# ALLERGYWATCH®

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

A Publication of The American College of Allergy, Asthma & Immunology

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## Rethinking Asthma Pathogenesis

THE airway inflammatory process accompanying asthma is associated with large numbers of interleukin-4 (IL-4)- and IL-13-producing CD4+ cells. The CD4 cell-surface marker has recently been found to be expressed by CD1d-restricted natural killer T cells, as well as by conventional class II-restricted CD4+ T cells. The frequency and distribution of CD1d-restrictued invariant natural killer T cells were assessed in the lungs and circulating blood of patients with asthma.

The study included 14 patients with moderate to severe persistent asthma, along with 6 healthy controls. Also included were 5 patients with sarcoidosis, another respiratory inflammatory disease associated with high numbers of CD4+ Th1 cells. The frequency and distribution of natural killer T cells in bronchoalveolar lavage fluid and peripheral blood were measured using CD1d tetramers, specific antibodies for natural killer T cells, and reverse-transcriptase polymerase chain reaction assays of the invariant T-cell receptor of natural killer T cells.

In the asthma patients, a mean 63% of CD4+ T cells in bronchoalveolar lavage fluid were invariant natural killer T cells, compared to less than 1% for healthy controls and sarcoidosis patients. The percentage of CD3+ T cells that were invariant natural killer T cells was 74% in the asthmatic patients, compared with less than 2% in the comparison groups. Inhaled corticosteroid therapy seemed to have no effect on the number of pulmonary invariant natural killer T cells. These cells were found to produce IL- 4 and IL-13, but little interferon-γ.

Patients with persistent asthma show high numbers of CD4+ CD3+ invariant natural killer cells, whereas the lungs of healthy controls or sarcoidosis patients have only very low numbers of such cells. Added to animal studies showing the importance of natural killer T cells in the development of allergen-induced airway hyperreactivity, the results suggest that invariant natural killer T cells play an important role in the development of airway inflammation in asthma. This discovery may lead to new therapeutic targets in patients with asthma. ➤➤

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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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**COMMENT:** *The more we think we know about asthma, the more we realize how complex it is at the molecular level. The myriad of cells and cytokines involved are mind-twisting. In the search for a central proinflammatory actor that makes asthma distinct from other pulmonary diseases, these authors have identified the highly concentrated prevalence of the "invariant natural killer T lymphocyte" in humans with asthma. This opens an avenue to investigate unique asthma therapies. In an editorial, Dr. A. Barry Kay calls this an "exciting finding of a potentially essential role" of a newly described cell type.*
R. J. M.

*Akbari O, Faul JL, Hoyte EG, et al: CD4+ Invariant T-cell-receptor+ natural killer T cells in bronchial asthma.*
**N Engl J Med**. 2006;354:1117-1129. ♦♦

## TNF-α Antagonist Offers Novel Asthma Therapy

REFRACTORY asthma is associated with high rates of death and morbidity. One uncontrolled study reported improvements in airway hyperresponsiveness in refractory asthma patients treated with the recombinant soluble tumor necrosis factor α (TNF-α) receptor etanercept. A pilot study used etanercept to evaluate the role of TNF-α in refractory asthma.

Ten patients with refractory asthma, ten patients with mild to moderate asthma, and 10 controls underwent measurement of TNF-α activity in peripheral blood monocytes. The refractory asthma group showed elevated expression of membrane-bound TNF-α, TNF-α receptor 1, and TNF-α converting enzyme. The mean ratio of fluorescence for antibody against membrane-bound TNF-α versus that for isotype-matched control was 8.9 in the refractory asthma group, compared to 3.3 in the mild to moderate asthma group and 3.8 in the control group.

Subjects were entered into a double-blind crossover study of treatment with etanercept versus placebo. Compared with placebo, 10 weeks of TNF-α antagonist therapy was associated with a significant difference in methacholine $PC_{20}$--the mean difference in doubling concentration change with etanercept was 3.5, compared with placebo. Patients with refractory asthma also had improvements in asthma-related quality of life and postbronchodilator $FEV_1$ after etanercept.

This pilot study shows evidence of TNF-α upregulation among patients with refractory asthma. Ten weeks of treatment with the TNF-α antagonist etanercept reduces expression of membrane-bound TNF-α while improving certain clinical outcomes. Tumor necrosis factor-α appears to contribute to the pathogenesis of refractory asthma.

**COMMENT:** *Some asthma patients are relatively refractory to conventional pharmacotherapies, including steroids. The current study demonstrates that this group has an upgraded axis of TNF-α and its receptors, and that use of the TNF-α inhibitor etanercept--already used for arthritides--provides measurable benefit to these difficult-to-treat patients.*
*R. J. M.*

*Berry MA, Hargadon B, Shelley M, et al: Evidence of a role of tumor necrosis factor alpha in refractory asthma.*
**N Engl J Med**. 2006;354:697-708. ♦♦

## Wheat Allergy: Food for Thought

WHEAT allergy is well documented in children but is generally regarded as uncommon in adults. Few studies have evaluated the clinical characteristics of wheat allergy in adults. Food challenges and other methods were used to investigate the frequency and severity of wheat aller-➤➤

gy in adult patients.

The study included 27 adults with presumed wheat allergy evaluated at two European allergy units. Double-blind, placebo-controlled food challenges using raw wheat were positive in 48% of patients. Most patients did not cross-react to grass pollen. Ten of eleven patients challenged with cooked wheat had positive results. Persistent erythema and urticaria were the most common symptoms on positive wheat challenge; more than half of positive reactions involved at least two organ systems. Provocative doses ranged from 0.1 to 25 g, with more than one-fourth of patients having a provocative dose of 1.6 g or less. Although specific IgE measurement was more sensitive than skin-prick testing, both tests had low specificity and predictive values.

In nearly half of adult patients with presumed wheat allergy, double-blind food challenges confirmed the diagnosis. Reactions to wheat can occur without grass pollen presensitization, to cooked and raw wheat, and often to very low doses of wheat. The diagnosis of wheat allergy should be considered in adults reporting reactions to wheat.

**COMMENT:** *Little by little, through scientific study, food allergy is becoming less mysterious. Wheat allergy is frequently suspected but not often confirmed, especially in adults. In this study, IgE-mediated wheat allergy was proven in a number of adults by oral challenges. The prick test and in vitro test were both lacking in sensitivity and specificity compared to the challenges. Cooking did not inhibit the allergenicity of wheat. Most of the allergic individuals were not allergic to grass.*
*R. J. M.*

*Scibilia J, Pastorello EA, Zisa G, et al: Wheat allergy: a double-blind, placebo-controlled study in adults.*
**J Allergy Clin Immunol**. 2006;117:433-439. ♦♦

## SIT Effective for Children with Asthma

SPECIFIC immunotherapy (SIT) is an effective treatment for allergic rhinoconjunctivitis in children as well as adults. However, few studies have evaluated its efficacy in children with allergic asthma. A randomized, controlled trial of grass pollen SIT for the treatment of pediatric seasonal allergic asthma is reported.

The trial included 39 children and adolescents, aged 3 to 16 years, with seasonal allergic asthma and confirmed sensitization to *Phleum pretense* grass pollen. All patients were taking inhaled corticosteroids, equivalent to 200 µg/d of inhaled beclomethasone; those who had symptoms of asthma or rhinoconjunctivitis outside of grass pollen season were excluded. Patients were randomly assigned to grass pollen or placebo SIT over two consecutive pollen seasons. The main efficacy outcome was combined asthma symptom-medication score at the end of the second pollen season.

Thirty-five patients completed the study. Grass pollen SIT was associated with a significant reduction in the asthma symptom-medication score: median score 0.5, compared with 1.0 in the placebo group. Patients receiving active SIT also had reductions in skin, conjunctival, and airway reactivity to grass pollen. Airway inflammation was not significantly affected, although there was a trend toward decreased inhaled corticosteroid dosage in the grass pollen SIT group. There were no serious adverse events, nor any treatment withdrawals because of adverse events.

Grass pollen SIT is a safe and effective treatment for monosensitized children and adolescents with seasonal allergic asthma. Especially since it can modify the long-term natural history of pollen allergy, SIT may be a particularly valuable treatment for children with allergic asthma.

**COMMENT:** *This relatively small study used meticulous methodologies and concluded that SIT is an effective treatment for children with seasonal allergic asthma. Although there was no change in lung function or exhaled nitric oxide with SIT, there was an impressive improvement in symptom scores and medication usage in the SIT-treated children. One wonders whether the results would have been more robust if these children had received multiple-allergen immunotherapy, instead of single-allergen SIT.*
*S. M. F.*

*Roberts G, Hurley C, Turcanu V, Lack G, et al: Grass pollen immunotherapy as an effective therapy for childhood seasonal allergic asthma.*
**J Allergy Clin Immunol**. 2006:117:263-268. ♦♦

## SIT Also Effective in Resistant SAR

ALTHOUGH specific immunotherapy (SIT) has become a common treatment for seasonal allergic rhinitis (SAR), there is a lack of data from large-scale clinical trials. The use of SIT is limited in the United Kingdom. This large U.K. study evaluated the use of SIT in patients with treatment-resistant SAR.

The randomized, double-blind trial included 410 patients with moderately severe SAR that was inadequately controlled by conventional drug treatments. Two groups of patients were assigned to a single season of SIT using Alutard grass pollen at a maintenance dose of 10,000 or 100,000 standardized quality units (SQ-U). The remaining patients received placebo SIT. The main outcomes of interest were symptom scores and medication use during grass pollen season.

Three hundred forty-seven patients completed treatment. Compared with the placebo group, patients assigned to the 100,000 SQ-U SIT group had a mean 29% reduction in symptom score and a mean 32% reduction in medication score. The differences were greatest during peak pollen season. The difference in outcomes between the 100,000 and 10,000 SQ-U groups was significant only during peak pollen season. Subjective evaluations also favored the higher dose of SIT. On quality of life assessment, both SIT doses were superior to placebo. Clinically significant side effects occurred only in the 100,000 SQ-U group, but there were no life-threatening reactions. ➤➤

For patients with treatment-resistant SAR, one season of SIT yields significant improvements in symptoms and medication use. A better clinical response is achieved with a 100,000 SQ-U regimen, although a 10,000 SQ-U regimen causes fewer adverse events. This large-scale trial confirms the benefits of SIT for moderately severe SAR, beyond the effects of conventional medications.

**COMMENT:** *In Great Britain, allergen immunotherapy for rhinitis is discouraged by the authorities, probably for economic reasons. This study reaffirms the utility of SIT in seasonal grass-allergic people who are at the more severe end of the spectrum. In the process, they reconfirm that there is a dose-response relationship with SIT. Other than travel tickets to another hemisphere, SIT is the only alternative to drugs for these patients.*
*R. J. M.*

*Frew AJ, Powell RJ, Corrigan CJ, et al: Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis.*
**J Allergy Clin Immunol** 2006; 117:319-325. ♦♦

## An Intensive Look at HAE

PATIENTS with hereditary angioedema (HAE) caused by C1 inhibitor deficiency have unpredictable attacks of edema affecting the skin, GI tract, and upper airway. Many questions remain about this disease, including the rates of involvement of different organ systems during long-term follow-up. This survey study looked for patterns of attacks specific for HAE caused by C1 inhibitor deficiency.

Two hundred twenty-one patients receiving outpatient treatment for angioedema completed standardized questionnaires regarding their episodes of edema. The patients, from 108 kindreds, all had inherited C1 inhibitor deficiency. Twelve had experienced no clinical symptoms--the remaining 209 patients provided data on a total of 131,110 episodes of edema. The patients were 127 women and 82 men; mean age at onset was 11.2 years.

Total follow-up was 5,736 years, of which only 370 years (6.5%) were symptom free. Ninety-seven percent of episodes were associated with swelling of the skin, including the extremities, face, genitals, and trunk; and with abdominal attacks. About one percent were associated with laryngeal edema. The remaining episodes involved a wide range of manifestations, including edema of the soft palate, swelling of the tongue, headache, and episodes involving the bladder, chest, muscles, joints, kidneys, and esophagus. Essentially all patients had skin swellings, most often involving the upper extremities. Facial swelling was relatively rare, but carried a high risk of upper airway obstruction. The clinical course tended to be more severe in women and in patients with an earlier disease onset.

The findings suggest a typical pattern of attacks associated with HAE caused by C1 deficiency. Symptoms most often begin in childhood, followed by recurrent attacks of extremity swellings mixed with facial and genital swellings and, less often, trunk and neck swellings. A wide range of other organs may be infrequently involved; symptom-free years appear relatively uncommon.

**COMMENT:** *These authors studied data from 221 patients with C1 inhibitor deficiency to learn as much as possible about their edema episodes. The study is partially retrospective, but the data assimilated are remarkable for the specific temporal and spatial pattern of episodes. The depth of organ involvement in addition to the skin, GI tract, and larynx was especially illuminating. I recommend this paper be readily available to every allergist who confronts HAE.*
*E. J. B.*

*Bork K, Meng G, Staubach P, Hardt J, et al: Hereditary angioedema: new findings concerning symptoms, affected organs, and course.*
**Am J Med**. 2006;119:267-274. ♦♦

## Autoimmunity in Children with Chronic Urticaria

CHILDREN with chronic urticaria (CU) pose a diagnostic challenge. One study reported a 30% rate of antibodies to the high-affinity IgE receptor (FcεRIα) in children with CU, a finding which may have implications for diagnosis, treatment, and prognosis. A series of children with CU was studied to determine the frequency of FcεRIα autoantibodies.

The study included 80 children evaluated for CU in a South African clinic. Thirty-eight children with atopic eczema dermatitis syndrome (AEDS) were studied for comparison. Each patient underwent a complete blood count and total IgE measurement; CAP-RASTs for egg, codfish, soy, milk, and peanut; and examination of a stool sample for parasites. The prevalence of autoantibodies to FcεRIα was assessed using a functional anti-FcεRIα assay.

Basophil and eosinophil counts were similar between the CU and AEDS groups. The CAP-RAST food panel screen was positive in 26% of patients with CU vs 82% with AEDS. Stool samples were positive for parasites in 2.5% and 0%, respectively. Forty-seven percent of the children with CU had anti-FcεRIα antibodies, compared to none in the AEDS group. The patients with FcεRIα autoantibodies had a mean histamine release of 28.3%; another 11 patients had borderline histamine release. Thirteen percent of the CU patients had non-IgG histamine-releasing factors.

As in adults, autoantibodies to FcεRIα are commonly detected in children with CU. These children have no evidence of food allergy or helmintic infection as the underlying cause of CU, nor any reduction in circulating basophils compared to children with AEDS. The clinical significance of FcεRIα autoantibodies in children with CU remains to be determined. ➤➤

**COMMENT:** *In my experience, severe, persistent urticaria is much less common in childhood, although we do see such patients. This paper suggests an autoimmune mechanism in children, similar to studies of corticosteroid-dependent or persistent urticaria in adults. A caveat to keep in mind is the low sensitivity and specificity of the autologous serum skin test. Additional studies are needed with identification of specific antibody to the alpha chain of the IgE receptor, as well as proof that the antibody is associated with the urticaria.*
*D. K. L.*
*Toit GD, Prescott R, Lawrence P, et al: Autoantibodies to the high-affinity IgE receptor in children with chronic urticaria.*
**Ann Allergy Asthma Immunol**. 2006;96:341-344. ♦♦

## Inhaled Corticosteroids: More Good Than Harm

FEARS of growth retardation or adrenal suppression may make physicians hesitant to prescribe inhaled corticosteroids for asthmatic children. A group of children receiving long-term ICS therapy for asthma were studied to assess the presence of and relationship between adrenal suppression and growth retardation.

The 72 children had been receiving low to moderate doses of inhaled budesonide for a median of 18 months. Thirty healthy controls were studied as well. Both groups underwent low-dose Synacthen testing; subjects with a peak serum cortisol level of less than 495 nmol/L were classified as having adrenal suppression. Growth assessment included the height standard deviation score as well as height standard deviation in the past year.

The criterion for adrenal suppression was met by 20.8% of children taking ICS; none had symptoms of adrenal suppression. Both height measures were similar for children with vs without adrenal suppression. The degree of adrenal suppression was unrelated to dose and duration of ICS treatment.

Some children taking low- to moderate-dose ICS therapy show mild, biochemical adrenal suppression. Growth deceleration is not a significant predictor of adrenal suppression. The results add to the evidence that children with asthma should receive ICS at the lowest effective doses for as long as necessary.

**COMMENT:** *This study evaluated 72 asthmatic children, median age 9.4 years, with a median dose of 363 μg of budesonide. Approximately 21% of the patients had evidence of mild adrenal suppression with a low-dose cosyntropin test. These subtle findings cannot be predicted by growth decelerations. It is important to understand that similar effects on growth and the HPA axis are not consistent.*
*B. E. C.*
*Priftis KN, Papdimitriou A, Gatsopoulou E, et al: The effect of inhaled budesonide on adrenal and growth suppression in asthmatic children.*
**Eur Respir J**. 2006;27:316-320. ♦♦

## Anaphylotoxins and Aspirin-Induced Asthma

STUDIES of the pathogenesis of aspirin-induced asthma (AIA) suggest that overproduction of cysteinyl leukotrienes, along with receptor overexpression, plays an important role. However, blockade of the cysteinyl leukotriene pathway does not completely protect against AIA. Using a proteomics approach, the investigators compared expression of various proteins in patients with AIA vs aspirin-tolerant asthma (ATA).

Aspirin challenge testing identified 30 patients with AIA and 24 with ATA; 21 normal controls were studied for comparison. In the AIA group, 8 proteins showed significant upregulation or downregulation after aspirin, including complement components. Enzyme-linked immunosorbent assay confirmed that patients with AIA had elevated plasma concentrations of C3a and C4a, compared to ATA patients. Median C3a level was 148.03 ng/mL in the AIA group, 99.32 ng/mL in the ATA group, and 98.08 ng/mL in normal controls. Plasma C4a concentrations were 814.6, 274.5, and 342.4 ng/mL, respectively.

Both groups of asthma patients had a drop in plasma C3 after aspirin challenge. However, AIA patients had a significant increase in plasma C3a. The $FEV_1$ response to aspirin challenge was significantly correlated with the patients' plasma C3a and C4a levels, as well as with the C3a/C3 and C4a/C4 ratios.

Aspirin-induced asthma is associated with alterations in plasma complement components. Patients with AIA have elevated plasma levels of C3a and C4a, compared to those with ATA, and these changes are correlated with pulmonary function. Complement may contribute to the pathogenesis of AIA; other proteins identified in the proteomic study--including apolipoprotein and albumin complexed with myristic acid--may participate as well.

**COMMENT:** *Aspirin-induced asthma effects between 5% and 10% of all adults with asthma. Inhibition of the 5-lipoxygenase pathway does not completely protect from AIA. Lee and colleagues, using a proteomics approach, found that plasma concentrations of activated complement components C3a and C4a were elevated in patients with AIA, but not ATA. These data suggest that complement activation may play a role in the pathogenesis of AIA and may be a potential therapeutic target.*
*B. E. C.*
*Lee S-H, Rhim TY, Choi Y-S, et al: Complement C3a and C4a increased in plasma of patients with aspirin-induced asthma.*
**Am J Respir Crit Care Med**. 2006;173:370-378. ♦♦

## Immunotherapy with Latex

IT has recently been suggested that allergen immunotherapy (IT) could have an undesired effect: new sensitization to proteins contained in the allergen extracts used for IT. This issue was addressed in a study of health care workers undergoing latex IT.

The study included 24 health care workers enrolled in the placebo-controlled trial of IT using natural rubber latex. Baseline and 6-month follow-up serum samples were studied by immunoblotting and specific IgE measurement to assess positive new IgE sensitizations to various recombinant latex allergens.

Three of sixteen patients undergoing active latex IT developed new sensitizations: one each to Hev b 5, Hev b 11, and Hev b 6.01. Immunoblotting showed increased IgE binding in a 22 kDa band, possibly reflecting Hev b 6.01. Independent of these immunologic changes, latex IT was clinically effective in reducing latex allergy.

Hev b 6.01 and Hev b 5 appear to be important allergens in latex-allergic health care workers. Latex IT can lead to new sensitization in patients undergoing latex IT, although the clinical relevance of this finding is questionable. At least in some latex-allergic health care workers, a panel of allergens may improve in vitro diagnosis.

**COMMENT:** *This unique study assessed whether IT can induce new IgE sensitizations to the allergens contained in the vaccine. Twenty-four subjects were evaluated in a controlled natural rubber latex IT study. Hev b 6.01 and Hev b5 were noted to be important sensitizing allergens in healthcare workers. As well, levels of specific IgE to Hev b 6.01 may predict the maximal tolerated dose of allergen during IT. Several cases of new sensitization were observed, but these were at very low levels and did not have an adverse impact on either efficacy of IT or its safety.*
*E. J. B.*

*Sastre J, Raulf-Heimsoth M, Rihs H-P, et al: IgE reactivity to latex allergens among sensitized healthcare workers before and after immunotherapy (IT) with latex.*
**Allergy**. 2006;61:206-210. ♦♦

## $NO_2$: Impact on Asthma

STUDIES of the respiratory effects of exposure to nitrogen dioxide have yielded inconclusive results. Data from a cohort study were used to evaluate the relationship between indoor $NO_2$ exposure and respiratory symptoms among asthmatic children.

The analysis included 728 children with active asthma, drawn from the Yale Childhood Asthma Study. Mothers were interviewed to assess the children's respiratory symptoms and medication use. Questions about housing characteristics included the use of natural gas appliances. Palmes tubes were used to measure household exposure to $NO_2$.

Homes with gas stoves had significantly higher $NO_2$ levels: median 25.9 ppb, compared to homes with electric ranges. Nitrogen dioxide levels were also higher in multifamily homes, compared with single-family homes, and higher for Hispanic families than for whites. On analysis controlling for a wide range of subject and home characteristics, the presence of a gas stove and higher levels of $NO_2$ were both associated with respiratory symptoms.

For children living in multifamily homes, gas stoves were associated with increased odds of wheezing, odds ratio (OR) 2.27; shortness of breath, OR 2.33; and chest tightness, OR 4.34. Higher levels of $NO_2$ were also related to respiratory symptoms. Each 20 ppb increment in $NO_2$ was associated with an increased likelihood of any wheezing or chest tightness, OR 1.52 and 1.61; and with increased days of wheezing or chest tightness, rate ratio 1.33 and 1.51, respectively.

Home exposure to increased levels of nitrogen dioxide is associated with increased respiratory symptoms in children with asthma. The $NO_2$ levels reported in this study, although below peak levels for outdoor exposure, are common in U.S. homes with gas stoves. The association between measured $NO_2$ and respiratory symptoms is significant only for children living in multifamily homes.

**COMMENT:** *Chronic exposure to indoor nitrogen dioxide is a major public health concern. This is a cohort of 728 children, all younger than 12, who had lived in the house for at least 2 months and had asthma symptoms or used asthma maintenance medications in the previous year. In homes with gas stoves, nitrogen dioxide was approximately three times higher. The presence of elevated nitrogen dioxide levels was associated with respiratory symptoms. It should be noted that these are levels well below the U.S. EPA outdoor standard of 53 ppb.*
*B. E. C.*

*Belanger K, Gent JF, Triche EW, et al: Association of indoor nitrogen dioxide exposure with respiratory symptoms in children with asthma.*
**Am J Respir Crit Care Med**. 2006;173:297-303. ♦♦

## Fungal Sinusitis Occurs in Children Too!

UP to 10% of adults undergoing surgery for chronic sinusitis have hypersensitivity to fungi in the paranasal sinuses--ie, allergic fungal sinusitis (AFS). Few studies have focused on AFS in children.

A 12-year review of patients undergoing functional endoscopic sinus surgery at two children's hospitals identified 20 patients meeting diagnostic criteria for AFS. There were 13 males and 7 females, median age 16 years. Presenting signs and symptoms included atopy and nasal symptoms in all cases, while 18 of 20 patients had nasal polyps. Other common features included recurrent headaches, asthma, proptosis, and ocular symptoms.

All patients had radiographic evidence of sinusitis, including high-attenuation opacification in at least two sinuses. Allergy tests were positive, most common- ➤➤

ly for *Curvularia* and *Alternaria*. Laboratory findings included elevated IgE levels in 8 of 9 patients and eosinophilia in 10 of 15. All patients underwent surgery after failure of intranasal and oral steroids. Pathologic findings included fungal growth in 17 specimens, allergic mucin in 11 specimens, hyphae or fungal debris in 9, and Charcot-Leyden crystals in 2. Eleven patients required repeat surgery; the 1-year relapse rate was 55%.

Allergic fungal sinusitis is a possibility in children and adolescents evaluated for sinus disease. Clinical features include recurrent sinusitis and nasal polyps, sometimes with accompanying proptosis and asthma. Surgery is an important part of treatment, but relapses are common.

**COMMENT:** *Allergic fungal sinusitis remains enigmatic for many physicians. In this retrospective study from a single center, affected children appear to present with similar features to adults. As the authors point out, it will be important to have prospective longitudinal data on children with documented AFS. While further study is required, these data remind us to be watchful for AFS in children and to include AFS--along with cystic fibrosis and primary immunodeficiency--in the differential diagnosis of patients with chronic paranasal sinus disease and polyposis.*
*A. M.*

*Campbell JM, Graham, M, Gray HC, et al: Allergic fungal sinusitis in children.*
**Ann Allergy Asthma Immunol**. 2006;96:286-290. ♦♦

## Beyond the Obvious in the Wheezy Child

THE young child with severe, recurrent wheezing poses a diagnostic and treatment challenge. When these patients do not respond to conventional asthma treatments, other possibilities must be considered. The authors review their experience with an aggressive approach to diagnosis in young children with severe, recurrent wheeze.

Over a 2-year period, 47 children aged 5 years or younger were evaluated for severe recurrent wheezing. The patients were 25 boys and 22 girls, median age 26 months; 87% had been hospitalized for acute wheezing at least once. Specific tests were ordered for each patient, including blood tests, a sweat test, chest CT scanning, esophageal pH monitoring, and bronchoscopy.

None of the children had abnormal results on nasal ciliary brushing or sweat tests. Just 2 patients had a total IgE value more than 2 standard deviations above normal for age; 39% had at least one positive radioallergosorbent test. High-resolution chest CT scans yielded abnormal results in 15 patients, including structural abnormalities in 2, small airways disease or air trapping in 6, bronchial wall thickening in 4, and bronchiectasis in 2. When esophageal pH monitoring was performed, the results were abnormal in 68% of cases. Bronchoscopy yielded abnormal findings in 37 patients, including structural abnormalities in 36%, increased mucus in 54%, and visible inflammation in 27%. Diagnoses included asthma in 41% of children, gastroesophageal reflux disease in 23%, and an infectious process in 13%. No definite diagnosis was made in 23%.

The authors propose an approach to diagnostic investigation in a highly selected group of infants and preschoolers with severe recurrent wheezing. Gastroesophageal reflux disease is a frequent finding, while bronchoscopy yields a high rate of abnormal results. Airway eosinophilia may be present, with or without reflux, but does not confirm the diagnosis of asthma.

**COMMENT:** *Forty-seven children, ranging from 5 to 58 months, underwent investigation for severe, recurrent wheezing. Thirty-nine percent were atopic, 66% had gastroesophageal reflux, and 79% had abnormal bronchoscopy. It is important to consider alternative diagnoses when working up a group of children less than 5 years of age who have persistent wheezing and do not respond promptly to standard controller medications.*
*B. E. C.*

*Saglani A, Nicholson AG, Scallan M, et al: Investigation of young children with severe recurrent wheeze: any clinical benefit?*
**Eur Respir J**. 2006;27:29-35. ♦♦

## Mites, Mold, and Asthma

ATOPY is a known risk factor for asthma in children, but its importance in adults is unknown. Previous studies have linked molds and dust mites to asthma risk in adults. Atopy and specific IgE antibodies to mites and molds were evaluated as risk factors for adult-onset asthma.

The population-based study included 485 Finnish adults with a new clinical diagnosis of asthma, along with 665 randomly selected controls. The diagnosis of asthma was based on lung function studies showing reversible airways obstruction. The presence of atopy was assessed from total IgE levels and Phadiatop score. Specific IgE antibodies to dust mites and common molds were measured as well.

As total IgE level and Phadiatop scores increased, asthma risk increased in dose-dependent fashion. Particularly strong associations were noted for specific IgE antibodies to two mites, *Dermatophagoides pteronyssinus* and the storage mite *Acarus siro*; and two molds, *Aspergillus fumigatus* and *Cladosporum herbarum*. The authors estimated that 30% of cases of adult-onset asthma in the population were attributable to sensitization to common aeroallergens.

The presence of atopy--reflected by total IgE level and specific IgE to common aeroallergens--is a strong risk factor for new-onset asthma in adults. Specific IgE to certain species of mites and molds is also associated with increased risk of adult-onset asthma. Interventions to reduce atopy might help to prevent a substantial proportion of adult-onset asthma cases. ➤➤

**COMMENT:** *Using population-based, incident case-controlled data, these Finnish researchers analyzed serum samples from adults with newly diagnosed asthma and found that specific IgE antibodies to dust mites and certain molds resulted in an increased risk of developing asthma. Interestingly, the risk of asthma increased as the total IgE and antigen-specific IgE increased. It is well-known that atopy in childhood predisposes the development of childhood asthma. These data suggest that atopy is also an important predisposing factor for new-onset adult asthma as well.*
*S. M. F.*
*Jaakkola M, Ieromnimon A, Jaakkola JJK: Are atopy and specific IgE to mites and molds important for adult asthma?*
**J Allergy Clin Immunol**. 2006;117:642-648. ♦♦

## More on Breast-Feeding

PREVIOUS studies have suggested that the benefits of breast-feeding are "dose-responsive." However, the risk of respiratory infections with 4 vs 6 months of breast-feeding remains unclear. A secondary analysis of National Health and Nutrition Examination Survey (NHANES) III data was performed to assess the impact of breast-feeding duration on the rate of respiratory infections.

The analysis included data on 2,277 children, aged 6 to 24 months. Parents provided data on respiratory tract infections: pneumonia, repeated episodes of colds/influenza or otitis media, and wheezing. Relationships with breast-feeding were adjusted for income, family size, day care, smoke exposure, and other factors.

For 223 infants breast-fed exclusively for 4 months but less than 6 months, risk of pneumonia was 6.5%, compared to 1.6% for 136 infants who were fully breast-fed for at least 6 months. Other outcomes were similar between groups, including three or more episodes of cold/influenza or otitis media, wheezing, and first episode of otitis media before age 12 months. On adjusted analysis, pneumonia risk was significantly increased for infants breast-fed for at least 4 but less than 6 months, odds ratio 4.27. Infants with the shorter duration of breast-feeding were also less likely to have recurrent otitis media, odds ratio 1.95.

Otitis media and wheezing were more frequent for children in day care but less frequent for African-American children. Children exposed to passive smoke had higher rates of recurrent upper respiratory infections, otitis media, and wheezing.

Exclusive breast-feeding for 6 months reduces the risk of some respiratory tract infections, compared to breast feeding for 4 but less than 6 months. The evidence is strongest for a protective effect against recurrent otitis media. The findings support the current American Academy of Pediatrics recommendation that infants should be breast-fed exclusively for the first 6 months of life.

**COMMENT:** *How long is long enough? Based on these NHANES data, there is a difference in risk of respiratory tract infection between breast-feeding 4 months' and 6 months' duration. This study, however, does not demonstrate continued greater protection against respiratory tract infections through 6 years of age. The study relies on patient recollection of the length of time of breast-feeding as well as the precise number of infections. As a mother with previous breast-feeding experience, I know I could recall the precise length of time, yet I do not know that I can recall the number of infections, especially in multiple children. Chart review may have been a more accurate way to collect data on number of respiratory tract infections. However, these data may give us an answer to mothers who ask, "How long is long enough?"*
*T. L. H.*
*Chantry CJ, Howard CR, Auinger P: Full breastfeeding duration and associated decrease in respiratory tract infection in US children.*
**Pediatrics**. 2006;117:425-432. ♦♦

## Do ICS Really Prevent Remodeling?

FOR patients with asthma, inhaled corticosteroids (ICS) reduce not only the clinical manifestations of disease, but also the chronic airway inflammation. A previous population-based study reported a faster decline in lung function among patients with asthma, but did not include information on asthma medications. Long-term follow-up data were analyzed to determine the rate of $FEV_1$ decline in asthma patients with and without ICS treatment.

The analysis included 234 asthma patients enrolled in the population-based Copenhagen City Heart Study. The annual decline in $FEV_1$ over 10 years' follow-up was compared for 44 patients who received ICS throughout this period vs 190 who did not.

Patients in the ICS group had reduced lung function, increased wheezing and other asthma characteristics, and a reduced prevalence of smoking, compared with the non-ICS group. The annual rate of decline in $FEV_1$ was 25 mL for patients who took ICS during follow-up vs 51 mL in those not taking ICS. Treatment with ICS was also associated with a smaller difference in the percent predicted $FEV_1$ and in $FEV_1$/FVC ratio. Although $FEV_1$ decline was more rapid among smokers, this effect was lessened by ICS treatment.

For asthma patients, treatment with ICS is associated with a slower rate of decline in $FEV_1$. The results support the suggestion that long-term ICS treatment can help to prevent or reverse airway modeling in patients with asthma.

**COMMENT:** *Inhaled corticosteroids are the mainstay of asthma treatment. They are recommended as essential therapy in asthma patients with more than occasional respiratory symptoms. These authors studied the observation that asthma patients have a more rapid decline of lung function over time, resulting* ➤➤

*in significant irreversible airways obstruction. They studied the $FEV_1$ decline over 10 years in patients with asthma using ICS over the entire observation period. Although the study has some limitations, the results showed that ICS significantly reduced the decline in ventilatory function.*
*E. J. B.*
*Lange P, Scharling H, Ulrik CS, Vestbo J: Inhaled corticosteroids (ICS) and decline of lung function in community residents with asthma.*
**Thorax**. 2006;61:100-104. ♦♦

## Severity and Control of Severe Asthma

USE of fluticasone propionate/salmeterol (FSC) in combination improves asthma disease control, compared with fluticasone propionate (FP) alone. Once disease control is achieved, guidelines call for attempts to reduce the medication dosage. However, few studies have evaluated strategies for dose reduction, particularly for patients receiving combination therapies. This randomized trial compared two approaches to "stepping down" treatment for asthma patients whose disease was well-controlled with FSC.

Six hundred forty-one patients with asthma received 12 weeks of open-label treatment with FSC, 250/50 µg twice daily. Four hundred thirty-five patients with good disease control during the last 4 weeks of this period were randomized to receive FSC in a stepped-down dose of 100/50 µg twice daily; or FP alone, 250 µg twice daily. Both treatments continued for 12 weeks; the main outcome measure was morning peak expiratory flow.

Adjusted mean change in morning peak expiratory flow was -0.3 L/min for patients assigned to FSC, compared with -13.2 L/min for those assigned to FP alone. The stepped-down dose of FSC also improved secondary outcomes such as asthma symptoms, rescue albuterol use, and asthma control. At the end of the 12-week step-down period, disease was well-controlled in 86% of the FSC group and 79% of the FP group. Disease was totally controlled in 56% and 48% of patients, respectively.

For patients whose asthma is well-controlled with FSC, stepping down to a lower FSC dose yields better clinical outcomes than switching to FP alone. Although most patients maintain good disease control with either approach, the proportion is higher for patients using the stepped-down dose of FSC. Questions remain about the optimal period of disease control before attempting step-down.

**COMMENT:** *These overseas researchers compared step-down asthma treatment in patients whose asthma symptoms had been controlled with FSC. Those patients reducing to a lower dose of FSC had better control than those who dropped the salmeterol and used the same dose of FP alone. Although there was a surprisingly high rate (10%) of randomized patients excluded from the analysis, the data are nevertheless compelling for the use of a long-acting bronchodilator in combination with even low-dose corticosteroid in patients with persistent asthma.*
*S. M. F.*
*Bateman E, Jacques L, Goldfrad C, et al: Asthma control can be maintained when fluticasone propionate/salmeterol (FSC) in a single inhaler is stepped down.*
**J Allergy Clin Immunol**. 2006;117:563-570. ♦♦

# CLINICAL TIDBITS

## Sublingual vs IM Epinephrine

A sublingual formulation of epinephrine might help to overcome problems with underuse of epinephrine autoinjectors for anaphylaxis. A new fast-disintegrating sublingual epinephrine tablet was evaluated in a validated rabbit model. Sublingual epinephrine, up to 40 mg, achieved epinephrine plasma concentrations comparable to those of a 0.3 mg intramuscular epinephrine injection. The bioavailability of sublingual epinephrine increased linearly along with dosage, suggesting that absorption followed first-order kinetics. With further research, sublingual epinephrine could be a useful alternative for emergency treatment of anaphylaxis.

**COMMENT:** *Although prompt epinephrine injection is the treatment of choice for anaphylaxis, many patients are still reluctant to use self-administered parenteral epinephrine. Using the highest concentration (40 mg) of a rapidly dissolving tablet of epinephrine given sublingually, there was a plasma concentration that was similar to IM epinephrine. Sublingual epinephrine would be a welcome option for patients, particularly children, with anaphylaxis. We hope that it will be just as effective in humans as it is in rabbits.*
*S. M. F.*
*Rawas-Qalaji M, Simons FE, Simons K: Sublingual epinephrine tablets versus intramuscular injection of epinephrine: dose equivalence for potential treatment of anaphylaxis.*
**J Allergy Clin Immunol**. 2006;117:398-403. ♦♦

## Influenza A Is Becoming Resistant

THE adamantane antiviral drugs play an important role in the response to community outbreaks of influenza A. The frequency of adamantane resistance was evaluated in influenza A virus isolates submitted from 26 states to the U.S. Centers for Disease Control and Prevention from October through December, 2005. Of 209 influenza A(H3N2) viruses screened, 92.3% had an M2 gene mutation associated with resistance to both amantadine and rimantadine. Resistant viruses were submitted from all 26 states. The results show an alarmingly high prevalence of adamantane-resistant influenza A viruses in the United States, underscoring the need for rapid surveillance for antiviral resistance. ➤➤

**COMMENT:** *Influenza A viruses are a major cause of morbidity and mortality, infecting 10% to 15% of the population annually. These authors investigated the frequency of adamantane-resistant influenza A viruses circulating in the United States in the initial months of the 2005-06 season. Over 90% of isolated viruses demonstrated adamantane resistance. This suggested that the latter drugs "should not be used for prophylaxis or treatment…until susceptibility to adamantanes has been reestablished among circulating isolates."*
*E. J. B.*
*Bright RA, Shay DK, Shu B, et al: Adamantane resistance among influenza A viruses isolated early during the 2005-2006 influenza season in the United States.*
**JAMA**. 2006;295:891-894. ♦♦

## To Humidify or Not in Croup?

ALTHOUGH humidification has long been used as a treatment for croup, scientific evidence for this practice is lacking. One hundred forty children seen in the emergency department for moderate to severe croup were randomly assigned to receive 100% or 40% humidity, with water particles of mass median diameter 6.21 µm, delivered by nebulizer; or standard "blow-by" humidity. At 30 and 60 minutes, there were minimal differences in the clinical Westley croup score between groups. Other outcomes were similar as well, including pulse and respiratory rates, oxygen saturation, and need for additional treatment or hospitalization. The use of nebulizer-delivered 100% humidity does not improve clinical outcomes in children with croup.

**COMMENT:** *Allergists/immunologists often care for or advise in the care of croup because of the associated wheezing. This study has flaws but provides solid information that humidification is of no value. Humidification treatment is often used for croup and asthma, and the utility is suspect in both.*
*D. K. L.*
*Scolnik D, Coates AL, Stephens D, et al: Controlled delivery of high vs low humidity vs mist therapy for croup in emergency departments: a randomized controlled trial.*
**JAMA**. 2006;295:1274-1280. ♦♦

## Is $FEV_1$ Reliable in EIA?

A 10% or greater drop in $FEV_1$ in response to eucapnic voluntary hyperventilation (EVH) or exercise challenge has been suggested as the "gold standard" for diagnosis of exercise-induced asthma (EIA). Some reports have suggested that mid-expiratory flow measurements might be more sensitive to small airway obstruction. One hundred sixteen elite athletes, 60 asthmatic, underwent exercise or EVH challenge with analysis of maximal voluntary flow-volume loops. The $FEV_1$ and $FEF_{50}$ responses were strongly correlated with each other. Sixty athletes met the $FEV_1$ criterion for EIA. On its own, the $FEF_{50}$ criterion of a 26% or greater drop would have led to a false-negative rate of 35%. Just 1 athlete met the $FEF_{50}$ criterion without meeting the $FEV_1$ criterion. Measuring mid-expiratory flow reduces sensitivity in the diagnosis of EIA in elite athletes.

**COMMENT:** *The clinical diagnosis of EIA is relatively inaccurate. Athletes who are clinically symptomatic after exercise and who exhibit performance decrement may have normal spirometric values. It has been suggested that $FEF_{25-75}$ and $FEF_{50}$ are more sensitive to airway obstruction in the small airways than $FEV_1$. These authors clearly demonstrate that including $FEF_{50}$ in the diagnosis of EIA reduces the sensitivity and does not enhance the sensitivity and specificity of the diagnosis.*
*E. J. B.*
*Dickinson JW, Whyte GP, McConnell AK, et al: Mid-expiratory flow versus $FEV_1$ measurements in the diagnosis of exercise induced asthma (EIA) in elite athletes.*
**Thorax**. 2006;61:111-114. ♦♦

## Grazax: Ready for Prime Time?

GRASS allergen tablets--*Phleum pretense*, 75,000 SQ-T (Grazax)--have been shown safe and effective as specific immunotherapy for rhinoconjunctivitis. One hundred fourteen grass-allergic patients with asthma and rhinoconjunctivitis were randomly assigned to immunotherapy using grass allergen tablets or placebo. During the subsequent pollen season, asthma medication and symptom scores were minimally different between groups. Rhinoconjunctivitis medication and symptom scores were reduced by approximately 40%. There were no serious adverse events. In this group of patients, grass allergen tablets are safe, improving rhinoconjunctivitis without worsening asthma control.

**COMMENT:** *Recent progress with sublingual immunotherapy has been the development of allergen tablets as an alternative to drops. These authors confirmed the safety of grass tablets 75,000 SQ-T (equivalent to 15 µg Ph1 p5) in that no serious adverse events were observed. Moreover, they confirmed a significant reduction in symptom score as well as in medication score, similar to what has been observed in prior studies with drops. The treatment did not impair asthma control. It remains to be seen whether future long term studies will bear this out. I personally foresee considerable hurdles to having such therapy approved by the FDA.*
*E. J. B.*
*Dahl R, Stender A, Rak S: Specific immunotherapy with SQ standardized grass allergen tablets in asthmatics with rhinoconjunctivitis.*
**Allergy**. 2006;61:185-190. ♦♦

## Exercise-Induced Rhinitis

EXERCISE is a well-recognized trigger for asthma and other allergic diseases, but its relationship to allergic and nonallergic rhinitis is unclear. A questionnaire regarding exercise-induced rhinitis (EIR) was administered to 164 patients receiving allergy immunotherapy and to a comparison group of health club members. Indoor EIR that adversely affected athletic performance was reported by 40% of subjects overall, including 53% of allergy patients and 28% of the comparison group. Rhinorrhea was the most common symptom. Outdoor EIR, reported by 56% of subjects, was also more frequent in the allergy group. Exercise-induced rhinitis is a problem for people with and without allergic disease. The effects of exercise should be specifically considered in the clinical evaluation of rhinitis.

**COMMENT:** *The physiology of exercise is multifaceted and profound in its effect on the entire respiratory tract. In this important survey, the authors highlight how commonly exercise affects the upper airway in allergic and nonallergic athletes. The authors emphasize the importance of further study, but encourage clinicians to include historical questions on the effect of exercise as a potential trigger for rhinitis. Further study will allow us to make appropriate therapeutic decisions that could potentially improve both upper and lower airway function.*
*A. M.*
*Silvers WS, Poole JA: Exercise-induced rhinitis: a common disorder that adversely affects allergic and nonallergic athletes.*
**Ann Allergy Asthma Immunol**. 2006;96:334-340. ♦♦

## REVIEWS OF NOTE

**COMMENT:** *Treatment of acute anaphylaxis is well-described, although studies still demonstrate the failure of emergency rooms to provide optimal treatment. The subject of this review, however, is the identification of causes of anaphylaxis and the long-term management of this scary population of patients. Risk reduction strategies and education are emphasized.*
*R. J. M.*
*Simons ER: Anaphylaxis, killer allergy: long-term management in the community.*
**J Allergy Clin Immunol**. 2006;117:367-377. ♦♦

**COMMENT:** *One of the more common reasons for referral to an allergist is the problem of reactions to antibiotics. This is a concise review, most appropriate for the primary care practitioner, that deals with such issues as skin testing and graded challenge, use of cephalosporins in patients allergic to penicillin, drug desensitization, and drug allergy in HIV, among other topics. I will send this with my consultation letter to the referring doc.*
*R. J. M.*
*Gruchalla RS, Pirmohamed M: Antibiotic allergy.*
**N Engl J Med**. 2006;354;6:601-609. ♦♦

**COMMENT:** *This is an excellent, well-illustrated review of the immune mechanisms involved during allergen-specific sublingual immunotherapy (SLIT) compared with subcutaneous immunotherapy. The authors also look to the future of second-generation vaccines based on recombinant allergens to improve results with SLIT.*
*E. J. B.*
*Moingeon P, Batard T, Fadel R, et al: Immune mechanisms of allergen-specific sublingual immunotherapy.*
**Allergy**. 2006;61:151-165. ♦♦

**COMMENT:** *With the recent increase in public anxiety for molds causing allergy symptomatology, this well-referenced position paper is a useful tool for the practicing allergist. It provides evidenced-based and logical criteria to help evaluate patients presenting with these concerns.*
*S. M. F.*
*Bush RK, Portnoy JM, Saxon A, et al: The medical effects of mold exposure.*
**J Allergy Clin Immunol**. 2006;117:326-333. ♦♦

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