, exhalation at 0.2 L/sec, and the humming method. For the latter approach, a tuning fork was used to train patients to hum at a frequency around 128 Hz. Other assessments included peak nasal inspiratory flow (PNIF), the Sinonasal Outcomes Test 20 score, symptoms, olfaction, and polyp grade.

The humming technique showed the greatest difference in nasal NO from before to after steroid treatment: geometric mean-fold ratio 4.9, compared to 1.5 with aspiration and 2.1 with exhalation. Standardized response means were 1.61, 0.97, and 1.05, respectively. The changes in nasal NO were accompanied by decreases in polyp size and symptoms and increases in PNIF.

The humming nasal NO technique appears more sensitive than the aspiration and exhalation techniques in assessing the response to oral steroid therapy for CRSNP. Humming nasal NO may be a useful noninvasive indicator of sinus ostial patency.

COMMENT: *Good clinical studies are challenging to perform. I congratulate the senior investigator in this group as he has made numerous contributions to the clinical science literature. Clinicians recognize the obstacles in assessing and monitoring acute and chronic sinus disease. I am not confident I have sufficient pitch recognition to teach someone to hum at 128 Hz...but if I could and if I could afford to perform nasal NO measurements, I'd have a potential tool that could be used to monitor sinus disease. There are a lot of "ifs" but still very interesting.*
D.K.L.
Vaidyanathan S, Williamson P, Anderson K, Lipworth B: Effect of systemic steroids on humming nasal nitric oxide in chronic rhinosinusitis with nasal polyposis.
Ann Allergy Asthma Immunol. 2010;105:412-417. ♦♦

What's the Real Impact of Obesity in Asthma?

IT has been suggested that obesity is an independent risk factor for asthma, and that it affects asthma severity and quality of life (QOL). However, past studies of this issue have had significant limitations--for example, respiratory symptoms may be related to physiologic impairment from obesity rather than asthma. Data from a large prospective study were used to analyze the impact of obesity in asthma.

The study included 902 children and adults with asthma, drawn from underserved populations. Patients were randomly assigned to disease management versus usual care. Relationships between body mass index (BMI) and asthma severity, spirometric variables, health care utilization, and quality of life were analyzed.

Forty-five percent of the pediatric asthma patients were obese: 17% had BMIs above the 85th percentile and 28% at or above the 95th percentile. Of the adults, 58% were obese: BMI 30 or higher. In children, BMI was not related to any of the asthma characteristics or outcomes analyzed. In adults, quality of life was significantly reduced for obese patients with asthma. There was an inverse relationship between BMI and forced vital capacity; other spirometry findings were unrelated to body weight.

Obesity does not affect asthma severity, spirometric variables, quality of life, or health care utilization in asthmatic children. Forced vital capacity is lower in obese adults, which may mask an obstructive defect. Obese adults with asthma also show evidence of reduced quality of life, but no difference in disease severity or health care utilization.

COMMENT: *Obesity is generally accepted as a comorbidity or complicating factor for asthma and asthma management. This paper questions that relationship. The issues of dyspnea due to deconditioning, increased gastroesophageal reflux disease with increased weight, and spirometry changes related to central adiposity make it challenging to assess the relationship between obesity and asthma.*
D.K.L.
Peters JI, McKinney JM, Smith B, et al: Impact of obesity in asthma: evidence from a large prospective disease management study.
Ann Allergy Asthma Immunol. 2011;106:30-35. ♦♦

Perennial and Seasonal Allergic Responses Are Different

TO develop more effective immunologic therapies for allergic disease, more complete information on allergen-specific $CD4^+$ T cell responses is needed. A recent study using a major histocompatibility complex (MHC) class II peptide tetramer approach showed distinct responses to seasonal birch pollen antigen in allergic versus healthy individuals. This study used the same technique to compare $CD4^+$ T cell responses to seasonal versus perennial allergens.

The study used MHC class II peptide tetramers developed to monitor T cell responses to seasonal birch allergen, Bet v 1; and perennial dust mite allergens, Der p 1 and Der p 2. $Tetramer^+$ cells were detected in 19 patients allergic to mite, 7 allergic to birch, and 13 allergic to birth both mite and birch. They were also detected ➤➤

in 9 nonallergic patients with an HLA-DRB1*0101, *0301, *1501 or an HLA-DPB1*0401 background.

The immunodominant Bet v $1_{141-155}$ epitope elicited high-avidity T cells, while the Der p $1_{16-30,110-124,171-185}$ and Der p $2_{26-40,107-121}$ epitopes induced broader, low-avidity T cells. The response to Bet v 1 involved effector (CDL62 low, CCR7 low) memory cells in allergic subjects and central ($CD62L^+$, $CCR7^+$) memory cells in nonallergic individuals. In contrast, the response to mite allergens consisted mainly of central memory cells. In nonallergic subjects, interferon-γ and interleukin-10 were produced in response to both mite- and Bet v 1-specific T cells. Whereas Bet v 1 induced a Th2 response, mite allergens induced polymorphic responses in allergic subjects, including Th1, Th2/Th17 or mixed Th1/Th2 profiles. In blood samples, mite-specific T cell frequencies were between 1 to 6 X 10^{-4} $CD4^+$ T cells year round.

This study using MHC class II peptide tetramers finds that perennial and seasonal allergen stimulation elicit different types of memory $CD4^+$ T cell responses. The finding of variable $CD4^+$ T cells responses in patients with mite allergy may have important implications of allergen immunotherapy.

COMMENT: *These authors used an interesting MHC II tetramer technique to examine T cell responses to dust mite and birch pollen. It was not surprising that the patterns of T cell responses in allergic patients and nonallergic controls were different. The more interesting finding was that among patients allergic to birch and/or dust mite, there were significant general differences between T cell responses to these two allergens. For example, dust mite T cell responses involved more epitopes and had low avidity, compared with the high-avidity responses to the few birch epitopes. The authors speculate that these differences relate to the perennial versus seasonal exposure to the allergens, and that there is potential for altering our immunotherapy strategies to address these differences.*
S.A.T.

Wambre E, Bonvalet M, Bodo VB, et al: Distinct characteristics of seasonal (Bet v 1) vs. perennial (Der p 1/Der p 2) allergen-specific $CD4^+$ T cell responses.
Clin Exp Allergy. 2010;41:192-203. ♦♦

Basophil Activation Test May Reduce Positive Oral Challenges In Cow's Milk Allergy

MOST children with IgE-mediate cow's milk allergy (CMA) outgrow their allergy. Oral challenges are the gold standard for determining when tolerance has developed and cow's milk can be safely reintroduced. The ability of a simple basophil activation test to predict the response to oral challenge was evaluated in children with CMA.

The study included 112 children with CMA undergoing oral challenge. All underwent the basophil activation test, performed by measuring upregulation of the cell-surface marker CD63 in response to incubation with milk proteins. The value of this test for predicting the results of oral challenge were assessed.

Oral challenge was positive in 32% of children. The mean percentage of activated basophils was 20.9% in children with a positive challenge versus 3.9% in those with a negative challenge. The basophil test result was also well correlated with the eliciting dose of cow's milk. Test efficiency was 90%, sensitivity 91%, specificity 90%, and positive and negative predictive value 81% and 96%, respectively. Area under the receiver operating characteristic curve was 0.866.

The basophil activation test had better predictive performance than skin prick testing or IgE measurement. An algorithm combining this test with specific IgE and skin prick testing correctly identified 94% of children with persistent CMA or milk tolerance.

The basophil activation test can help to predict the results of oral milk challenge in children with CMA. Used with IgE measurement and skin testing, this test could help to reduce the number of unnecessary, expensive, and hazardous positive oral challenges.

COMMENT: *Safely finding out when a patient has outgrown CMA has been a perplexing challenge for decades. These authors present data supporting the utility of the "basophil activation test" for improving the sensitivity and specificity of skin testing and in vitro specific IgE testing in predicting tolerance of cow's milk in children with a history of immediate reactions. Although additional validation studies are necessary, this test would be a welcome diagnostic tool if it can improve our current algorithms.*
S.A.T.

Rubio A, Vivinus-Nébot M, Bourrier T, et al: Benefit of the basophil activation test in deciding when to reintroduce cow's milk in children.
Allergy. 2011;66:92-100. ♦♦

Are We Now 'Overdiagnosing' Asthma?

THERE has been a sharp increase in the number of U.S. adults reporting a history of asthma. The extent to which this trend reflects increased asthma awareness vs a true increase in prevalence is unclear. The results of methacholine challenge testing in a group of adults with a self-reported history of asthma are presented.

The study included 304 responders to advertisements recruiting patients for asthma research studies. All reported a history of physician-diagnosed asthma. All participants underwent an evaluation including methacholine challenge, spirometry, and physician assessment.

Twenty-seven percent of participants had a negative methacholine challenge test, Characteristics associated with a negative result included adult onset of asthma symptoms, normal FEV_1, and no history of asthma exacerbations requiring oral steroids. Sixty percent of participants with negative methacholine challenges reported weekly symptoms such as cough, dyspnea, chest tightness, or wheezing. Thirty-nine percent had visited the emergency department for asthma-like symptoms. ➤➤

One-fourth of adults reporting physician-diagnosed asthma have negative results on methacholine challenge testing. Typically these patients have symptom onset in adulthood and normal or near-normal spirometric results. Additional tests, including bronchoprovocation studies, are warranted in this situation.

COMMENT: *In recent years there has been considerable energy devoted to reducing asthma underdiagnosis. This is a worthy goal, especially for patients who might suffer poor outcomes without proper treatment. However, in some cases we may go too far. In this study, more than 1 in 4 adult respondents to asthma research study advertisements had negative methacholine challenges despite having prior physician-diagnosed asthma. In this era of sometimes prescribing multiple controller medications for a patient with consistently normal spirometry, we should keep in mind other objective testing options to help establish the diagnosis.*
S.A.T.

McGrath KW, Fahy JV: Negative methacholine challenge tests in subjects who report physician-diagnosed asthma.
Clin Exp Allergy. 2011;41:46-51. ♦♦

Mite, Cat, and Dog Allergens Activate Respiratory Epithelial Cells

BOTH seasonal and indoor allergens can cause sensitization and lead to allergic airway disease. A previous study found that the non-proteolytic major house dust mite (HDM) allergen Der p 2 stimulated proinflammatory responses in bronchial epithelial cells. The current study assessed whether other clinically important nonproteolytic allergens also produced activation of respiratory epithelial cells.

The study used in vitro cultures of the human bronchial epithelial cell line BEAS-2B, normal human bronchial epithelial cells (BECs), and the alveolar epithelial cell line A549. The cells were exposed to several nonproteolytic allergens, including HDM (recombinant [r]Der p 2, natural [n]Der f 2, and rEur m 2), storage mites (rLep d 2), cat (r/nFel d 1), dog (rCan f 2), birch (rBet v 1) and timothy (rPhl p 5a) allergens. Secreted mediators and expression of cell adhesion receptors in response to these allergens were assessed.

In BECs, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor, interleukin (IL)-6, IL-8, monocyte-chemotactic protein-1 and macrophage inflammatory protein-3α secretion were all induced by rDer p 2, nDer f 2, rEur m 2, rLep d 2, r/nFel d 1, and rCan f 2. The same allergens also induced surface expression of intracellular adhesion molecule-1. The cells were not activated by pollen allergens, and alveolar epithelial cells were not affected by any of the allergens studied.

Respiratory epithelial cells are activated by mite allergens as well as by structurally unrelated cat and dog allergens. Activation appears to occur through adjuvant-like protease-independent mechanisms. This adjuvant-like effect could participate in asthma pathogenesis in several different ways.

COMMENT: *It is known that both seasonal or indoor allergens may cause sensitization and airway diseases, and that proteolytic HDM allergens can activate inflammation in respiratory epithelial cells. Österlund and colleagues determined whether clinically relevant nonproteolytic aeroallergens from HDMs, storage mites, cat, dog, birch and timothy activate respiratory epithelial cells. A significant increase in G-CSF secretion was observed after exposure to all of these allergens, while increased secretion of other mediators included was consistently not observed. However, an earlier in vitro study by Huang, Leyko, and Frieri* (**Ann Allergy Asthma Immunol**. 2005;95:443-451, 2005) *using human BECs stimulated with HDM did detect secretion of IL-4, tumor necrosis factor α, and transforming growth factor β. In this study, mite, cat, and dog allergens activated respiratory epithelial cells by adjuvant-like protease-independent mechanisms. Thus direct interaction of an allergen with the respiratory epithelium resulting in a local inflammatory response may affect the outcome of exposure.*
M.F.

Österlund C, Grönlund H, Gafvelin G, Bucht A: Nonproteolytic aeroallergens from mites, cat and dog exert adjuvant-like activation of bronchial epithelial cells.
Int Arch Allergy Immunol. 2011;155:111-118 ♦♦

CLINICAL TIDBITS

How Does FAHF-2 Prevent Peanut Anaphylaxis?

A Chinese herbal combination called Food Allergy Herbal Formula-2 (FAHF-2) provides lasting prevention of anaphylactic reactions in peanut-allergic mice. Further experiments were performed to assess the effects of FAHF-2 on mast cell and basophil numbers and IgE-mediated activation.

Peanut-allergic mice treated with FAHF-2 for 7 weeks were protected against anaphylaxis in response to peanut challenge at 1 day and 4 weeks after therapy. Basophil numbers in peripheral blood began to decrease during the first week of treatment and continued decreasing for at least 4 weeks thereafter. Numbers and FcεRI expression of peritoneal mast cells were also decreased.

Murine mast cells (MC/9) cells treated with FAHF-2 showed reductions in IgE-induced FcεRI expression, FcεRI γ mRNA subunit expression, proliferation, and histamine release in response to challenge. In rat basophilic leukemia cell 2H3 (RBL-2H3) and human mast cells, degranulation was inhibited by fraction 2 (of 4) from FAHF-2. Three compounds included in fraction 2 inhibited RBL-2H3 cell degranulation via suppression of spleen tyrosine kinase phosphorylation.

The findings add to the evidence that FAHF-2 may be a useful new treatment to prevent peanut anaphylaxis. Its protective effects may involve reduction of basophil and mast cell numbers and suppression of IgE-mediated mast cell activation.

➤➤

COMMENT: *Food allergy herbal formula 2 (FAHF-2) is a water-based Chinese herbal formulation containing nine different herbs. It has previously been shown to prevent anaphylaxis in peanut-allergic mice. This study further elucidates the mechanism of action, showing that FAHF-2 reduces basophil and mast cell numbers and reduces FcεRI expression, suppressing IgE activation and proliferation. Three major alkaloids in the formulation act synergistically to suppress spleen tyrosine kinase phosphorylation in antigen-stimulated rat basophil leukemia cells in vitro. Dissecting the mechanism of FAHF-2 helps explain its dramatic clinical benefit for peanut-allergic individuals, as least in mice. It will be more impressive if these results can be extended to humans as well.*
S.M.F.
Song Y, Qu C, Srivastava K, et al: Food allergy herbal formula 2 protection against peanut anaphylactic reaction is via inhibition of mast cells and basophils.
J Allergy Clin Immunol. 2010;126:1208-17 ♦♦

Moving Beyond the pH Probe

MULTIPLE intraluminal esophageal impedance recording with pH monitoring (MII-pH) provides data beyond that of pH monitoring alone, detecting significantly more reflux episodes. This study compared the findings of MII-pH monitoring with symptoms of reflux in infants.

The researchers analyzed 225 MII-pH tracings performed in infants and children with suspected reflux-related symptoms. Seventy tracings were excluded from the analysis because of technical problems or absence of symptoms.

Of all symptoms observed, 52% occurred within a 2-minute window before or after a reflux episode. Forty-five percent of symptoms were associated with acid reflux (AR), 51% with weakly AR, and 3% with alkaline reflux. Vomiting was the symptom most strongly associated with reflux. The association with cough was stronger in older children, who also had more symptoms associated with AR. Seventy percent of patients had symptoms associated with proximal reflux.

The symptom index (over 50%) was positive for all reflux episodes in 83% of patients and for AR in 49% of patients. The symptom association probability (SAP) (over 95%) was positive for all reflux episodes in 46% of patients and for AR in 47%. The SAP for crying was independent of AR or weakly AR. The SAP for cough was positive in one-third of patients--mainly with AR in 6- to 12-month-old infants and with weakly AR in other age groups.

Compared to pH monitoring, MII-pH monitoring doubles the changes of finding an association between symptoms and reflux episodes in infants and children. Young infants are more likely to have symptoms associated with weakly AR than with AR.

COMMENT: *Where available, MII-pH is replacing the traditional pH probe technique as the modality of choice to assess reflux in adult and pediatric patients. Although imperfect, this newer modality shows much promise in its ability to detect a broader spectrum of esophageal events, including weakly acidic reflux.*
K.R.M.
Salvatore S, Arrigo S, Luini C, Vandenplas Y: Esophageal impedance in children: symptom-based results.
J Pediatr. 2010;157:949-954. ♦♦

REVIEWS OF NOTE

COMMENT: *Allergen-specific immunotherapy (SIT) has worked empirically for 100 years. With modern immunology, we are now learning why. This is a very readable summary of the evidence regarding the mechanisms of SIT. After this, you'll be able to dazzle your friends with terms like "forkhead box protein 3-positive CD4+ CD25+ Treg cells." Be prepared for the "nerd" comments at the next cocktail party.*
R.J.M.
Akdis CA, Akdis M: Mechanisms of allergen-specific immunotherapy.
J Allergy Clin Immunol. 2011;127:18-27. ♦♦

COMMENT: *This excellent review details interactions between viral respiratory infections and asthma development/exacerbations, with a focus on viruses associated with eosinophilia. It describes the role of infections in infancy and asthma development, and the possible role of human rhinovirus and asthma exacerbations. The hygiene hypothesis, atopy and respiratory viral infections, and markers during virus-induced asthma exacerbations versus those found in non-viral-allergen asthma exacerbations are all reviewed.*
M.F.
Callaway Z, Kim CK: Respiratory viruses, eosinophilia and their roles in childhood asthma.
Int Arch Allergy Immunol. 2011;155:1-11. ♦♦

COMMENT: *This is a comprehensive view of the bronchial smooth muscle contribution to airway hyperresponsiveness and structural changes in the airway.*
B.E.C.
Bara I, Ozier A, Tunon de Lara J-M, et al: Pathophysiology of bronchial smooth muscle remodeling in asthma.
Eur Respir J. 2010;36:1174-1184. ♦♦

COMMENT: *This thorough overview for pediatricians, from our colleagues in the AAP Section on Allergy and Immunology, underscores the need for food allergy education for our patients, parents, and school systems. Allergists must play a key role in educating all about the nature of food allergy, the prevention of reactions, and appropriate treatment when needed.*
Sicherer SH, Mahr T, et al: Management of food allergy in the school setting.
Pediatrics. Pediatrics. 2010;126:1232-1239. ♦♦

COMMENT: *Is there a predictable dose-response curve in younger children who take inhaled corticosteroids for persistent asthma, which could guide our optimal dosing? This meta-analysis attempts to address the question, but in conclusion reveals significant gaps in our knowledge, based on the available randomized controlled trials.*
K.R.M.
Zhang L, Axelsson I, Chung M, Lau J: Dose response of inhaled corticosteroids in children with persistent asthma: a systematic review.
Pediatrics. 2011;127:129-138. ♦♦