AllergyWatch®

" 10th Anniversary Volume "

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

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SLIT Takes a Hit

A growing body of evidence supports the efficacy of sublingual immunotherapy (SLIT) for the treatment of allergic rhinitis. Nearly all of these studies have involved single-allergen treatment. In the United States, most patients are treated for multiple clinically relevant sensitivities. The response to SLIT with multiple versus single allergens was assessed.

After an observational season, 54 patients sensitized to timothy grass pollen were randomly assigned to SLIT monotherapy with timothy extract, 19 µg Phl p 5 daily; SLIT combination therapy with the same dose of timothy extract, plus nine additional extracts; or placebo SLIT.

There were no major differences in symptom and medication scores in the two SLIT groups compared to the placebo group, possibly reflecting very low grass pollen levels during the study season. Patients receiving timothy monotherapy had increased thresholds for titrated nasal challenge and skin prick tests, increased serum-specific IgG_4, and decreased interferon-γ. In contrast, in the multiallergen therapy group, the only significant response was a small improvement in titrated skin prick tests.

Otherwise, the two SLIT groups had similar outcomes, including a higher rate of adverse events than in the placebo group. No systemic reactions occurred.

Consistent with previous studies, the results support the efficacy of SLIT monotherapy using timothy extract. However, there is evidence of reduced efficacy in patients receiving SLIT using multiple allergens. Although further study is needed, SLIT may be of lesser value in polysensitized patients.

SUBLINGUAL immunotherapy has become commonly used in Europe, and its efficacy is supported by five recent meta-analyses. The authors performed an evaluation of the published meta-analyses of SLIT, focusing on the consistency and magnitude of the treatment effect and the robustness of the findings. ➤➤

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The American College of Allergy, Asthma & Immunology expresses its appreciation to Schering-Plough for its unrestricted 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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A literature search identified five meta-analyses of SLIT published through June, 2008. Of the 43 total studies, 17 were included in more than one meta-analysis. The investigators found discrepancies between meta-analyses in data reported from the identical studies--for 16 of 17 studies, either different estimates were reported for the same outcome or the same estimates for different outcomes.

Of 15 major outcomes evaluated by the meta-analyses, 10 showed statistically significant benefits of SLIT. However, funnel plots showed asymmetry from 7 of these outcomes; adjustment for publication bias reduced the effect sizes and, in 4 cases, led to loss of significance. The reported benefits of SLIT varied in terms of age, diagnosis, allergen, symptoms, and medication use.

The evaluation suggests discrepancies, inconsistencies, and lack of robustness in previous meta-analyses of SLIT. The findings are sufficient to question the routine use of SLIT in patients with allergic asthma or rhinoconjunctivitis, the investigators believe. They highlight the need to assess for possible publication bias in future meta-analyses.

COMMENT: *Although SLIT is frequently used overseas, it is still considered investigational here in the United States. The researchers in Denver found that SLIT to timothy grass pollen was not as effective when other allergens where added to the extract. Although lower grass pollen counts during the posttreatment season may have been a confounder, immune response measures were also reduced in the multiallergen group compared to the monotherapy patients.*

The JACI *editors followed this study with a meta-analysis on SLIT for allergic respiratory diseases. The meta-analysis, including 43 studies, did not show sufficiently robust evidence to support the use of SLIT. The specifics of the funnel plots and analyses for this meta-analysis can be found online. The take-home message is that there are still many unanswered questions about SLIT, including dose, safety, and efficacy both with single-allergen and multiallergen administration.*

S.M.F.

Amar S, Harbeck RH, Sills M, et al: Response to sublingual immunotherapy with grass pollen extract: monotherapy versus combination in a multi-allergen extract. **J Allergy Clin Immunol**. 2009;124:150-156.

Nieto A, Mazon A, Pamies R, et al: Sublingual immunotherapy for allergic respiratory diseases: an evaluation of meta-analyses. **J Allergy Clin Immunol**. 2009;124:157-161.

♦♦

Weighing in on Obesity in Childhood Asthma

OVERWEIGHT children may be at increased risk of asthma. It is still unclear how being overweight during early childhood, and changes in weight status later in childhood, affect asthma risk. These questions were addressed in a large birth cohort study.

The analysis included 3,756 Dutch children born in 1996-97. Height and weight and allergic disease outcomes were assessed by parental questionnaire. The children were followed up to age 8, at which time they underwent testing for allergic sensitization and bronchial hyperresponsiveness.

At age 8 years, 7.3% of children had wheezing, 9.6% had dyspnea, and 7.1% had a recent prescription for inhaled corticosteroids. Risk of allergic disease outcomes at age 8 was increased for children who had a high body mass index (BMI) throughout childhood or at age 6 or 7: adjusted odds ratios (ORs) were 1.68 for dyspnea and 1.66 for bronchial hyperresponsiveness. These risks were not increased for children who had a high BMI during early childhood but normal BMI at age 6 or 7. Childhood BMI was unrelated to sensitization.

Children with a currently high BMI are at higher risk of some allergic disease outcomes at age 8. However, those who have a currently normal BMI are not at increased risk, even if they had a high BMI in early childhood. ➤➤

Thus for young children who are overweight, moving to normal weight status may avoid an increased risk of asthma.

DATA on the association between obesity and asthma in children are relatively sparse, with some conflicting results. Although obesity is commonly defined in terms of BMI, other indicators of obesity might be more closely related to asthma risk. Anthropometric markers of central obesity were evaluated as risk factors for asthma in children.

The study included 1,123 children and adolescents, aged 5 to 18, seen at a children's hospital allergy clinic. Of 584 children with allergic rhinitis, 320 had asthma and 264 did not. Measures of central obesity--waist circumference, waist/height ratio, and conicity index--were compared between groups, along with BMI.

Nearly 40% of children classified as obese based on waist circumference were not obese according to BMI percentile. There were also high rates of discordance based on waist/height ratio (17%) and conicity index (46%). Children classified as obese on the measures of central obesity were more likely to have moderate to severe asthma. Among children with allergic rhinitis, the obesity measures explained 8% to 24% of the variance in FEV_1. Among asthmatic children, central obesity was associated with reduced atopy.

In children with allergic rhinitis, asthma and asthma severity are more strongly related to measures of central obesity than to BMI. The authors recommend that waist circumference be incorporated into clinical assessment of obesity-related asthma risk in children. Many children classified as obese or nonobese based on BMI will be classified differently by these anthropometric measures.

COMMENT: *Both of these reports investigate the association of obesity and asthma in children. The large birth cohort study from the Netherlands found that children with high BMI at 8 years of age were at increased risk of asthma symptoms, dyspnea, and bronchial hyperreactivity, compared to those children who had normal BMI, but had previously been overweight.*

The other study, from Cincinnati Children's Hospital, questions the utility of BMI in predicting the risk for asthma in children. The data suggest that measures of central obesity--such as waist circumference, waist/height ratios, and conicity indexes--may be superior to BMI in assessing the risk for asthma and abnormal lung function in children. The take-home message is that obesity indexes are important in the assessment and monitoring of children with allergies and asthma.
S.M.F.

Scholtens S, Wijga AH, Seidell JC: Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age.
J Allergy Clin Immunol 2009;123:1312-1318.

Musaad SMA, Patterson T, Ericksen M, et al: Comparison of anthropometric measures of obesity in childhood allergic asthma: central obesity is most relevant.
J Allergy Clin Immunol. 2009;123:1321-1327. ♦♦

Neighborhood Factors Affect Childhood Asthma Risk

IN Chicago, which has one of the highest asthma rates in the United States, the childhood asthma rate varies by neighborhood. Some negative physical factors associated with the community environment may affect asthma risk, such as air pollution and housing conditions. This study evaluated the possible protective effects of positive social and community factors.

The researchers analyzed cross-sectional asthma screening data from the Chicago Initiative to Raise Asthma Health Equity, including children from 105 public and Catholic elementary schools. The children were coded as living in 287 different Chicago neighborhoods, which were classified into quartile groups with mean asthma prevalences of 8%, 12%, 17%, and 25%. A Community Vitality Index CVI was used to grade each neighborhood based on positive community factors, including social capital, economic potential, and community amenities.

Overall community vitality score was higher in neighborhoods with low asthma prevalence: 54%, compared to 44% for neighborhoods with high asthma prevalence. Scores for economic potential were 64% in low-asthma neighborhoods versus 38% in high-asthma neighborhoods. There were also significant differences in scores for neighborhood interaction, 36% versus 73%; and stability, 40% versus 53%. The positive factors assessed on the CVI accounted for 21% of the variation in asthma prevalence.

After controlling for race/ethnicity, the positive community factors remained higher in African American neighborhoods with low asthma prevalence. On analysis including sociodemographic and individual factors, variations in asthma prevalence were affected by overall community vitality and by social capital.

Positive social-environmental factors are related to the prevalence of childhood asthma in Chicago. Neighborhoods with low childhood asthma rates have greater economic potential and higher levels of diversity and civic engagement. A deeper understanding of community factors that protect against asthma may help in developing interventions to reduce childhood asthma.

COMMENT: *Can a family's neighbors influence the development of asthma in their children? These researchers report a novel approach to evaluating asthma prevalence. Using data from asthma screening in Chicago's grade schools, asthma prevalence was lower in those communities that had a higher community vitality index. This index consists of social capital, including community diversity and civic engagement; economic vigor, which includes commercial vitality and workforce potential; and community amenities, including cultural and entertainment facilities. Once again, external factors, particularly the neighborhood, can play a critical role in the prevalence of childhood asthma.*
S.M.F.

Gupta RS, Zhang X, Sharp LK, et al: The protective effect of community factors on childhood asthma.
J Allergy Clin Immunol. 2009;123:1297-1304. ♦♦

Increased Remodeling in Severe Asthma with Persistent Obstruction

SOME patients with severe asthma have apparently irreversible reductions in airway function, while others have intermittently normal airway function. The authors hypothesized that severe asthma with increased airway remodeling might be associated with chronic persistent airflow obstruction. They report an in-depth investigation of patients with severe asthma and chronic persistent versus intermittent airway obstruction.

The study included 34 patients with severe asthma, 16 of whom had chronic persistent airway obstruction (FEV_1 less than 70% of predicted at each clinic visit). Investigations included endobronchial biopsy analysis, induced sputum measures, and high-resolution CT measurement of airway thickness.

Age at onset was 19 in patients with chronic persistent airway obstruction versus 33 in those with intermittent obstruction; disease duration was 30 versus 12 years, respectively. Chronic persistent obstruction was associated with increased sputum inflammatory cells and greater smooth muscle area: 15.65%, compared to 8.96% in the intermittent obstruction group. Individual sputum biomarkers were not significantly different between groups. However, on principal component analysis, interleukin (IL)-12, IL-13, and interferon-γ predominated in the chronic persistent obstruction group, whereas IL-9, IL-17, monocyte chemotactic protein 1, and RANTES were dominant in the intermittent obstruction group. There were no differences on airway imaging studies.

Among patients with severe asthma, those with chronic persistent airway obstruction show increased airway smooth muscle and continuing Th1 and Th2 inflammatory responses. This subgroup cannot be detected by high-resolution CT scanning or induced sputum analysis. New treatment approaches are needed for this group of patients, targeting airway wall remodeling as well as inflammation.

COMMENT: *Data from this well-designed study suggest that there are two distinct subtypes of severe asthma: patients with chronic persistent airway obstruction who have earlier age of onset, longer disease duration, more sputum inflammatory cells, higher exhaled nitric oxide, and increased airway smooth muscle; and those with severe asthma and intermittent obstruction. The authors suggest that newer therapies such as bronchial thermoplasty--that aim at reducing the increased airway smooth muscle--may be helpful for asthmatic patients with chronic persistent airway obstruction.*
S.M.F.

Kaminska M, Foley S, Maghni K, et al: Airway remodeling in subjects with severe asthma with or without chronic persistent airflow obstruction.
J Allergy Clin Immunol. 2009;124:45-51. ♦♦

Exhaled NO Linked to RTI Risk in Preschoolers with Wheezing

IN school-aged children with asthma, exhaled nitric oxide (eNO) may be a useful tool for monitoring airway inflammation. In contrast, there are few data on the clinical role of eNO measurement in preschoolers. This study examined factors associated with eNO in preschool-aged children with moderate to severe wheezing.

The study included 89 children, aged 1 to 5 years, with moderate to severe intermittent wheezing. Exhaled NO was measured using the offline tidal breathing technique. Elevated eNO (over the 75th percentile, 24 ppb) was evaluated for association with risk of respiratory tract infections (RTIs), disease burden, and atopy.

The risk of RTI during 1 year's follow-up was nearly four times higher for children with elevated eNO: adjusted relative risk 3.80. Children in the highest quartile of eNO also had more positive skin test results for aeroallergens. However, there were no differences in other atopic characteristics or in indicators of past illness burden (office visits, courses of corticosteroids, etc).

For preschool-aged children with moderate to severe intermittent wheezing, a high eNO is associated with an increased frequency of RTIs. Children with elevated eNO may also be sensitized to more aeroallergens. Exhaled NO may be a useful tool for treatment planning in this group of children, although the effectiveness of strategies to prevent wheezing episodes will need to be established.

COMMENT: *Therapeutic planning is a challenge for children with episodic, usually infection-related wheezing who appear normal during intervals. Exhaled nitric oxide may be helpful in predicting episodes, but it is not at all clear that any treatment option would change this course of events. We yearn for airway markers that predict risk but remain largely in the dark. Please, someone turn on the lights!*
D.K.L.

Beigelman A, Mauger DT, Phillips BR, et al: Effect of elevated exhaled nitric oxide levels on the risk of respiratory tract illness in preschool-aged children with moderate-to-severe intermittent wheezing.
Ann Allergy Asthma Immunol. 2009;103:108-113. ♦♦

In Response to Asthma Treatment, eNO Improves First

EXHALED nitric oxide (eNO) and exhaled breath condensate (EBC) are useful, noninvasive indicators of airway inflammation. It has been suggested that they may be useful in assessing response to asthma treatment, but the time course of the responses is unclear. Time-dependent eNO and EBC responses to inhaled corticosteroid therapy for asthma were evaluated, along with other clinical responses.

The study included 11 steroid-naive adult asthma patients receiving mometasone furoate via dry pow- ➤➤

der inhaler, 400 µg/d, for mild to moderate persistent asthma. Treatment continued for 8 weeks, followed by a 4-week washout period. The time course of changes in eNO, EBC, FEV_1, and bronchial hyperresponsiveness was analyzed.

From baseline to 8 weeks, mean FEV_1 increased from 3.01 to 3.24 L (82% to 87% predicted). The methacholine concentration required to produce a 20% decline in FEV_1 (PC_{20}) increased from 1.28 to 2.99 mg/mL by 8 weeks, remaining stable during the washout period. Within the first week, eNO decreased from 31.1 to 20.6 ppb. The reduction persisted throughout treatment, then returned to baseline during the washout period. Median EBC pH increased nonsignificantly, from 7.81 to 8.02, within the first 4 weeks of treatment. The EBC nitrite level decreased from 17.6 µM at baseline to 9.3 µM at week 8; the reduction remained significant during washout. The eNO and methacholine PC_{20} values were correlated with each other.

Exhaled NO decreases promptly in response to inhaled corticosteroid therapy for persistent asthma, and increases again after treatment is stopped. Changes in EBC values are slower to occur but longer lasting. More study is needed to assess the use of eNO in monitoring asthma control and treatment response.

COMMENT: *This study is limited by small size and lack of a placebo arm. Nevertheless, the data provide clinical confirmation of the time course of the effects of inhaled corticosteroids: eNO improves first and bronchial hyperreactivity last, with changes in EBC and spirometry in between.*
D.K.L.

Mehta V, Stokes JR, Berro A, et al: Time-dependent effects of inhaled corticosteroids on lung function, bronchial hyperresponsiveness, and airway inflammation in asthma.
Ann Allergy Asthma Immunol. 2009;103:31-37. ♦♦

Purified Venom Extracts Reduce Severe Local Reactions

IN Europe, purified extracts are available for use in venom immunotherapy (VIT) for patients with honeybee or yellow jacket allergy. These extracts may be better tolerated than unpurified venom extracts, but there have been no direct comparisons of the associated local and systemic reactions. The safety and tolerability of purified versus unpurified venom extracts were compared.

The trial included 94 patients allergic to yellow jacket or honeybee venom. Patients were randomly assigned to VIT with purified or unpurified venom extract. In both groups, VIT consisted of a 2- or 7-day ultrarush induction phase followed by an 11-week maintenance phase. Local and systemic reactions to a total of 1,401 VIT injections were analyzed.

There were 6 systemic reactions in 4 patients (all with honeybee allergy), for a rate of 4% of patients and 0.4% of injections. Of these 4 patients, 1 was receiving purified extract and 3 were receiving unpurified extract. Local extensive reactions occurred in 9% of patients receiving purified venom extract versus 24% of those receiving unpurified extract. The overall rate of systemic and large local reactions was 11% in patients receiving purified extracts vs 30% in those receiving unpurified extracts. Per-injection rates were 0.9% vs 2.7%, respectively.

This randomized trial shows a lower rate of severe local reactions in patients receiving VIT with purified venom extracts, compared to unpurified extracts. The difference likely reflects the elimination of low-molecular-weight compounds from purified aqueous extracts. A much larger study would be needed to show a significant difference in systemic reactions.

COMMENT: *Purified venom preparations, ultrafiltered and dialyzed, are not available in the United States, but have been shown to have enhanced skin test response and now reduced local reactions with injection immunotherapy. Venoms contain factors that have direct effects on mast cells. Perhaps these factors are responsible for sting anaphylaxis in subjects with monoclonal mast cell activation syndrome and no detectable, specific IgE for venom proteins. Research often results in more questions than answers but makes life interesting.*
D.K.L.

Bilò MB, Severino M, Cilia M, et al: The VISYT trial: venom immunotherapy safety and tolerability with purified vs nonpurified extracts.
Ann Allergy Asthma Immunol. 2009;103:57-61. ♦♦

Breast-Feeding Protects Against Nonatopic Wheezing Only

EVEN after decades of study, there is continued uncertainty over the protective effects of breast-feeding against allergic disease. The effect on childhood wheezing may differ for more- versus less-affluent countries. Data from the International Study of Asthma and Allergy in Childhood (ISAAC) Phase II were used to investigate the relationship between breast-feeding and asthma in children.

The analysis included questionnaire data on disease and exposure variables from a random sample of 54,000 schoolchildren, aged 8 to 12, from 27 centers in 20 countries. The countries were classified as affluent or nonaffluent. The study included data on skin-prick testing in nearly 32,000 children and on bronchial hyperreactivity and lung function in nearly 5,000.

Meta-analysis using random effect models found that children who received any breast-feeding had lower rates of wheezing. This was so in both affluent and nonaffluent countries: adjusted odds ratios 0.87 and 0.80, respectively. However, on further analysis, the only significant association was a reduced risk of nonatopic wheezing in nonaffluent countries: OR 0.69. In both groups of countries, breast-feeding had no effect on atopic wheezing or objective measures of allergy (skin prick tests or specific IgE levels). In affluent countries, breast-feeding was associated with a higher predicted FEV_1, mean ratio 1.11.

This large cross-sectional analysis shows that, ➤➤

especially in nonaffluent countries, breast-feeding is associated with a lower risk of nonatopic childhood wheezing. However, there is no apparent association with atopic wheezing or with other allergic disease indicators. The difference by wheezing phenotype may help to explain some of the discordant results on the effect of breast feeding on respiratory symptoms.

COMMENT: *The notion of breast-feeding as a protective strategy against the development of atopic disease has been debated actively for many years. This study confirms the presence of an apparent protective effect against nonatopic wheezing. It also shows no protective effect of breast-feeding on other allergic manifestations. This may explain some of the discordant results seen in previous studies.*
B.E.C.
Nagel G, Büchele F, Weinmayr G, et al: Effect of breast-feeding on asthma, lung function and bronchial hyperreactivity in ISAAC Phase II.
Eur Respir J. 2009;33:993-1002. ♦♦

Long-term Outcomes of Acute Irritant-Induced Asthma

PATIENTS with acute irritant-induced asthma (IIA), also called reactive airways dysfunction syndrome, develop respiratory symptoms and sometimes bronchial obstruction after some type of inhalational accident. There are few data on long-term outcomes. The authors evaluated the outcomes of IIA more than 10 years after diagnosis.

The study included 35 patients diagnosed with and receiving compensation for acute IIA after inhalational accidents at work. Mean time since the accident was 13.6 years; the involved agent was chlorine in 57% of cases.

All patients still had respiratory symptoms at follow-up, and about two-thirds were using inhaled steroids. Pulmonary function values were unchanged. Results of methacholine testing were normal in only 6 of 23 patients. Six of twelve had at least 10% improvement in FEV_1 in response to bronchodilator. An eosinophil percentage of 2% or greater was found in induced sputum from 6 of 27 patients. Indicators of inflammation and airway remodeling were higher than in normal controls, but similar to those of patients with allergic occupational asthma. Other findings included reduced scores on quality of life and depression assessments.

Acute IIA has a significant long-term impact on pulmonary function, quality of life, and psychologic outcomes. The prognosis appears similar to that of allergic occupational asthma.

COMMENT: *Reactive airway dysfunction syndrome was first described by Stuart Brooks in 1985 (Chest. 1985;88:376-384). The detrimental effect on first responders to the World Trade Center on September 11, 2001, adds to this literature. This study shows a significant long-term impact on pulmonary function, quality of life, and psychosocial parameters in patients exposed to acute irritant-induced asthma.*
B.E.C.
Malo J-L, L'Archevêque J, Castellanos L, et al: Long-term outcomes of acute irritant-induced asthma.
Am J Respir Crit Care Med. 2009;179:923-928. ♦♦

Can We Use eNO for Asthma Monitoring in Smokers?

THROUGH some mechanism that remains unclear, smoking causes a reduction in exhaled nitric oxide (eNO) measurements. Because of this, the use of eNO for asthma monitoring in patients who smoke is unclear. Exhaled NO was evaluated as a marker of asthma control in smokers.

The study included Asthma Control Questionnaire (ACQ) scores and eNO measurements from 411 nonsmokers and 59 smokers with asthma. Data from at least two visits were available in 345 and 51 patients, respectively.

Mean ACQ score was 1.5 in nonsmoking patients with asthma versus 1.7 in patients who smoked. However, mean eNO was 33.7 ppb in nonsmokers versus 18.1 ppb in smokers. An eNO reduction of less than 20% was associated with lack of improvement in asthma control in both groups: negative predictive values (NPV) were 78% in nonsmokers and 72% in smokers. In both groups, patients with an eNO increase of less than 30% were unlikely to have worsening asthma control: NPV 86% and 84%, respectively.

Exhaled NO levels are significantly reduced in asthmatic patients who smoke. However, changes in eNO are still related to asthma control. Thus exhaled NO measurement may be of value in asthma management among smokers.

COMMENT: *Smoking occurs in approximately 25% of the general population and a similar percentage of patients with asthma in the TENOR study. Although eosinophils are probably not the primary effector cell for airway inflammation in smoking asthmatics, this study allows for better analysis of the eNO levels that can be expected in asthma patients who smoke. The order of magnitude of change that may be expected in these patients after therapy is discussed as well.*
B.E.C.
Michils A, Louis R, Pechè R, et al: Exhaled nitric oxide as a marker of asthma control in smoking patients.
Eur Respir J. 2009;33:1295-1301. ♦♦

Risk Stratification for Egg Allergy: Consider Titrated Skin Testing

ALTHOUGH it is the gold standard for diagnosis of food allergy, oral food challenge (OFC) is not convenient for clinical use. Efforts have been made to predict positive OFC results by specific IgE measurement or conventional skin testing. This study evaluated the use of skin testing with titration curves to predict the response to OFC.

The study included 47 children, mean age 6.2 ➤➤

years, with suspected hen's egg allergy. All children underwent standard skin prick tests as well as skin prick tests with end-point titration. In the latter test, the highest dilution producing a mean weal diameter of 3 mm or greater was defined as the observed endpoint dilution. The children underwent open OFC as well. Receiver operating characteristic (ROC) analysis was performed to identify the predictive decision points for a positive OFC result, based on specific IgE concentration, weal size, and endpoint titration.

The response to OFC was positive in 42.5% of children. Endpoint titration produced the greatest area under the ROC curve: 0.99, compared to 0.88 for weal size and 0.83 for specific IgE levels. An extract dilution of 1:256 was 95% sensitive and 100% specific in discriminating a positive from a negative OFC.

Endpoint titration may make skin-prick testing more accurate in predicting the response to OFC in children with suspected allergy to hen's egg. The technique is readily applicable to clinical use, requiring just a few minutes to prepare the dilutions. Additional studies in other patient populations will be needed.

COMMENT: *We currently rely on prick skin test wheal diameter and/or ImmunoCAP in vitro testing to help estimate the risk that a patient having an allergic reaction after ingesting the food. This study used OFC to raw egg as the gold standard. A skin test extract dilution of 1:256 discriminated positive from negative oral egg challenge with 95% sensitivity and 100% specificity. These impressive results suggest that endpoint titration skin testing to egg may be the best way to stratify risk when managing egg allergy.*
S.A.T.

Tripodi S, Di Rienzo Businco A, Alessandri C, et al: Predicting the outcome of oral food challenges with hen's egg through skin test end-point titration.
Clin Exp Allergy. 2009;39:1225-1233. ♦♦

Pets at Home Don't Prevent Asthma

HAVING pets in the household during early life has been linked to a lower risk of allergic sensitization in schoolchildren. However, some studies have reached conflicting conclusions; recall bias may contribute to the discrepancy. The effects of early life pet exposure on sensitization and other outcomes were evaluated in a birth cohort study.

The analysis included data on 2,951 children enrolled in the PIAMA birth cohort study. Data on symptoms and cats or dogs at home, along with potential confounders, were obtained at intervals from the last trimester of pregnancy to age 8.

On event history analysis, children who had a pet at home at age 3 months were at lower risk of sensitization to inhalant allergens at age 8. For children with a cat at home, the odds ratio (OR) for house dust mite sensitization at age 8 was 0.68; for those with a dog, the OR for pollen sensitization was 0.49. However, neither type of pet significantly affected the risk of asthma during follow-up. Starting at age 2, children with a dog at home were at higher risk of wheezing, OR 1.52; and dry nighttime cough, OR 1.28. The associations were significant only in children with a positive family history. When the dog was removed from the home, the risk of asthma symptoms increased.

Having a dog or cat at home during early childhood is associated with a reduced incidence of sensitization to inhalant allergens at age 8. However, pets do not reduce the risk of asthma, and may be associated with more frequent intermittent asthma symptoms. There is evidence of significant recall bias related to physician diagnosis of asthma.

COMMENT: *There is a growing consensus that the presence of household pets early in life is associated with reduced subsequent sensitization to aeroallergens. However, preventing asthma by having pets has been harder to demonstrate. This study analyzed data from the PIAMA birth cohort study of nearly 3,000 subjects. Children with a cat or a dog at age 3 months were, in general, less likely to be sensitized to other inhalant allergens by age 8. However, there was no evidence that household pets were associated with a lower incidence of asthma.*
S.A.T.

Kerkhof M, Wijga AH, Brunekreef B, et al: Effects of pets on asthma development up to 8 years of age: the PIAMA study.
Allergy. 2009;64:1202-1208. ♦♦

Clinical Factors Predict Biphasic Anaphylactic Reactions in Children

AFTER their condition has stabilized, children with anaphylaxis are often hospitalized to observe for possible biphasic reaction. Predictive factors are needed that would help to identify the small percentage of children who will have biphasic reactions. This issue was addressed in a retrospective study.

The analysis included 109 episodes of anaphylaxis in 104 children seen at one pediatric emergency department over 5 years. Uniphasic reactions accounted for 87% of episodes and biphasic reactions for 11%. There were 2 protracted reactions, 1 of which was fatal.

More than one dose of epinephrine was required for treatment of the initial anaphylactic reaction in 58% of patients with biphasic reactions, compared to 22% of those with uniphasic reactions. A fluid bolus was used in 42% of biphasic versus 8% of uniphasic reactions. Patients with neither of these factors were highly unlikely to have biphasic reactions: negative predictive value 99%. For those with either factor, positive predictive value for a biphasic reaction was 32%. In all children with biphasic reactions in which the second phase was anaphylactic, initial treatment included either multiple doses of epinephrine, a fluid bolus, or both.

The treatment required for the primary anaphylactic reaction in children identifies those at increased risk of a biphasic reaction. A 24-hour observation period is recommended for children who receive more than one dose of adrenaline and/or a fluid bolus.

COMMENT: *This retrospective study provides practical information: If management of the primary* ➤➤

anaphylactic reaction does not require more than one epinephrine injection or an intravenous fluid bolus, then the risk of a biphasic anaphylactic reaction is quite low and it is probably safe to discharge the patient from the emergency department without prolonged observation.
S.A.T.
Mehr S, Liew WK, Tey D, Tang LK: Clinical predictors for biphasic reactions in children presenting with anaphylaxis.
Clin Exp Allergy. 2009;39:1390-1396. ♦♦

Sleep-disordered Breathing Linked to Behavioral Problems in Asthmatic Kids

CHILDREN with asthma reportedly have higher levels of behavior problems. Some asthmatic children also have sleep-disordered breathing (SDB), which may be linked to behavior problems. The relationship between SDB and behavior problems was studied in inner-city children with asthma.

The study included 194 children, age 4 to 10 years, from a school-based asthma intervention program. Mean age was 8.2 years; most of the children were African American and had Medicaid insurance. The presence of SDB was assessed using the snoring and sleepiness subscales of the Sleep-Related Breathing Disorder Questionnaire. Troubled behaviors were assessed using the Behavior Problem Index.

Based on a sleep score of greater than 0.33, SDB was present in 33% of the children. The children with SDB had a higher overall score for behavior problems, with differences in 8 of 9 subdomains: externalizing, internalizing, anxious/depressed, headstrong, antisocial, hyperactive, peer conflict, and immature. After adjustment for covariates, SDB remained significantly associated with overall behavioral problems and with externalizing, internalizing, anxious/depressed, headstrong, and hyperactive behaviors.

Asthmatic children with SDB have increased rates of behavior problems. Children with asthma should be screened for sleep problems, and SDB considered a potential risk factor for behavior problems. It remains to be seen whether treatment for SDB would reduce behavior problems.

COMMENT: *An important potential link between SDB and behavioral issues is identified in this study of pediatric patients with asthma. If the findings hold true, the likelihood of such problems may be increased in children with asthma. The limitations of this study are its cross-sectional design and lack of correlation between relative asthma severity (other than whether intermittent vs persistent) and SDB by parental history. It is also possible that parents might have misidentified some asthma symptoms as SDB in answering study questions.*
K.R.M.
Fagnano M, van Wijngaarden E, Connolly HV: Sleep-disordered breathing and behaviors of inner-city children with asthma.
Pediatrics. 2009;124:218-225. ♦♦

Depression May Affect Asthma Morbidity via 'Vagal Bias'

STRESS and depression may contribute to asthma morbidity in children. The pathways of this association are unknown, but could involve the autonomic nervous system. The link between depression, autonomic dysregulation, and airway function was studied in children with asthma.

From 171 asthmatic children and adolescents seen in an emergency department for asthma exacerbations, the investigators identified 45 patients with high depressive symptoms and 45 with no or low depressive symptoms. Under controlled laboratory conditions, the children's vagal and sympathetic reactions to emotional scenes from a movie were evaluated, along with airflow and airway resistance.

A subgroup of asthmatic children with high depressive symptoms had increased airway reactivity, with nonmedicated FEV_1 of less than 80% predicted. These children had evidence of increased airway resistance under all study conditions, and of vagal bias in response to the emotional movie scenes. Children with high depressive symptoms had a significant vagal response to sad scenes, including depictions of family distress/loss, dying, and death. The nondepressed children showed sympathetic activation in response to scenes showing loneliness and dying. Depressive symptoms were associated with respiratory resistance and vagal bias during the scene showing family distress/loss; vagal bias during this scene was correlated with airway resistance after the movie.

Asthmatic children with high depressive symptoms show vagal bias in response to emotional distress. A subgroup of depressed children with increase airway reactivity show increased airway resistance. Vagal bias may contribute to disease activity in asthma.

COMMENT: *The interplay of emotions and many diseases is evident. In asthma, there may be ample reason to suspect an interaction between emotional state (in this study, depression in asthmatic children) and autonomic determinants of airway function. This study confirmed that the group with a "vagal (cholinergic) bias" in response to depressive stimuli had increased airway resistance, compared to the nondepressed group.*
R.J.M.
Miller BD, Wood BL, Lim JH, et al: Depressed children with asthma evidence increased airway resistance: "vagal bias" as a mechanism?
J Allergy Clin Immunol. 2009;124:66-73. ♦♦

LABAs Have No Anti-Inflammatory Effect

ADD-on long-acting β_2-agonist (LABA) therapy has been recommended for patients with chronic persistent asthma. However, there are conflicting data regarding the anti-inflammatory effects of LABAs. A meta-analysis was performed to evaluate evidence on the anti-inflammatory effect of LABAs, compared with ➤➤

placebo and in addition to inhaled corticosteroids (ICS).

The investigators performed a systematic review to identify placebo-controlled trials comparing the in vivo anti-inflammatory effect of LABAs with placebo, as well as trials of LABA plus ICS vs ICS alone in patients with asthma. Meta-analyses were performed using data on 1,105 participants from 32 studies. Inflammatory outcomes of interest included cell counts and cell activation markers in sputum, bronchoalveolar lavage (BAL) fluid, and bronchial biopsy, as well as exhaled nitric oxide.

The pooled data showed no effect of LABAs on inflammatory cells in sputum, BAL fluid, or mucosa in adults or children with asthma. There was evidence of decreases in exhaled NO and in BAL fluid albumin levels in adults, and of small reductions in serum eosinophils and interleukin-4 in children.

The findings question whether LABAs have any significant anti-inflammatory (or proinflammatory) effect. The synergistic effect of LABAs plus ICS on clinical outcomes must be explained by other factors, such as the bronchorelaxant effects of LABAs. Based on the reduction in BAL fluid albumin levels, LABAs may have a modulating effect on microvascular leakage.

COMMENT: *This meta-analysis differentiates the benefit of adding LABA to ICS between bronchodilation and inflammation. A review of 32 relevant studies demonstrates no significant anti-inflammatory effects of LABA. The authors propose that control of (eg, eosinophilic) inflammation should be maximized prior to adding LABA. This has some support in guidelines for treatment of moderate persistent asthma.*
S.F.W.

Sindi A, Todd DC, Nair P: Antiinflammatory effects of long-acting β_2-agonists in patients with asthma.
Chest 2009;136;145-154. ♦♦

Skin Horny Layer Markers for Evaluation of AD Skin

NEW approaches to evaluating the complex disease activity associated with atopic dermatitis (AD) are needed. Studies using mass spectrometry have found increased expression of certain proteins in the horny layer of the skin in patients with AD. These HL proteins were HL evaluated for use in evaluating the skin condition of lesions in AD patients.

The study included 36 patients with AD, 8 patients with psoriasis, and 16 healthy volunteers. Immunoblotting was performed to measure expression of six proteins in the HL: fatty acid binding protein-5 (FABP-5), squamous cell carcinoma antigens 2 (SCCA2), α-enolase, annexin II, apolipoprotein A-I, and albumin. The findings were compared with clinical features.

All six proteins were present at high levels in AD skin lesions but very low levels in normal controls. There was a significant correlation between FABP-5 and the local severity of skin involvement skin. Correlations were noted between annexin II, apoprotein A-I and albumin and the severity of specific eruptions, as well as between SCCA2 and total serum IgE level. The skin of patients with psoriasis had very low albumin levels, compared to AD skin.

Certain HL proteins are potentially useful biomarkers of inflammation and barrier function in the skin of patients with AD. Functional studies of the marker proteins are underway.

COMMENT: *Atopic dermatitis is a common chronic and relapsing inflammatory disorder, caused by the complex interaction of genetic, immunologic, barrier dysfunction and environmental factors. These authors attempted to develop a new, objective, and noninvasive method for evaluating AD, based on biochemical markers in the skin's horny layer. The HL proteins FABP-5, albumin, and some others seem to be useful as biomarkers to evaluate inflammation and skin barrier conditions in AD patients. The authors believe that these proteins, in part, contribute to the development of AD symptoms. When the pathologic significance of the aberrant expression of these marker proteins is elucidated, their measurement would become a more important tool to characterize or evaluate complicated skin conditions in AD patients. It would also be useful for choosing the best clinical treatments for AD.*
M.F.

Yamane Y, Moriyama K, Yasuda C, et al: New horny layer marker proteins for evaluating skin condition in atopic dermatitis.
Int Arch Allergy Immunol. 2009;150:89-101. ♦♦

CLINICAL TIDBITS

Predictors of Pneumonia in Wheezing Children

THE diagnosis of pneumonia in children with wheezing can be difficult to make. Clinical factors associated with a radiographic diagnosis of pneumonia were prospectively evaluated in 526 children with wheezing seen in the emergency department (ED).

The children's mean age was 1.9 years; nearly half had a history of wheezing. Radiographs showed pneumonia in 4.9% of patients. Factors associated with radiographic pneumonia included history of fever at home, positive likelihood ratio (LR) 1.39; history of abdominal pain, LR, 2.85; triage temperature of 38.0° C or higher, LR 2.03; maximal ED temperature of 38.0° C or higher, LR 1.92; and triage oxygen saturation less than 92%, LR 3.06. Only 2.2% of children with temperatures less than 38.0° C had radiographic pneumonia.

These clinical predictors will help to identify wheezing children who are more or less likely to have radiographic pneumonia. Chest radiography should not be routinely performed in afebrile children with wheezing.

COMMENT: *The questions we are frequently asked by parents of acutely ill, wheezing children--"Could this be pneumonia?" and "Do you think obtaining a chest x-ray would help?"--seem to be addressed definitively by this large prospective study of wheezing pediatric patients seen in an ED. Fever less than 38.0° C* ➤➤

alone is a useful predictor arguing against pneumonia–a finding quite helpful for clinical practice. An important caveat here is that chest x-rays were not ordered in all wheezing children who presented to the ED, just in those in whom pneumonia was suspected. The results may therefore overestimate the likelihood of pneumonia, even at 2.2%.
K.R.M.
Mathews B, Shah S, Cleveland RH, et al: Clinical predictors of pneumonia among children with wheezing.
Pediatrics. 2009;124:e29-e36. ♦♦

Cough or Sneeze: Which Is Best to Predict Intermittent Wheeze?

MODERATE to severe intermittent wheezing is common in preschoolers with acute respiratory tract illness (RTI). Parents caring for these children at home need information on what symptoms are associated with exacerbation of wheezing.

This issue was addressed in a study including 238 preschoolers with moderate to severe intermittent wheezing. Parent questionnaires were used to identify signs and symptoms present at the onset of RTIs. The first identified symptoms were "nose symptoms" in 41% of children, "significant cough" in 29%, and "insignificant cough" in 13%. Of these, cough was the strongest predictor of subsequent wheezing: specificity 78% and positive predictive value 74%.

In preschoolers with a history of severe intermittent wheezing, significant cough at the start of acute RTI is a reliable indicator of subsequent wheezing. However, the authors emphasize that other types of symptoms may also precede wheezing episodes.

COMMENT: *This useful study seems intuitive from a clinical practice standpoint. Our youngest patients experience frequent episodes of viral respiratory illness, and a significant proportion will have worsening lower respiratory symptoms before wheezing is evident. Nasal symptoms were the earliest initial symptoms identified, but "significant cough" had better predictive value for later wheezing. These findings have obvious ramifications for teaching parents what to watch for, when reviewing the asthma action plan for a young child.*
K.R.M.
Rivera-Spoljaric K, Chinchilli VM, Camera LJ, et al: Signs and symptoms that precede wheezing in children with a pattern of moderate-to-severe intermittent wheezing.
Pediatrics. 2009;154:877-881. ♦♦

Are Auto-Injector Needles Long Enough for Children?

FOR optimal treatment of anaphylaxis, epinephrine should be injected intramuscularly (IM) rather than subcutaneously. This study sought to determine whether the needles of epinephrine auto-injectors are sufficiently long for IM epinephrine injection in children.

The study included 256 children, aged 1 to 12. Based on ultrasound measurement of depth from the skin to the vastus lateralis muscle, a significant proportion of children would not receive IM epinephrine injection using current auto-injectors. Needle length was likely to be inadequate in 12% of children who would be prescribed the 0.15 mg auto-injector (weight less than 30 kg) and 30% of those in whom the 0.3 mg auto-injector would be prescribed.

Many children will not reliably achieve IM injection of epinephrine using current auto-injectors. Longer needle lengths would help to optimize epinephrine delivery during community treatment of anaphylaxis in children.

COMMENT: *The research of Dr. F. Estelle R. Simons and others is complemented by this study, which asks whether epinephrine auto-injector needles are long enough for consistent IM administration in children. In adults, research has shown that many would receive a subcutaneous rather than IM injection, in particular overweight and obese women. Given the current rate of childhood obesity, it makes sense to investigate the question in children.*

Not surprisingly, the results show the potential for inadequate medication delivery. My primary critique of this study is that pressure was not applied to the thigh directly to simulate auto-injector use (other than what was obtained with an ultrasound probe). Later, possibly in response to similar editorial concern, an estimated correction was done to simulate distance to the vastus lateralis muscle under pressure. *Even with these calculations, a significant number of children would likely receive their epinephrine subcutaneously!*
K.R.M.
Stecher D, Bulloch B, Sales J, et al: Epinephrine autoinjectors: is needle length adequate for delivery of epinephrine intramuscularly.
Pediatrics. 2009;124:65-70. ♦♦

Peanut Allergy: More Evidence on Inducing Oral Tolerance

THERE is currently no disease-modifying treatment for peanut allergy. Previous reports have described the use of oral immunotherapy (OIT) for treatment of hen's egg and cow's milk allergy. The results of OIT for peanut allergy in 4 children are presented.

After assessment of dose thresholds, the children--including one with documented anaphylaxis--received OIT with daily doses of peanut flour, increasing from 5 to 800 mg of protein. All patients tolerated the OIT regimen, with no need for epinephrine injection. All were able to tolerate oral peanut challenge, performed 6 weeks after the final OIT dose. Each child was able to consume at least 10 whole peanuts, with up to a 478-fold increase in dose threshold.

In children with severe peanut allergy, OIT may successfully induce tolerance of peanut. In this small study, all patients were able to tolerate a peanut challenge far greater than any likely accidental ingestion.

COMMENT: *The recent buzz in the food allergy world has focused on oral tolerance as a possible long-* ➤➤

term treatment to prevent catastrophic reactions due to accidental ingestion of the offending food. This uncontrolled study achieved impressive tolerance in 4 peanut-allergic patients, 2 of whom had baseline peanut ImmunoCAP levels greater than 100 kU/L. This adds to the evidence that oral tolerance induction may become a routine part of food allergy treatment. However, before using this treatment in our patients we must wait for results from larger-scale studies.
S.A.T.
Clark AT, Islam S, King Y, et al: Successful oral tolerance induction in severe peanut allergy.
Allergy.2009;64:1218-1220. ♦♦

Probiotics for Eczema: Cochrane Says "No!"

TRIALS of probiotic therapy for eczema have yielded conflicting results. The findings of a Cochrane review of probiotics for the treatment of eczema are reported.

A literature search identified 12 randomized controlled trials of live orally ingested micro-organisms for the treatment of eczema, including a total of 781 patients. Based on meta-analysis of data from 5 trials, probiotics yielded no significant reduction in eczema symptoms. Data from 7 trials showed no effect on eczema severity, as rated by investigators. There was no patient subgroup who benefited from probiotic therapy. Some case reports described sepsis and bowel ischemia related to probiotics.

This review and meta-analysis does not support the efficacy of probiotics for eczema. The studies show significant heterogeneity, although trials using the same probiotic strain report consistent results.

COMMENT: *Although dietary intake clearly affects eczema control in a subset of patients, the results from studies examining the utility of treating eczema with probiotics have been less consistent. This meta-analysis used the rigorous Cochrane methodology and found absolutely no evidence that probiotics have a positive treatment effect. Given these results, probiotics should probably not be used for the treatment of eczema.*
S.A.T.
Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, et al: Probiotics for the treatment of eczema: a systematic review.
Clin Exp Allergy. 2009;39:1117-1127. ♦♦

RSV Infection Doesn't 'Cause' Childhood Asthma

INFANTS with respiratory syncytial virus (RSV)-related bronchiolitis are at increased risk of childhood asthma, but the nature of this association is unclear. Data on 8,280 Danish twin pairs were used to analyze the association between severe RSV infection and asthma.

With linkage to hospital discharge data and parental questionnaires, the study showed a positive association between RSV hospitalization and asthma, with complete overlap in the genetic determinants of the two diseases. Models of causal direction suggested it was more likely that asthma "causes" RSV hospitalization than the other way around. The results were the same after adjustment for sex, birth weight, and maternal smoking during pregnancy.

The link between RSV infection and childhood asthma does not appear to be a causal one. Rather, severe RSV infections may reflect a genetic predisposition to asthma. Further research into the interaction of these two factors is needed.

COMMENT: *There has been a long-held association between RSV infections and a higher incidence of asthma. The COAST study has shown us that rhinovirus is in fact the major culprit. This study gives supporting data that RSV infections severe enough to warrant hospitalization do not appear to cause asthma.*
B.E.C.
Thomsen SF, van der Sluis S, Stensballe LG, et al: Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study.
Am J Respir Crit Care Med. 2009;179:1091-1097. ♦♦

Allergic vs Nonallergic Rhinitis and Sleep Apnea

THERE is a recognized association between allergic rhinitis and obstructive sleep apnea syndrome (OSAS). This study compared the effects of allergic and nonallergic rhinitis on OSAS and other sleep disturbances.

Overnight polysomnography was performed in 25 adults with allergic rhinitis and 23 with nonallergic rhinitis. Other assessments included a health-related quality of life questionnaire and the Epworth Sleepiness Scale. In both groups, snoring was the most common sleep symptom. Both groups had frequent arousals, but sleep duration and sleep efficiency were better in patients with allergic rhinitis. A diagnosis of OSAS was made in 83% of patients with nonallergic rhinitis, compared to 36% of those with allergic rhinitis. Severe OSAS was found only in the nonallergic rhinitis group. The two groups had similar impairment in quality of life.

Although both allergic and nonallergic rhinitis are associated with sleep apnea, risk appears higher in patients with nonallergic rhinitis. Sleep quality is an important treatment consideration in patients with rhinitis.

COMMENT: *The role of rhinitis in sleep apnea should be an area of focus for the allergy/immunology community. We should be engaged in research investigating the long-term effect of rhinitis on sleep as well as treatment strategies to reduce the contribution of rhinitis to sleep apnea and/or intolerance to CPAP devices. As the complexity of our patients increase (at least mine are), we need to become experts in the co-morbidities of* ➤➤

allergic and nonallergic airway disease. The train is leaving. . .we better get on board.
D.K.L.
Kalpaklioglu AF, Kavut AB, Ekici M: Allergic and nonallergic rhinitis: the threat for obstructive sleep apnea.
Ann Allergy Asthma Immunol. 2009;103:20-25. ♦♦

Clinical Findings of HAE Caused by Factor XII Mutations

MUTATIONS of the factor XII gene are now known to cause a form of hereditary angioedema (HAE) that occurs mainly in women. The clinical findings of 35 women with HAE caused by factor XII mutations are presented.

The women, with two different factor XII mutations, came from 13 unrelated families. Over an average of 8.4 years, they averaged 12.7 angioedema attacks per year. Swelling occurred in the face in all patients, and less frequently in other locations. Trauma, physical pressure, and emotional stress could all trigger attacks. Symptoms were commonly initiated or worsened by oral contraceptives or pregnancy. C1 inhibitor concentrate was an effective treatment for attacks; progesterone was an effective preventive therapy. There were no clinical differences between the two mutation groups.

The symptoms, triggering factors, and treatment of HAE caused by factor XII mutations are presented. Estrogens appear to have a significant but variable influence on this condition.

COMMENT: *Hereditary angioedema is often caused by C1-INH deficiency. But there is a more-recently described type of HAE caused by defined mutations of the coagulation factor XII (Hageman factor) gene, with normal C1-INH function. The effector molecule is postulated to also be bradykinin, but that is unproven. There is a female predominance in this F-XII type, and estrogen seems to be related to the pathogenesis. The treatments for this type of HAE seem to be the same as for C1-INH deficiency.*
R.J.M.
Bork K, Wulff K, Hardt J, et al: Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy.
J Allergy Clin Immunol. 2009;124:129-134. ♦♦

CITATIONS OF NOTE

COMMENT: This paper provides a succinct overview of the issues related to flu pandemics in general and H1N1 in particular. It may be useful in providing advice this fall.
D.K.L.
Stein RA: Lessons from outbreaks of H1N1 influenza.
Ann Intern Med. 2009;151:59-62. ♦♦

COMMENT: It seems like there have been more patients needing oral food challenges in the office in recent years. This report by the AAAAI workgroup helps to standardize the procedure.
S.M.F.
Nowak-Wegrzyn A, Assa'ad AH, Bahna S, et al: Work Group report: Oral food challenge testing.
J Allergy Clin Immunol. 2009;123:S365-S383. ♦♦

REVIEWS OF NOTE:

COMMENT: *This excellent review summarizes data regarding the role of eosinophils and neutrophils in asthma pathophysiology.*
B.E.C.
Fahy JV: Eosinophilic and neutrophilic inflammation in asthma: insights from clinical studies.
Proc Am Thorac Surg. 2009;6:256-259. ♦♦

COMMENT: *Filaggrin gene defects may represent the new frontier when it comes to allergic sensitization and subsequent development of allergic phenotypic conditions. This meta-analysis strongly implicates filaggrin gene defects in atopic dermatitis. In fact, the authors suggest that future investigation of this association in this condition is unnecessary. However, studies will be needed to characterize the association of filaggrin gene defects and respiratory allergic conditions. Interventions to decrease skin sensitization or barrier repair will be important for treatment of prevention of atopic dermatitis and possibly asthma, allergic rhinitis, food allergy, and anaphylaxis. Read: all conditions that allergists treat.*
S.F.W.
van den Oord RAHM, Sheikh A: Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis.
BMJ. 2009;339;b2433. ♦♦