AllergyWatch®

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

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Xolair Is *Not* Associated with Cancer Risk

ANTI-IgE therapy with omalizumab provides a new option for add-on therapy in patients with inadequately controlled, severe persistent allergic asthma. A 2003 analysis of clinical trial data suggested an increased number of malignancies among omalizumab-treated patients versus controls: 0.5% versus 0.2%. This association was re-evaluated in an updated pooled analysis.

The analysis included data from 67 phase I to IV clinical trials of omalizumab performed over two decades. Of 11,459 unique patients in 67 studies, 7,789 received omalizumab. The main outcome of interest was the rate of primary malignancies among patients in 32 randomized, double-blind, placebo-controlled trials: 7,432 patients, of whom 4,254 received omalizumab.

In this primary analysis, there were 14 malignancies in patients treated with omalizumab and 11 in those treated with placebo. Incidence rates were not significantly different between groups: 4.14 and 4.45 per 1,000 patient-years, respectively. Omalizumab was not associated with any specific histologic type of malignancy, and risk did not increase with duration of exposure.

The updated pooled analysis helps to alleviate previous concerns that omalizumab might be associated with increased cancer risk. "[A] causal relationship between omalizumab therapy and malignancy is unlikely," the investigators conclude.

COMMENT: *Recent pooled analysis of 67 phase I to IV clinical trials of omalizumab showed that the rate ratio of malignancy was below unity. This suggests a reassuring lack of association between a risk of malignancy and use of omalizumab in the 7,789 patients studied in the clinical trials. However, it is to be noted that malignancy was not a predefined adverse event of special interest in the studies reviewed, and small sample size precluded specific conclusions in pediatric, elderly, or nonwhite patients. Additional omalizumab long-term safety data from the 5-year EXCELS study are eagerly awaited.* ➤➤

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

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

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

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C.D.

Busse W, Buhl R, Fernandez Vidaurre C, et al: Omalizumab and the risk of malignancy: results from a pooled analysis.
J Allergy Clin Immunol. 2012;129:983-989. ♦♦

Lymph Node Injection for Immunotherapy: Initial Trial

THE long course of treatment required for conventional subcutaneous immunotherapy limits its uptake. The authors evaluated intralymphatic immunotherapy (ILIT)--injecting allergen directly into a lymph node, thus targeting the MHC class II pathway--as an alternate approach to immunotherapy for cat allergy.

The investigators developed a modular antigen transporter (MAT) vaccine by fusing recombinant major cat dander allergen Fel d 1 to a translocation sequence and to part of the human invariant chain. The MAT-Fel d 1 vaccine was evaluated in a randomized, double-blind, placebo-controlled trial in 20 patients with cat allergy. In the ILIT approach, injections were made into a superficial inguinal lymph node under ultrasound guidance.

There were no adverse events of the ILIT injections with MAT-Fel d 1. After three injections within 2 months, patients assigned to ILIT had a 74-fold increase in nasal Fel d 1 tolerance. In contrast, patients receiving placebo injections had less than a threefold increase in nasal tolerance. The ILIT injections were associated with stimulation of regulatory T-cell response as well as more than a fivefold increase in cat dander-specific IgG_4 levels. The latter response was significantly and positively correlated with interleukin-10 production.

Initial human trials support the safety and effectiveness of ILIT with MAT-Fel d 1 for the treatment of cat allergen. Substantial responses are noted after just three MAT-Fel d 1 injections, suggesting that the ILIT approach has the potential to shorten the number and duration of immunotherapy injections. Further studies in larger numbers of patients are needed.

COMMENT: *Allergen immunotherapy is the only truly disease-modifying treatment available for our patients with inhalant allergic respiratory illnesses. In an effort to improve safety and efficacy of immunotherapy, these researchers used a recombinant cat dander vaccine and injected it directly into the inguinal lymph node. After only 3 monthly injections, there were impressive clinical improvements based on nasal provocation, allergy skin tests, and quality of life, as well as humoral and cellular immunologic improvements. The authors suggest that this type of safe, efficacious immunotherapy using only a limited number of injections could be more acceptable for our patients than our current subcutaneous or even sublingual approaches. Stay tuned....*
S.M.F.

Senti G, Crameri R, Kuster D, et al: Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections.
J Allergy Clin Immunol. 2012;129:1290-1296. ♦♦

FOCUS ON OBESITY

This issue we focus on some new studies of associations between body weight and asthma.

To Sleep, Perchance to . . . Breathe

OBESITY is associated with an increased risk of developing childhood asthma, but its association with asthma severity is unclear. Clinical experience suggests a high rate of sleep-disordered breathing (SDB), and other comorbid conditions associated with obesity, among asthmatic ➤➤

children. Associations among obesity, SDB, and asthma severity were assessed in a referral population of children with asthma.

The study included 108 sequential children treated at a children's hospital asthma clinic. The children's mean age was 9 years; two-thirds were boys and 45% African-American. Disease severity was assessed after 1 year of follow-up and guideline-based therapy, using a composite measure of controller medication, symptom burden, and health care utilization. Associations of asthma severity with obesity and SDB were assessed by multivariate analysis.

Obesity was present in 42.6% of patients and SDB-defined as habitual loud snoring and intermittent nocturnal hypoxia, assessed on overnight finger pulse oximetry--in 29.6%. With adjustment for obesity, rate, and sex, the presence of SDB was significantly associated with severe asthma at 1 year of follow-up: odds ratio 3.62. Obesity was not associated with asthma, but the association between SDB and severe asthma was stronger at increasing body mass index.

Even after 1 year of treatment in a specialty asthma clinic, SDB is associated with increased severity of childhood asthma. The prevalence of SDB is high among obese children in this population, and possibly among African American children as well. Further research is needed to determine whether treatment for SDB improves asthma morbidity.

COMMENT: *The question remains: Is SDB a cause or an effect of severe asthma? Whether improving the underlying sleep disorder improves asthma severity or control is still unknown. This study is an extension of previously published data regarding the relationship between pediatric asthma severity and obesity (no relationship in those data). Perhaps SDB is the missing puzzle piece . . . .*
K.R.M

Ross KR, Storfer-Isser A, Hart MA, et al: Sleep-disordered breathing is associated with asthma severity in children.
Pediatrics. 2012;160:736-742. ♦♦

Obesity-Related Childhood Asthma--A Separate Disease?

IT has been suggested that differences in immune pathogenesis may make obesity-associated asthma a distinct clinical entity. Contributing factors might include obesity-mediated inflammation and mechanical fat load. This study examined Th1/Th2 responses in pediatric obesity-associated asthma, including associations with anthropometric measures and pulmonary function test results.

The study included four groups of 30 children: obese and nonobese children, with and without asthma. All underwent pulmonary function testing and serum cytokine measurement. Assessment of systemic Th-cell phenotype included T-cell responses to mitogen, phorobol 12-myristate 13-acetate (PMA), and tetanus toxoid and dust mite antigens.

Compared to nonobese children with asthma, those in the obese asthmatic group had increased Th1 responses to PMA and tetanus toxoid and reduced Th2 responses to PMA and dust mite. The responses did not differ between obese and nonobese children without asthma. Obese children with asthma had reduced FEV_1/FVC and residual volume/total lung capacity ratios. These pulmonary function test results were significantly and negative correlated with serum interferon-inducible protein 10 and interferon-γ levels. Pulmonary function levels were unrelated to anthropometric measures.

The results show evidence of Th1 polarization in children with obesity-associated asthma, compared to asthma in nonobese children. The study also finds an inverse correlation between obesity-mediated inflammation and pulmonary function. The results add to the evidence that pediatric obesity-associated asthma is a distinct entity that may require different treatment strategies.

COMMENT: *This study highlights the obvious impairment and risk of asthma in obese children. There was lack of typical Th2 responses in this cohort. But evidence of Th1 activation was the same in obese asthmatics or obese nonasthmatics, which implies a different phenotype. Missing from this study was objective lung function and/or demonstration of airway hyperreactivity.*
S.F.W.

Rastogi D, Canfield SM, Andrade A, et al: Obesity-associated asthma in children: a distinct entity.
Chest. 2012;141:895-905. ♦♦

Does BMI Affect Response to ICS in Asthma?

STUDIES have examined varying aspects of the association between asthma and obesity, but none have looked at the clinical effect of obesity on responses to inhaled corticosteroid (ICS). Budesonide dose-response effects were compared in overweight versus normal-weight patients with persistent asthma.

The post hoc analysis of randomized trial data included 72 patients with mild to moderate persistent asthma. Participants were classified as overweight or normal-weight, based on a body mass index cutoff of 25. In the trial, after an ICS washout period, patients received 4 weeks of treatment with inhaled (hydrofluoroalkane) budesonide, 200 µg/d, then 800 µg/d. The analysis compared indicators of response for overweight and normal-weight patients.

As budesonide dose increased from 0 to 200 to 800 µg/d, normal-weight asthma patients had greater improvements in exhaled nitric oxide and asthma symptoms, compared to overweight patients. For both indicators, most of the improvement occurred between the 0 and 200 µg/d doses. The overweight and normal-weight groups had similar responses in FEV_1 and methacholine PC_{20}.

Some responses to budesonide, particularly ➤➤

exhaled NO and asthma symptoms, are reduced for overweight patients with asthma. The findings included a trend toward attenuated cortisol suppression in overweight patients, suggesting that differences in ICS responsiveness may be linked to reduced peripheral lung deposition or absorption.

COMMENT: *Obesity is known to be associated with increased inflammation and diminished pulmonary mechanics, including forced residual capacity, leading to enhanced small airway resistance. These authors, using a dose-response to budesonide, demonstrate for the first time that overweight individuals with persistent asthma may have decreased symptom and exhaled NO responses to ICS, particularly at lower doses. There is no difference in methacholine or FEV_1 responses. Since the overweight group had decreased cortisol suppression, these findings suggest decreased bioavailability of inhaled steroids in overweight patients, with decreased peripheral lung deposition or absorption. Interestingly, the response to leukotriene modifiers is enhanced in obesity, as the result of upregulation of the receptor by the adipocyte hormone leptin.*
C.C.R.
Anderson WJ, Lipworth BJ: Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma?
Ann Allergy Asthma Immunol. 2012;108:237-242. ♦♦

Earlier Oral Corticosteroids in Acute Asthma--How Much of a Difference?

FOR children seen in the emergency department (ED) for moderate to severe acute asthma exacerbations, early administration of oral corticosteroids (OCS) can reduce the need for hospitalization. However, delayed initiation of treatment is common. This study evaluated the impact of ED nurse initiation of OCS for children with acute asthma.

The time-series controlled trial included 664 children seen in a children's hospital ED for acute asthma exacerbations: Pediatric Respiratory Assessment Measure score 4 or higher. At all times, triage nurses initiated bronchodilator therapy before the child was seen by the doctor. During one 4-month period, OCS was initiated by the physician, consistent with the existing standard of care. Over a subsequent 4-month period, trained ED nurses initiated OCS treatment before physician assessment. Time to clinical improvement was compared between the two periods, along with other outcomes.

Time to clinical improvement was a median of 24 minutes shorter for children treated during the nurse-initiated phase. Children receiving OCS at triage were also less likely to be admitted: odds ratio 0.56. Nurse-initiated OCS was associated with a median 44-minute reduction in time to steroid treatment, a 51-minute difference in time to mild-asthma status, and a 44-minute difference in time to ED discharge. The rate of repeat ED visits or subsequent hospitalization was not significantly different between groups.

Allowing ED nurses to initiate OCS leads to improved quality and efficiency of care for moderate to severe asthma exacerbations in children. Nurse-initiated treatment is associated with faster clinical improvement, reduced length of ED stay, and a reduced hospitalization rate. The authors believe this multidisciplinary team approach has the potential to reduce the burden of asthma in ED settings.

COMMENT: *Despite a lengthy time to peak effectiveness, studies have indicated that earlier administration of OCS reduces hospital admissions. How can this be best achieved? Allowing triage nurses to make the decision to administer OCS may be one answer. Prescribing our vulnerable patients an emergency OCS course to have on hand would be another.*
K.R.M.
Zemek R, Plint A, Osmond MH, et al: Triage nurse initiation of corticosteroids in pediatric asthma is associated with improved emergency department efficiency.
Pediatrics. 2012;129:671-680. ♦♦

No Th2 Cytokines in Pediatric Severe Asthma with Eosinophilia

DIAGNOSTIC evaluation of children with "difficult asthma" identifies a group with genuine severe therapy-resistant asthma (STRA). The basic mechanism and airway pathology in these cases are not well understood. The pathologic findings and mediators of inflammation and remodeling were evaluated in children with true STRA.

Of a series of 104 children referred for evaluation of problematic severe asthma, 53 were found to have true STRA. Evaluations included fiberoptic bronchoscopy, bronchoalveolar lavage (BAL), and endobronchial biopsy, with quantification of airway inflammation, airway remodeling, and Th2 cytokines in BAL fluid and biopsy specimens. Sixteen nonasthmatic patients were studied as controls.

Eosinophil counts in BAL fluid and biopsy tissues were elevated in the STRA group, although with significant interindividual variation. There were no differences in submucosal mast cells, neutrophils, or lymphocytes. The patients with STRA also had increased reticular basement membrane thickness and airway smooth muscle.

Bronchoalveolar lavage specimens from STRA patients did not show increased levels of interleukin (IL)-4, IL-5, or IL-13, which were rarely found in induced sputum specimens. There was also no increase in IL-5- and IL-13-positive cell counts in biopsy specimens. Fifteen of the children with STRA had detectable levels of Th2 cytokines in BAL fluid; this finding was associated with significantly reduced lung function.

This study demonstrates airway remodeling and variable airway eosinophilia in a group of children with genuine STRA. In contrast to adults, these pediatric STRA cases are not associated with neutrophilia and lack the classical Th2 cytokines thought to drive allergic asthma. The results suggest that treatments such as ➤➤

IL-5 antibody will be ineffective in many children with STRA.

COMMENT: *Fifty-three children with STRA were evaluated for airway inflammation, remodeling, and presence of Th2 cytokines. Both invasive and noninvasive methods were used to study the subjects and the 16 controls. Although children with STRA had evidence of airway remodeling and variable eosinophilia, there was, surprisingly, no neutrophilia. Even more startling was the absence/paucity of Th2 signature cytokines (IL4, IL5, IL13) that are typically associated with allergic inflammation. These cross-sectional findings may need further study.*
C.D.
Bosley CJ, Fleming L, Gupta A, et al: Pediatric severe asthma is characterized by eosinophilia and remodeling without T_H2 cytokines.
J Allergy Clin Immunol. 2012;129: 974-982. ♦♦

When Should Children Take Responsibility for Using Epi-Pens?

RECOGNIZING the symptoms of anaphylaxis and using self-administered epinephrine is a key part of management of severe allergies in children. There is little guidance on the age at which it is appropriate to transfer responsibility for self-injectable epinephrine from parents/caregivers to the patients themselves. This question was addressed in a survey of pediatric allergists.

Members of the Section on Allergy and Immunology of the American Academy of Pediatrics were asked when they typically transferred responsibilities for recognizing anaphylaxis and using self-injectable epinephrine from parents to their child and adolescent patients. Few of the 88 respondents started making this transition before the child was 9 to 11 years old.

In contrast, by age 12 to 14, around 90% of pediatric allergists expected their patients to describe anaphylaxis symptoms, demonstrate auto-injector use, carry and recognize the need for epinephrine, and learn to self-inject. Seventy-nine percent of respondents expected a 12- to 14-year-old patient to be able to self-inject epinephrine. Factors rated "very important" in beginning to transfer responsibility included medical history, developmental level, and ability to demonstrate auto-injector technique.

Pediatric allergists generally transfer responsibilities related to auto-injector use when the patient is 12 to 14 years old. The survey responses emphasize the importance of assessing readiness in the individual patient.

COMMENT: *When should we transfer responsibility from adults to children for awareness and knowledge of anaphylaxis and the use of self-injectable epinephrine for management? This survey of pediatric allergists suggests 12 to 14 years is the age most commonly used. Although there are no age-specific guidelines in the literature, more than half of unintentional injuries sustained with self-injectable epinephrine occur in individuals less than 17 years of age. At age 12 to 14, the child should begin to participate in the recognition and management of anaphylaxis. Timing for transfer should be individualized based on developmental maturity, family readiness, medical history, and, most important, demonstrated ability to self-administer epinephrine.*
C.C.R.
Simons E, Sicherer SH, Simons FER: Timing the transfer of responsibilities for anaphylaxis recognition and use of an epinephrine auto-injector from adults to children and teenagers: pediatric allergists' perspective.
Ann Allergy Asthma Immunol. 2012;108;321-325. ♦♦

Do Patients Trust They're Not Penicillin-Allergic When We Tell Them So?

SKIN testing for penicillin allergy is a useful and safe procedure. However, some studies suggest that patients, parents, and/or physicians may be reluctant to use penicillin-class antibiotics (PCAs) even after a negative skin test. This study evaluated subsequent PCA use in children who tested negative for penicillin allergy.

The study included 200 children who were evaluated for a history of penicillin allergy at a Canadian clinic and had negative results on skin testing and drug challenge. Parents were surveyed regarding their perceptions of the initial reaction, the child's subsequent antibiotic use, and any further antibiotic-related adverse reactions. Responses were received from 175 parents.

Seventy-six percent of the children had received antibiotics since their negative allergy evaluation. Of these, 45% had received PCAs. Eighteen percent of parents reported refusing a prescription for PCAs because they feared another reaction. Such refusals were more likely for parents who said they were "very frightened" by the initial reaction.

A significant minority of parents will decline PCA treatment even though their child has had negative results on penicillin skin testing and drug challenge. Parents who were very frightened by the initial reaction could be targeted for additional reassurance. Education for primary care physicians who are reluctant to prescribe PCAs could be helpful as well.

COMMENT: *This survey reminds us that fear is inherent after any allergic reaction. Despite both negative penicillin skin testing and oral challenge, almost a quarter of these pediatric patients were not treated with penicillin, due to either parental or physician preference. Reassuring was that nearly half of those with a negative skin test and drug challenge did tolerate penicillin without a reaction. I believe this gives the allergist the opportunity to further educate both the lay public and health care workers about the utility of the procedures we, as allergists, offer.*
V.H.-T.
Picard M, Paradis L, Nguyen M, et al: Outpatient penicillin use after negative skin testing and drug challenge in a pediatric population.
Allergy Asthma Proc. 2012;33:160-164. ♦♦

eNO: To Measure or Not to Measure?

EXHALED nitric oxide (eNO) is elevated in patients with rhinitis as well as those with asthma. The authors have postulated that elevated eNO in a patient without asthma symptoms could be a marker of "early asthma." This study evaluated elevated eNO levels as a predictor of subsequent rhinitis symptoms in adolescents.

A random sample of 959 adolescents, aged 13 to 14, filled out a questionnaire evaluating respiratory symptoms at baseline and 4 years' follow-up. After exclusion of participants with pre-existing asthma diagnosis or symptoms, the analysis included 657 teens. Baseline eNO levels were evaluated for association with new onset or persistent rhinitis symptoms at follow-up.

Both rhinitis outcomes were more frequent in teens with higher baseline eNO levels. For those with eNO above the 90th percentile for teens without baseline rhinitis, the odds ratio or for new-onset rhinitis at follow-up was 2.23. The association remained significant after excluding participants with allergic symptoms: OR 2.49. For the same level of baseline eNO, the risk of persistent rhinitis at follow-up was elevated fivefold: OR 5.11.

This population-based study finds that elevated eNO levels in early adolescence predict an increased risk of rhinitis at 4 years' follow-up. Exhaled NO appears to precede airway symptoms even in participants without previous allergic symptoms or a relevant family history. Follow-up, including testing for allergic sensitization, may be appropriate for adolescents with elevated eNO.

FOR patients with asthma, anti-inflammatory therapy reduces exhaled nitric oxide (eNO) in dose-dependent fashion. However, this effect varies with patient characteristics, leading to significant interindividual variations among clinically stable patients. This study examined the effects of demographic characteristics on persistent eNO variations among asthma patients treated with inhaled corticosteroids (ICS).

The prospective study included 250 patients with clinically stable asthma. After initial screening, cutoff points for poorly controlled asthma were determined based on an asthma control test score less than 20, FEV_1 less than 80% of predicted, or peak expiratory flow variability less than 80%. After 12 weeks, 229 patients with high or low eNO on treatment were identified, and independent predictors of high eNO were assessed.

An eNO level greater than 39.5 ppb was 67% sensitive and 76% specific in identifying patients with poor asthma control. Several factors were independently associated with persistently elevated eNO of 40 ppb or greater: past smoking, odds ratio (OR) 4.14; the number of eosinophils in the blood, OR 1.78; and chronic rhinosinusitis, OR 11.71. More than 90% of patients with persistently high eNO had at least one of these characteristics. The eNO response was unaffected by ICS dose or other medications.

In ICS-treated patients with asthma, persistent eNO elevation is associated with past smoking history, hypereosinophilia in blood, and chronic rhinosinusitis. Identification of these factors in patients with high eNO might be helpful in making treatment adjustments.

COMMENT: *Whether or not to measure eNO in clinic has become an interesting dilemma among asthma specialists. One reason some are reluctant is that sometimes asymptomatic patients have elevated eNO levels. The Malinovschi study reminds us that an elevated eNO in an asymptomatic patient is not simply a false positive, but actually predicts future development of airway symptoms.*

Another area of confusion with eNO measurements is that patients with well-controlled asthma often have persistently elevated eNO. The Matsunaga study points out important factors that may cause persistent inflammation in the airways despite clinically controlled asthma. These findings do not settle the debate about whether or when to measure eNO, but will help to advance the discussion.

S.A.T.

Malinovschi A. Alving K, Kalm-Stephens P, et al: Increased exhaled nitric oxide predicts new-onset rhinitis and persistent rhinitis in adolescents without allergy symptoms. **Clin Exp Allergy**. 2012;42:433-440.

Matsunaga K, Yanagisawa S, Hirano T, et al: Associated demographics of persistent exhaled nitric oxide elevation in treated asthmatics. **Clin Exp Allergy**. 2012;42:775-781. ♦♦

Few Children Have Complete Asthma Control

CURRENT guidelines for asthma treatment focus on achieving complete asthma control, thus improving quality of life and reducing use of health care resources. Control of childhood asthma often fails to meet this standard, perhaps related to overestimation of control by parents and doctors and low expectations of achievable control. This survey study evaluated asthma control in a large, international population of children with asthma.

The study included 983 asthmatic children, aged 4 to 15, in four European countries, Canada, and South Africa. The parents of 1,284 children with asthma, aged 4 to 15, were surveyed as well. In addition to interviews, assessments included the childhood asthma control test (C-ACT). Parent reports indicated that 11% of the children had at least one mild asthma attack per week, while 35% had at least one severe attack requiring oral corticosteroids or hospitalization per year.

Nearly three-fourths (73%) of parents said their child had mild or intermittent asthma. Yet 40% of the children had C-ACT scores of 19 or less, reflecting inadequate asthma control. Only about 9% met the Scottish Intercollegiate Guidelines Network/British Thoracic Society definition of control. More children had well-controlled asthma based on C-ACT scores than had guideline-defined asthma control. Activity restrictions were reported for 39% of children and family lifestyle changes for 70%.

In this worldwide sample of asthmatic children, only a minority have complete asthma control. Asthma control based on C-ACT scores and family reports does not meet the stringent guideline-based definitions. Parents tend to underestimate their child's asthma severity, ➤➤

which could be an important barrier to adequate treatment.

COMMENT: *This large observational study, done outside the United States, reinforces our understanding that childhood asthma is poorly controlled, with only 15% of patients achieving complete control. Asthma control is underestimated by casual observation. Although the C-ACT gives insight into the impairment domain, it does not evaluate the risk domain. More complete questioning is necessary, reflective of both the GINA and EPR-3 combined guidelines. These data support the findings of the TENOR and TRACK studies.*
B.E.C.
Carroll WD, Wildhaber J, and Bran PLP: Parent misperception of control in childhood/adolescent asthma: The Room to Breathe survey.
Eur Respir J. 2012;39:90-96. ♦♦

Longer Durations of Exclusive Breastfeeding Reduce Asthma Risk

BREASTFEEDING in infancy has been linked to a reduced incidence of childhood asthma. The effects of family history of atopy and the underlying mechanisms are unclear. These issues were addressed in a study of the duration and exclusiveness of breastfeeding on asthma risk in children.

The analysis included 5,369 children from a larger prospective cohort study. Breastfeeding duration and exclusiveness were evaluated for association with asthma-related symptoms through age 4.

Children who were never breast-fed had higher rates of asthma-related symptoms, compared to those with at least 6 months of breastfeeding. Odds ratios were 1.44 for wheezing, 1.26 for shortness of breath, 1.25 for dry cough, and 1.57 for persistent phlegm. Exclusive breastfeeding for 4 months showed similar protective effects. The strongest protective effects were noted for wheezing at the ages of 1 and 2 years. In adjusted analyses, the associations were partially explained by a reduction in respiratory tract infections, but not eczema.

Longer durations of breastfeeding and exclusive breastfeeding significantly reduce the rate of asthma-related symptoms through the preschool years, the new study suggests. The findings are consistent with an infectious, rather than atopic, mechanism.

COMMENT: *This study of over 1,000 children shows that exclusive breastfeeding for a mean of 4 months led to a lower incidence of wheezing during the first 4 years of life. The most significant effect occurred in the first 2 years of life. This was independent of family history of asthma or atopic disease, suggesting that an effect modification on viral-induced illness may have occurred.*
B.E.C.
Sonnenschein-van der Voort AM, Jaddoe VW, van der Valk RJ, et al: Duration and exclusiveness of breastfeeding and childhood asthma-related symptoms.
Eur Respir J. 2012:39;81-89. ♦♦

Updated Guidelines for Work-Related Asthma

WORK-related asthma is a common problem encompassing occupational as well as work-related asthma. Misdiagnosis is common, and legal definitions and regulations differ between countries. Based on a literature review of key issues, the authors developed updated guidelines for the management of work-related asthma.

The systematic review targeted five key concerns in work-related asthma: diagnostics, risk factors, management options and outcomes, medical screening and surveillance, and primary prevention through controlling exposure. A total of 1,329 papers underwent expert review for creation of evidence-based statements, from which recommendations were created in each area.

The recommendation for diagnosis focused on confirmation by objective physiologic tests, including immunologic tests for allergic cases. All patients with new or recurrent asthma, chronic obstructive pulmonary disease, or rhinitis symptoms should be asked about occupational factors, including whether their symptoms improve away from work. The recommendation for risk factors emphasized early recognition and diagnosis for better patient outcomes.

The recommendation on management options emphasized awareness that persistent exposure to the causal agent is likely to result in worsening disease. Complete avoidance is associated with the greatest probability of improvement; reduced exposure may be considered as an alternative, but cannot be recommended as a first-approach. Questionnaire screening for risk of work-related asthma was strongly recommended, with focused screening for at-risk subjects with likely exposure to high-molecular-weight agents. Exposure elimination was recommended as the strongest preventive approach.

Updated guidelines for work-related asthma are presented, including grading of the level of evidence in each area. The authors discuss priorities for further research.

COMMENT: *This is an important task force report regarding the guidelines for the management of work-related asthma, which is an ever-increasing problem affecting 15% to 20% of adults with chronic respiratory illness.*
B.E.C.
Baur X, Sisgaard T, Aasen TB, et al: Guidelines for the management of work-related asthma.
Eur Respir J. 2012;39:529-535. ♦♦

Bronchial Thermoplasty: A New Option for Severe Asthma

BRONCHIAL thermoplasty (BT) was recently approved for the treatment of severe asthma. The procedure consists of a series of bronchoscopies in which controlled thermal energy is delivered to the airway walls, thus reducing smooth muscle mass. Important clinical issues in BT are addressed in a ➤➤

concise review.

There is ongoing debate as to the role of the airway smooth muscle and the mechanism of action of BT. Randomized trials have shown significant improvement in quality of life after BT in patients with severe asthma, as well as reduced severe exacerbations, emergency department visits, and missed school/work days. No significant effect on airway hyperresponsiveness or FEV_1 has been demonstrated.

Because previous trials of BT have excluded patients with more than three asthma exacerbations per year, its generalizability to the larger population of patients with severe asthma remains to be demonstrated. Airway inflammation is the major short-term adverse event, with some more severe events requiring hospitalization. So far, there are limited data on long-term safety outcomes. However, trials have demonstrated good clinical and functional stability at 5 years' follow-up. The procedure has yet to be accepted by most insurance plans, which has limited its wider clinical adoption.

Evidence supports the clinical benefit of BT for patients with severe asthma that does not improve on maximal medical therapy. The authors emphasize the importance of proper patient selection and optimal pre- and post-procedural care. Key issues for further research include the durability of response to BT, long-term adverse events, and the mechanism of effect.

COMMENT: *Bronchial thermoplasty is a new technique allowing for adjunctive treatment for patients with very severe asthma who are refractory to currently available pharmacologic and immunologic interventions.*
B.E.C.
Wahidi MM, Kraft M: Bronchial thermoplasty for severe asthma.
Am J Respir Crit Care Med. 2012;185:709-714. ♦♦

Low Rate of Objective Testing for Asthma Diagnosis

CURRENT guidelines for asthma diagnosis specify the need for objective test results showing variable airflow obstruction or airway hyperresponsiveness. However, previous studies suggest low use of these confirmatory tests. Rates of objective pulmonary function testing at the time of asthma diagnosis were assessed in a population-based study.

Ontario health data were used to identify 465,866 patients, aged 7 years or older, who received a new physician diagnosis of asthma between 1996 and 2007. Rates of pulmonary function testing between 1 year before and 2.5 years after diagnosis were assessed, along with associated demographic and clinical factors.

Overall, just 42.5% of patients underwent pulmonary function testing during this period. Of those tested, more than 80% underwent spirometry alone. On multivariate analysis, objective testing was more likely for young adult patients, males, patients in higher socioeconomic groups, those in rural areas, and those diagnosed in spring or summer.

Even in Ontario, with universal access to health care, most diagnoses of asthma are made without confirmatory objective tests. Specialist care, patient age, and socioeconomic status appear to have the strongest effect on whether tests are performed. "Clinicians should be encouraged to routinely use pulmonary function testing for the diagnosis of asthma to facilitate more accurate diagnosis and improve management," the investigators conclude.

COMMENT: *It is disturbing to see the results of this article. Guidelines for the last 20 years have placed measurement of objective lung function as integral to the diagnosis of asthma! Specialists were about 2.5 times more likely to obtain lung function measurements. Perhaps primary care resistance to obtaining this critical measure will be affected by Accountable Care Organizations.*
S.F.W.
Gershon AS, Victor JC, Guan J, et al: Pulmonary function testing in the diagnosis of asthma: a population study.
Chest. 2012:141;1190-1196. ♦♦

A New 'Drug of Choice' for Allergic Rhinitis

MORE effective treatments for allergic rhinitis (AR) are needed, and must be compared with current guideline-based therapies. Intranasal corticosteroids are the most effective treatment, but require some time to take effect; intranasal H_1-antihistamines have a rapid onset of action. A new combination of fluticasone propionate with the H_1-antihistamine azelastine (MP29-02) was evaluated in patients with AR.

The authors report on 3 multicenter controlled trials including a total of 3,389 patients, aged 12 years or older, with moderate to severe AR. The MP29-02 combination was compared with intranasal azelastine, fluticasone, or placebo. MP29-02 consisted of azelastine 137 μg and fluticaseone 50 μg. The trials lasted for 14 days and were conducted during different allergy seasons. The main efficacy outcome was the sum of morning and evening change from baseline in the 0-to-24 reflective total nasal symptom score.

The MP29-02 combination was associated with a mean 5.7-point reduction in nasal symptom score, compared to 5.1 points with fluticasone alone, 4.4 points with azelastine alone, and 3.0 points with placebo. The benefits of MP29-02 were apparent on the first day of treatment, and included improvement in each nasal symptom evaluated--including the most severe cases of AR. The combination yielded greater efficacy and earlier response than either drug alone.

For patients with moderate to severe AR, a combination of azelastine and fluticasone is more efficacious than either first-line therapy on its own. One out of eight patients treated with MP29-02 showed complete or near-complete resolution of AR symptoms. Based on their results, the authors conclude, "MP29-02 can be considered the drug of choice for AR therapy."

COMMENT: *Intranasal corticosteroids have been* ➤➤

considered the "gold standard" for the treatment of moderate-to-severe AR. These authors report that a unique intranasal combination of azelastine with fluticasone (MP29-02) had more rapid onset of action and superior efficacy, including more complete symptom resolution, compared to either component alone. Interestingly, there were also fewer complaints of dysgeusia with MP29-02 compared to azelastine alone. Could this new combination nasal spray become the new "gold standard" for our AR patients?
S.M.F.
Carr W, Bernstein J, Lieberman P, et al: A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis.
J Allergy Clin Immunol 2012;129:1282-1289. ♦♦

Specific IgE to Ara h 2 Improves Accuracy in Diagnosis Peanut Allergy

THE diagnosis of peanut allergy can be challenging. Measurement of peanut-specific IgE can confirm sensitization, but does not always predict the response to oral food challenge (OFC). Previous reports have suggested that specific IgE to the dominant peanut allergen Ara h 2, found in 90% to 100% of patients with peanut allergy, could improve diagnosis.

This hypothesis was tested using data on infants from an Australian population-based study of pediatric food allergy. All underwent skin prick testing to assess peanut sensitization, followed by OFC to confirm peanut allergy. For the current study, fluorescence enzyme immunoassay was performed to measure specific IgE to whole peanut and to Ara h 2 in a stratified random sample of 200 infants: 100 with and 100 without OFC-confirmed peanut allergy.

Based on a whole peanut sIgE level of 15 kU_A/L--previously reported to have a positive predictive value of 95%--specificity in the study cohort was 98%. At an equivalent 98% specificity level, Ara h 2 sIgE identified 60% of children with true peanut allergy, compared to only 26% for whole peanut specific IgE. With a combination approach of specific IgE to whole peanut and Ara h 2, the number of OFCs required for diagnosis would be decreased by nearly two-thirds.

Measuring specific IgE to Ara h 2 increases accuracy in diagnosis of peanut allergy, compared to whole peanut specific IgE measurement. By increasing the ability to distinguish between children who can and cannot tolerate peanut, this test may reduce the number of patients requiring confirmatory OFC.

COMMENT: *Recently there have been reports that food allergic patients can be more accurately identified with component antigen testing. Data from children in the HealthNuts study in Australia showed that specific Ara h 2 plasma sIgE provided greater diagnostic accuracy of 60%, compared to 26% for whole peanut sIgE levels. This test is not infallible, since it did not identify 4 children with peanut allergy who had anaphylaxis with oral challenge. Current guidelines suggest that a combination of history, allergy skin and serum assays as well as oral challenge may be necessary to make an accurate diagnosis of food allergy.*
S.M.F.
Dang TD, Tang M, Choo S, et al: Increasing the accuracy of peanut allergy diagnosis by using Ara h 2.
J Allergy Clin Immunol. 2012;129:1056-1063. ♦♦

CXCL13: A New Therapeutic Target in Allergic Asthma?

B CELLS are known to contribute to allergic asthma, but the mechanism by which B cells become activated in the airways is unclear. Several lines of evidence suggest a role of CXCL13, a potent B-cell attractant. This study examined the role of CXCL13 in a mouse model of allergic inflammation, as well as in human asthma patients.

Ovalbumin challenge was used to induce allergic inflammation in Balb/c mice, leading to upregulation of CXLC13 and its receptor CXCR5. Associated airway changes included recruitment of B cells and CD4+ cells and development of bronchial-associated lymphoid tissue, in addition to airway inflammation. When sensitized mice were treated with an anti-CXLC13 antibody, cell recruitment, bronchial-associated lymphoid tissue, and airway inflammation all decreased.

The researchers also measured CXCL13 in bronchoalveolar lavage specimens from 15 symptom-free adults with atopic asthma and 13 healthy controls, using an enzyme-linked immunosorbent assay. Median CXCL13 level was 162 pg/mL in the asthmatic subjects versus 31 pg/mL in controls. CXCL13 was unrelated to the provocative dose of methacholine.

These animal and human findings support a role of CXCL13 in the airway inflammatory process involved in allergic asthma. The development of treatments targeting the CXCL13/CXCR5 pathway might provide a new approach to therapy for patients with allergic asthma.

COMMENT: *Originally named B-cell-attracting chemokine 1, CXCL13 is a potent B-cell attractant through the receptor CXCR5. This receptor has been shown to be produced constitutively by reticular cells, such as follicular dendritic cells in lymphoid follicles of human lymph nodes. The authors demonstrate upregulation of CXCL13 in a mouse model of OVA-induced allergic inflammation. Findings include an increase in the number of CXCL13-positive cells in the airway epithelium, around blood vessels, and in the lung interstitium. An extensive perivascular and peribronchial inflammatory cell infiltrate--which mainly comprised lymphocytes, macrophages, and eosinophils--was significantly reduced with anti-CXCL13 antibody. In humans with asthma, CXCL13 was significantly higher in asthmatic BAL fluid than in specimens from nonasthmatics.*

Taken together, there is evidence of CXCL13 in asthmatic inflammation. Further studies seem warranted.
S.F.W.
Baay-Guzman GJ, Huerta-Yepez S, Vega MI, et al: Role of CXCL13 in asthma: novel therapeutic target.
Chest 2012;141:886-894. ♦♦

Intranasal Steroids May Help Minimize Antibiotic Use

ACUTE rhinosinusitis--typically caused by viral rather than bacterial infection--causes inflammatory symptoms lasting no longer than 12 weeks. The concept of the "minimal-symptom day" has been used to evaluate treatments for this condition, highlighting the importance of clinically significant symptom reductions that allow patients to resume normal daily activities. This trial compared an intranasal corticosteroid with an antibiotic or placebo for the treatment of acute rhinosinusitis. The randomized, double-blind trial included 748 patients with acute rhinosinusitis symptoms present for at least 7 but no more than 28 days. All had a baseline major symptom score (MSS--rhinorrhea, postnasal drip, congestion, sinus headache, and facial pain) between 5 and 12.

Patients were randomly assigned to treatment with mometasone furoate nasal spray, 200 µg once or twice daily; amoxicillin 500 mg three times daily; or placebo. The main outcomes of interest were minimal symptom days, defined as an average morning/evening MSS of 4 or less; and minimal congestion days, defined as an average morning/evening congestion score of 0 or 1.

Patients assigned to twice-daily mometasone furoate had about 63% minimal symptom days, compared to 55% with once-daily mometasone, 54% with amoxicillin, and 50% with placebo. Twice-daily mometasone was also associated with increased minimal-congestion days: 73%, compared to 68% with once-daily mometasone, 64% with amoxicillin, and 57% with placebo. Patients taking twice-daily mometasone also had faster symptom resolution: median time to first minimal-symptom day sustained through the end of treatment was 8.5 days, compared to 11 days in the placebo group.

Mometasone furoate nasal spray twice daily is an effective treatment for acute rhinosinusitis, leading to increased minimal symptom days compared to either amoxicillin or placebo. Once-daily mometasone does not achieve the same degree of improvement. The results suggest that intranasal corticosteroid therapy can improve outcomes while potentially reducing inappropriate antibiotic use by patients with this common condition.

COMMENT: *Are intranasal steroids effective in minimizing utilization of antibiotics for acute rhinosinusitis? In a randomized placebo-controlled trial, Meltzer and colleagues demonstrated that mometasone furoate nasal spray 200 µg twice daily--but not once a day--significantly enhanced minimal symptom days versus amoxicillin or placebo in rhinosinusitis patients aged 12 years and older. This benefit was noted within 2 days and allowed patients to return to activity earlier. The results are promising that inhaled corticosteroid therapy can enhance outcome in rhinosinusitis, an inflammatory condition; while minimizing inappropriate antibiotic use, a major goal of contemporary medical practice.*
C.C.R.

Meltzer EO, Gates D, Bachert C, et al: Mometasone furoate nasal spray increases the number of minimal-symptom days in patients with acute rhinosinusitis.
Ann Allergy Asthma Immunol. 2012;108:275-279. ♦♦

CLINICAL TIDBITS

12-HETE: A New Biomarker for CSS?

EARLY diagnosis of Churg-Strauss syndrome (CSS) is important for prevention of serious complications. However, it may be difficult to distinguish CSS from asthma or hypereosinophilic syndrome (HES). Toward finding a useful biomarker of CSS, the researchers compared eicanosoid profiles in patients with these three conditions.

The researchers measured levels of 19 eicanosoids in exhaled breath condensate (EBC) and bronchoalveolar lavage fluid (BALF) samples from 23 patients with CSS, 30 with asthma, and 12 with HES, along with 24 controls. The results showed sharply higher levels of 12-hydroxy-eicosatetraenoic acid (12-HETE) in EBC specimens from CSS patients, compared to the other three groups. The BALF specimens also showed higher levels of 12-HETE and its metabolite 12-tetranor HETE in patients with CSS versus asthma. The BALF levels of 12-HETE and its metabolites were significantly correlated with CSS clinical activity, although EBF levels were not.

Elevated levels of 12-HETE in EBC and BALF specimens may be useful in making the diagnosis of CSS, and particularly in differentiating it from HES and asthma. The finding of elevated 12-HETE levels may also guide new insights into the pathogenesis of CSS.

COMMENT: *Distinguishing CSS from severe asthma and HES is often quite difficult. These authors found that the concentration of 12-HETE was elevated in exhaled breath condensate and BAL fluid of patients with CSS, relative to patients with asthma or HES. This finding sheds light on the pathogenesis of CSS and may become a practical diagnostic marker in the future.*
S.A.T.
Szczeklik W, Sanak M, Mastalerz L, et al: 12-hydroxy-eicosatetraenoic acid (12-HETE): a biomarker of Churg-Strauss syndrome.
Clin Exp Allergy. 2012;42:513-522. ♦♦

Magnesium Therapy in Acute Asthma?

RECENT reports have suggested that adding intravenous magnesium to emergency department (ED) treatment for severe asthma can decrease the hospi- ➤➤

talization rate. Rates of intravenous magnesium for children with asthma seen in Canadian pediatric EDs were analyzed.

The retrospective study included 1,116 otherwise healthy children with acute asthma seen at 6 EDs over a 6-month period. Nineteen of 154 hospitalized children received intravenous magnesium, a rate of 12.3%, compared to 2 of 962 discharged patients. Magnesium treatment was associated with previous ICU admission, odds ratio (OR) 11.2; hospitalization within the past year, OR 3.8; corticosteroid treatment before arrival, OR 4.0; and severe exacerbation at presentation. Most patients who received magnesium were treated at one ED: OR 14.9.

Based on limited data, about half of hospitalized children did not receive "intensive therapy"-- three inhalations of albuterol with ipratropium and corticosteroids within 1 hour of triage. These children were more likely to present with severe asthma: OR 8.9. Rates of all types of stabilization treatment varied between hospitals.

The results show a low rate of intravenous magnesium use at Canadian pediatric EDs for acute asthma requiring hospitalization. Use of other interventions also varies, including frequent albuterol and ipratropium or early corticosteroids.

COMMENT: *There are definite benefits to having been in practice awhile. Seeing older potential therapies resurrected after a considerable hiatus is one of them--not that medications are ever as trendy as say, your old bell-bottoms! Magnesium therapy for acute asthma is a prime example. How many of us have had any experience with this? Ironically, the basics of timely acute asthma management were lacking in a number of cases here. . . perhaps we should stick with the "basics"!*
K.R.M.
Schuh S, Zemek R, Plint A, et al: Magnesium use in asthma pharmacotherapy: A Pediatric Emergency Research Canada study.
Pediatrics. 2012;129:852-859. ♦♦

Passive Smoke and Children's Health: Meta-Analysis Shows Even Higher Risk

PREVIOUS reports on the effects of passive smoke exposure on respiratory health in children have been based on a limited number of studies. An updated meta-analysis incorporating several new prospective studies is reported.

A systematic review identified 79 prospective studies providing data on the association of exposure to prenatal or postnatal environmental tobacco smoke (ETS) with asthma or wheezing in subjects up to 18 years old. Meta-analysis showed a 30% to 70% increase in the incident risk of wheezing for children with passive smoke exposure. The strongest association was noted for wheezing in children aged 2 years or younger exposed to postnatal maternal smoking (based on four studies). Incident asthma was increased by 21% to 85% with ETS exposure. The strongest effect was in infants and young children exposed to prenatal maternal smoking (based on five studies).

The analysis helps to clarify the risks of wheezing and asthma in children exposed to passive smoke. Risk is increased by at least 20%, and possibly by 70% to 80%. To prevent childhood asthma, it is very important to prevent parental smoking.

COMMENT: *Prospective studies have allowed more precise measurement of the risks of passive tobacco smoke exposure in children. Previous estimates likely underestimated ETS effects on both wheezing and asthma. These pooled data should be sobering to parents who continue to smoke around their children.*
K.R.M.
Burke H, Leonardi-Bee J, Hashim A, et al: Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis.
Pediatrics. 2012;129:735-744. ♦♦

Should We Reconsider Mixing Fungal and Insect Extracts for Immunotherapy?

CURRENT guidelines support the practice of mixing fungal and insect extracts when preparing immunotherapy vaccines. The authors performed an in-depth analysis of *Alternaria* and German cockroach extracts in combination with other commonly used types of allergens.

The results suggested that allergen levels and activities were generally well maintained when extracts of the same phylogenetic groups were combined--ie, fungal-fungal and insect-insect. However, for some fungal-insect combinations at 10% to 25% glycerin concentrations, there was evidence of compromised allergen stability. In immunohistochemical tests measuring single or multiple allergens, allergen recovery varied between threefold and tenfold.

Contrary to current practice parameters, mixing fungal and insect extracts may lead to compromised allergen compatibilities. To ensure stable mixtures for immunotherapy injections, it may be necessary to separate these types of extracts into separate vials.

COMMENT: *Studies investigating the stability of mixtures of allergens high in proteases are sparse. This study investigated the mixtures of fungal-fungal, insect-insect, and fungal-insect extracts. The results showed compromise in the stability of some fungal-insect mixtures. They give the practicing allergist some food for thought regarding these allergens we use regularly in our practices.*
V.H.-T.
Grier TJ. LeFevre DM, Duncan EA, et al: Allergen stabilities and compatibilities in mixtures of high-protease and insect extracts.
Ann Allergy Asthma Immunol. 2012;108:439-447. ♦♦

REVIEWS OF NOTE

COMMENT: *How many of us have seen food-allergic children in whom--despite our best efforts--another serious food allergic reaction occurs and epinephrine is not administered? Parents of children with food allergy continue to be confused about when and how to administer epinephrine; misconceptions about food allergy and food labeling also exist. Any measure that enhances our parents' knowledge and ability to treat in an emergency would be helpful. The materials used for education in this study are available at no cost at http://www.cofargroup.org/*
K.R.M.
Sicherer SH, Vargas PA, Groetch ME, et al: Development and validation of educational materials for food allergy.
J Pediatr. 2012;160:651-656. ♦♦

COMMENT: *High-dose inhaled corticosteroids, long-acting β-agonists, and omalizumab have helped a large proportion of patients with severe asthma. But there are still many patients who suffer despite state-of-the-art treatment. This unmet need has been a fascinating challenge for translational researchers and the biotech industry. This excellent review includes a discussion of the next generation of therapeutic targets, including the interleukin (IL)-4/IL-13, IL-5/IL-33, and IL-17 signaling pathways.*
S.A.T.
Poon AH, Eidelman DH. Martin JG, et al: Pathogenesis of severe asthma.
Clin Exp Allergy. 2012;42:625-637.

COMMENT: *Here's a current review on chronic obstructive pulmonary disease, including epidemiology, pathogenesis, treatment, and future directions.*
S.F.W.
Decramer M, Janssens W, Miravitlles M: Chronic obstructive pulmonary disease.
Lancet. 2012;379:1341-1351. ♦♦

COMMENT: *What is the natural history of persistent peanut allergy? In this referral population, the postdiagnosis rate of accidental ingestion was 4.7% per year. Annual rates of severe reactions and reactions requiring epinephrine were 1.6% and 1.1%, respectively. These were low compared to previous, smaller studies, possibly reflecting increased public awareness, personal and public avoidance measures and legislative requirements for food labeling. The severity of reactions was most closely associated with the level of peanut specific IgE, while other factors such as age, sex, asthma and repeated exposures were not predictive.*
C.C.R.
Neuman-Sunshine DL, Eckman JA, Keet CA ,et al: The natural history of peanut allergy.
Ann Allergy Asthma Immunol. 2012;108:326-331. ♦♦

COMMENT: *Alopecia areata is a common autoimmune disease that has a devastating effect on the quality of life and self-esteem of the affected individual. The immunologic basis for this disorder is intriguing in that the hair follicle is normally in a setting of immunologic privilege. Collapse of this constitutive privileged state results in the clinical condition. This elegant review summarizes the pathogenesis, clinical presentation, and management of alopecia areata. The paper illustrates how this condition serves as an excellent model to investigate general principles concerning the generation, maintenance, collapse, and restoration of immune privilege.*
C.D.
Gillhar A, Etzioni A, Paus R, et al: Alopecia areata.
N Engl J Med. 2012;266:1515-1525. ♦♦