AllergyWatch®

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

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H1N1 Vaccine Is Safe for Egg-Allergic Children

THE H1N1 pandemic has led to renewed debate over the safety of influenza vaccination in patients with egg allergy. Recent studies have shown that trivalent influenza vaccine can safely be given to egg-allergic with skin testing and/or graded dose challenge. This study assessed the safety of H1N1 vaccine in children with egg allergy, including those with past anaphylactic reaction to egg.

The prospective trial included 105 children with egg allergy, mean age 5.5 years, and 19 nonallergic controls. Nearly one-fourth of the egg-allergic children had a history of anaphylaxis. Both groups underwent dilute and full-strength skin prick skin testing; if the results were negative, intradermal skin testing was performed. Patients with any positive skin test underwent graded challenge, with a 10% dose followed by the remaining 90% dose 30 minutes later. If indicated, a single booster dose was given from a different vaccine lot, without skin testing.

The overall rate of positive skin test results was 2.4% on skin prick testing and 33.1% on intradermal testing, including 1 child in the control group. The odds of a positive result on intradermal testing increased along with the vaccine ovalbumin content: 1.05 per 0.01 µg/mL increase. Forty-one children proceeded to graded vaccine challenge, including 13 of the 25 patients with a history of anaphylaxis. There were no allergic reactions to graded or standard vaccine administration. All children who underwent graded challenge--including 7 of those with a history of anaphylaxis--tolerated a subsequent single dose booster dose from a different, untested vaccine lot.

The results support the safety of H1N1 vaccination for children with a history of egg allergy, including those with a history of anaphylactic reactions. The authors believe that H1N1 vaccine can be given to egg-allergic children, with no need for skin testing or graded ➤➤

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- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
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- European Respiratory Journal
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challenge. They call for similar studies using the 2010 combination influenza vaccine.

COMMENT: *Although we no longer vaccinate with H1N1 separately, this is another piece of evidence supporting the safety of influenza vaccination for individuals with history of egg allergy, including those with a history of anaphylaxis. This is helpful, but I still have concerns: the package insert states administration is contraindicated, the* Red Book *has not yet changed its admonition, and the authors acknowledge these findings need confirmation in a larger population. In a litigious society, I personally feel that performing a skin test and graded challenge offers some evidence--albeit flimsy--that I am taking extra precautions to protect the recipient, just in case something unforeseen happens. We should encourage the flu vaccine even for patients with egg allergy.*
D.K.L.
Greenhawt MJ, Chernin AS, Howe L, et al: The safety of the H1N1 influenza A vaccine in egg allergic individuals.
Ann Allergy Asthma Immunol. 2010;105:387-393. ♦♦

Dose Adjustments in SCIT--Are They Safe?

THERE are several situations in which dose adjustments are recommended to reduce the risk of systemic reactions (SRs) for patients undergoing subcutaneous immunotherapy (SCIT), These include late injections, newly mixed vials after refills, and previous SR. However, the evidence basis for these recommendations is limited. A 4-year experience was reviewed to analyze the safety of one allergy clinic's dose adjustment protocol.

From 2005 to 2009, the authors' allergy department (located at a military medical center) followed a standard approach to dose adjustment in patients undergoing SCIT. The dose was adjusted for patients with late reactions, one dose for each week late, beginning after 2 weeks; newly mixed vials, a 50% dose reduction; or after SR, a 10-fold dilution. The rate of SRs immediately after dose adjustment was analyzed; the study included a total of 12,895 doses.

Dose adjustment was more common for male patients, odds ratio (OR) 1.15; for children, OR 1.19; and for maintenance-phase injections, OR 2.14 compared to late injections. The rate of dose adjustments was particularly high for maintenance-phase injections from newly mixed vials: OR 10.78. The frequency of SRs, and thus of post-SR dose adjustments, was twice as high in children and for buildup-stage doses.

A total of 82 SRs occurred in 66 patients, for a rate of 15.9% per patient and 0.64% per injection. In none of the three dose-adjustment scenarios was there any increase in the risk of subsequent SR.

The results identify several situations in which dose adjustments are more likely to be needed in patients receiving SCIT. Using the dose-adjustment protocol followed at the authors' center, there is no increase in the risk of subsequent SR. Prospective studies are needed to confirm the safety of a more standardized approach to dose adjustment.

COMMENT: *The lack of evidence-based guidelines for what we do encourages efforts to develop evidence. This retrospective review of almost 13,000 allergy injections confirms the recommendations to reduce the dose with freshly prepared vials of vaccine in patients with a previous systemic reaction, and to delay administration of the subsequent dose. With dose reduction, no subsequent serious adverse events occurred. Controlled trial data are desirable, but these retrospective data are helpful.*
D.K.L.
Webber CM, Calabria CW: Assessing the safety of subcutaneous immunotherapy dose adjustments.
Ann Allergy Asthma Immunol. 2010;105:369-375. ♦♦

'Patient-Friendly' Approach to Oral Immunotherapy for Milk Allergy

COW'S milk allergy (CMA) is a very common clinical condition in children, and one that can be difficult to manage. Oral desensitization approaches have been reported, but are considered impractical. The authors analyzed a more "patient-friendly" approach to oral immunotherapy for CMA.

The randomized controlled trial included 30 children with IgE-mediated CMA, confirmed by double-blind placebo-controlled food challenge. Patients were randomly assigned to desensitization using cow's milk or, as a control, soy milk. Oral immunotherapy consisted up weekly up-dosing, targeting an oral intake of 200 mL of milk at 18 weeks. Reactions were evaluated after each dose; desensitization was stopped if the patient experienced a severe reaction. Cow's milk-specific IgE and IgG4 levels were measured at baseline, 8 weeks, and 18 weeks.

There were 2 dropouts in the cow's milk group and 1 in the control group, none related to reactions. Of 13 study completers in the cow's milk group, 10 achieved full tolerance of 200 mL of cow's milk, while 1 additional patient achieved partial tolerance. Two patients in the cow's milk group dropped out because of severe reactions. A significant increase in specific IgG4 levels was observed in the cow's milk group but not the soy milk group.

With close medical supervision, this oral immunotherapy protocol appears "effective and relatively safe" for children with CMA. Consistent immunologic changes are achieved using this approach. Further studies will be needed to assess the permanence of desensitization.

COMMENT: *The oral immunotherapy drumbeat continues, getting louder with time. This small study demonstrates the benefits of oral immunotherapy for milk allergy using a practical protocol. Although the results are positive, the size of the study groups limits the generalizability of the results or the confidence in the findings. I would be very cautious about jumping aboard the bandwagon because of the potential risk of anaphylaxis early or late in treatment. Finally, sublingual or oral immunotherapy may aggravate or cause eosinophilic gastrointestinal disease, including eosinophilic esophagitis.*
D.K.L.

Pajno GB, Caminiti L, Ruggeri P, et al: Oral immunotherapy for cowís milk, allergy with a weekly up-dosing regimen: a randomized singled blind controlled study.
Ann Allergy Asthma Immunol. 2010;105:376-381. ♦♦

There's Something Special about *Alternaria*

ALLERGIC sensitization to *Alternaria* is common, but it can be difficult to establish a causal relationship between exposure to *Alternaria* spores and the occurrence of asthma symptoms. The diagnostic efficiency of *Alternaria* skin testing and serum-specific IgE to *Alternaria* were evaluated, compared to bronchial-specific *Alternaria* challenge.

Bronchial challenge with an *Alternaria alternata* allergenic extract was performed in 74 asthmatic patients with *Alternaria* sensitization. Patients also underwent skin testing and specific IgE measurement. The results were analyzed by receiver operating characteristic (ROC) curve analysis; sensitivity, specificity, and positive and negative predictive values were determined for different cutoff points.

The results of bronchial *Alternaria* challenge were positive in 61% of patients. The skin-prick test results predicted the results of bronchial challenge "almost perfectly"--area under the ROC curve was 0.957. In contrast, intradermal testing had only moderate efficacy, with an area under the ROC curve of 0.777 to 0.782.

The probability of positive bronchial challenge was only 4% in patients with a negative skin-prick result, compared to 90% for those with a wheal diameter of 5.5 mm. Serum-specific IgE measurement correctly classified 86% of patient responses to bronchial challenge. Accuracy in predicting a positive bronchial challenge result was 99% at a CAP value of 16 kU_A/L or greater versus 33% at values under 0.35 kU_A/L.

Asthmatic patients with positive results on *Alternaria* skin-prick testing are highly like to have a positive response to bronchial-specific challenge. Patients with *Alternaria*-related asthma should be educated about high-risk situations, environmental control measures, and the need to follow prescribed medications. Immunotherapy may be a valid treatment option.

COMMENT: *It is well-accepted that a patient with seasonal respiratory symptoms and positive skin tests to corresponding pollens very likely has pollen-induced allergic disease. In contrast, correlating mold sensitization, exposure, and allergic respiratory symptoms has been problematic. Part of the problem is the polymorphic life cycle of many molds, geographic variation in the existence of a "mold spore season," and the fact that molds may also elicit symptoms via irritant mechanisms. This impressive study found that a 5.5 mm skin test wheal correlated with a 90% probability of positive* Alternaria *bronchial challenge, while a negative* Alternaria *skin test had only 4% probability of a positive challenge.* Alternaria *sensitization is therefore very likely relevant in asthmatic patients exposed to significant levels of* Alternaria *spores.*
S.A.T.

Fernández C, Bevilacqua E, Fernández N: Asthma related to Alternaria *sensitization: an analysis of skin-test and serum-specific IgE efficiency based on the bronchial provocation test.*
Clin Exp Allergy. 2010; DOI: 10.1111/j.1365-2222.2010.03645.x ♦♦

Atopic March or Atopic Scramble?

EARLY childhood eczema is commonly believed to go into remission in most patients. Epidemiologic studies suggest that eczema is more prevalent in boys during childhood, but in girls after puberty. Data from a birth cohort study were used to analyze trends in the prevalence of eczema from infancy through adolescence.

The researchers analyzed long-term follow-up data on 1,456 children enrolled in the 1989 Isle of Wight birth cohort. Detailed information on eczema was collected at age 1, 2, 4, 10, and 18 years; the children underwent skin prick testing at age 4, 10, and 18 years. Age- and sex-specific differences in atopic and nonatopic eczema were assessed.

From infancy through adolescence, the point prevalence of eczema showed little change, with a range of 11.9% to 14.2%. There was no sex difference in prevalence from infancy up to age 10. However, between 10 and 18 years, eczema prevalence was higher in girls: 16.3% versus 8.3%. This reflected a higher positive transition rate in girls, 9.4% versus 4.3%; along with a higher negative transition rate in boys, 65.4% versus 50%. The difference in positive transition in girls was greatest for nonatopic asthma: 5.9% versus 1.5%.

In this long-term follow-up study, the prevalence of eczema shows only a small decline from childhood to adolescence. Girls are more likely to develop eczema during adolescence, whereas boys are more likely to outgrow it. More research is needed to understand the gender-specific factors affecting the development or remission of eczema after puberty.

COMMENT: *The concept of the "atopic march" creates an image of the orderly progression from eczema in early childhood to inhalant allergen respiratory diseases such as rhinitis and asthma. In this model, eczema is merely a temporary nuisance in early childhood. In this study, the authors analyzed data from the Isle of Wight Study, which has carefully followed a 1989 English birth cohort. In fact, there was only minimal reduction in the prevalence of eczema between childhood and adolescence. Much of this was due to new-onset "nonatopic" eczema in girls.*
S.A.T.
Ziyab AH, Raza A, Karmaus W, et al: Trends in eczema in the first 18 years of life: results from the Isle of Wight 1989 birth cohort study.
Clin Exp Allergy. 2010;40:1776-1784. ♦♦

The 'United Airway': Remodeling of the Nasal Mucosa in Allergic Rhinitis

FEW studies have examined the structural changes associated with upper airway remodeling in allergic rhinitis, compared to asthma. Organ tissue remodeling in other inflammatory diseases has been linked to expression of small leucine-rich repeat proteoglycans, collagen, and lymphangiogenesis. These characteristics were compared in mild and severe persistent allergic rhinitis vs healthy controls.

The study included nasal mucosa samples from 30 patients with mild persistent allergic rhinitis, 30 with severe persistent allergic rhinitis, and 30 healthy controls. The three groups were compared for expression and distribution of collagen; the small-proteoglycan families decorin, biglycan, and lumican; and lymphatic vessels. Expression of matrix metalloprotein (MMP) 2 and 9 and tissue inhibitors of metalloproteinases (TIMP) 1 and 2 were evaluated as well.

Specimens from patients with severe persistent allergic rhinitis showed more intense collagen staining in the superficial and submucosal layers, compared to mild cases or healthy controls. All groups showed light staining of decorin, with similar percentage areas and optical density of staining. In contrast, both allergic rhinitis groups showed strong immunoreactivity for lumican and biglycan, verified by Western blotting. The number and endothelial length density of lymphatic vessels was also increased in the allergic rhinitis groups, compared with controls. Severe allergic rhinitis specimens showed increased expression of MMP 9.

The results show alterations in the distribution of collagen, proteoglycans, and lymphatic vessels in the nasal mucosa of patients with persistent allergic rhinitis, with significant differences between mild and severe cases. These findings could modulate the mucosal remodeling and accelerated nasal obstruction seen in patients with allergic rhinitis.

COMMENT: *Following up on observations that chronic perennial allergic rhinitis has the potential to result in irreversible nasal obstruction, these authors examined the extracellular matrix composition in nasal mucosa. They found distinct differences between normal controls and patients with allergic rhinitis, including significant deposition of proteoglycans and collagen. Possible pathophysiologic mechanisms are discussed.*
S.A.T.
Kim TH, Lee JY, Lee SH, et al: Remodelling of nasal mucosa in mild and severe persistent allergic rhinitis with special reference to the distribution of collagen, proteoglycans, and lymphatic vessels.
Clin Exp Allergy. 2010;40:1742-1754. ♦♦

Want to Avoid Allergies? Grow Up on a Farm!

PREVIOUS studies have documented a lower prevalence of allergic disease among farmers and their offspring. There is some evidence that this protective effect persists into adulthood, but it's unclear if that applies to subjects who spend their childhood on a farm but later move to urban areas. This issue was addressed in a large survey study.

A respiratory health questionnaire was mailed to a random sample of adults, aged 16 to 75, in West Sweden. The effects of being raised on a farm (through age 5) and degree of urbanization (from small town to major city) on the prevalence of allergic rhinitis were assessed. The analysis was adjusted for family history, smoking, ➤➤

and occupational exposures, among other factors.

The survey response rate was 62%. Across age strata, participants who were raised on a farm had a lower prevalence of allergic rhinitis. The strength of the association was similar for younger and older respondents: odds ratio 0.82 for those aged 46 to 75 and 0.78 for those aged 16 to 45. Rates of allergic rhinitis tended to increase with degree of urbanization, independent of being raised on a farm.

Spending childhood on a farm is associated with a lasting reduction in allergic disease risk, even among those who move to cities later in life. Allergic rhinitis risk increases with degree of urbanization, regardless of farm vs non-farm upbringing. The latter finding highlights the role of both childhood and adult exposures on allergic disease risk.

COMMENT: *It is well known that children living on a farm are less likely to develop allergic rhinitis. In this study the prevalence of allergic rhinitis was lower among urbanized adults who spent their childhoods on farms. This suggests that the protective effect of living on a farm in childhood is permanent.*
S.A.T.

Eriksson J, Ekerljung L, Lötvall J, et al: Growing up on a farm leads to lifelong protection against allergic rhinitis.
Allergy. 2010;65:1397-1403. ♦♦

Trends in Status Asthmaticus: A Mixed Picture

STATUS asthmaticus accounts for much of the morbidity and mortality from asthma, but relatively little is known about its epidemiology. Children with severe asthma are commonly admitted to community hospitals, many of which lack pediatric subspecialists and advanced pediatric care. Fifteen-year data from New Jersey were used to analyze trends in the epidemiology of pediatric status asthmaticus.

The study used an administrative database including information on all status asthmaticus hospitalizations in New Jersey in 1992, 1995, and 1999 to 2006. A total of 28,309 admissions for status asthmaticus in children were identified, representing 22.8% of all pediatric asthma hospitalizations. Changes over time in the hospitalization characteristics of children with status asthmaticus were analyzed, including comparison of patients admitted to hospitals with and without pediatric intensive care units (PICUs).

The rate of pediatric admissions for status asthmaticus decreased by half during the period studied: from 1.98 per 1,000 children in 1992 to 0.93 per 1,000 in 2006. This trend was accompanied by a 70% reduction in the number of children admitted to adult hospitals. At the same time, there was a threefold increase in the rate of ICU care among children admitted to PICU hospitals. The result was a sharp increase in the costs of pediatric status asthmaticus hospitalizations: from $6.6 million in 1992 to $9.5 million in 2006. There was no significant change in the use of mechanical ventilation or in mortality rate.

The results show a decrease in the number of children hospitalized for status asthmaticus, but an increase in the percentage of patients admitted to PICUs. The increased rate of PICU care has led to a significant rise in the costs of hospital care for this diagnosis. The authors call for further study to find out how decisions about hospital care for pediatric status asthmaticus are made, and how those decisions affect patient outcomes.

COMMENT: *What has actually happened with admissions for severe asthma exacerbations in the past 15 years? The authors selected New Jersey, a state with both large urban and rural populations, and had access to a reasonable dataset. While there are some limitations to these data, results suggest that urban - dwelling children admitted to hospitals with PICUs are much more likely to require ICU care than their rural counterparts, in non-PICU hospitals. What this means is not exactly clear. Thankfully, admissions over time were significantly reduced, but cost increases for PICU stays exceeded any savings yielded by the lowered overall admission rates.*
K.R.M.

Hartman ME, Linde-Zwirble WT, Angus DC, et al: Trends in admission for pediatric status asthmaticus in New Jersey over a 15-year period.
Pediatrics. 2010;126:e904-e911. ♦♦

Primary Care Use of Office Spirometry

SPIROMETRY is regarded as an important test for the diagnosis and clinical monitoring of asthma. However, few primary care physicians use spirometry to aid in the management of childhood asthma. Pediatricians and family physicians were surveyed regarding their use of spirometry, including knowledge, attitudes, and perceived barriers.

A questionnaire was mailed to a random national sample of office-based pediatricians and family physicians. The physicians were asked about their use of spirometry and peak flow meters, as well as attitudes and perceived barriers to spirometry use. The survey included a clinical vignette to assess spirometry's effects on physician recognition of asthma and the choice of treatments. Responses were received from 210 pediatricians and 150 family physicians who treated children with asthma.

Fifty-two percent of respondents said they used spirometry in clinical practice: 75% of family physicians versus 35% of pediatricians. Use of peak flow meters was 87% and 76%, respectively. Just 35% of the physicians felt comfortable in interpreting spirometric results, whereas 79% were comfortable interpreting peak flow readings. Three-fourths of respondents agreed that spirometry is the more useful test for classifying asthma severity. Only about half of physicians correctly interpreted the spirometric results as showing "moderate obstruction" in the clinical vignette. About two-thirds correctly rated asthma severity as "moderate persistent," and most chose the correct treatment.

The results show significant shortcomings in the ➤➤

use of spirometry by primary care physicians who treat children with asthma--especially pediatricians. If the use of spirometry is to be increased in accordance with current guidelines, major training initiatives will be needed.

COMMENT: *A pediatric practice in my area recently started doing spirometry assessment to supplement peak flow monitoring in their office. On the whole, this has been a positive development. However, there have been some "interpretation challenges" created by improper assessment of patient technique, unfamiliarity with pulmonary function test parameters, and related issues yielding erroneous conclusions.*

As allergist/immunologists, we are uniquely poised to offer guidance to our primary care colleagues performing spirometry, whose assessments should be considered an adjunct *to cost-effective, routine specialty care. Therefore, it is of concern that this insurance-sponsored study neglects to mention such specialty care.*

K.R.M.

Dombkowski KJ, Hassan F, Wasilevich EA, Clark SJ: Spirometry use among pediatric primary care physicians.

Pediatrics. 2010;126:682-687. ♦♦

Burden of Influenza Hospitalization in the US

ESTIMATED hospitalization rates for influenza among U.S. children vary widely. This information has important implications for prevention and treatment programs. Data from the Center for Disease Control and Prevention's Emerging Infections Program Network were used to evaluate rates of hospitalization for seasonal influenza in children from 2003 to 2008.

The researchers analyzed population-based surveillance data covering 5.3 million children in 10 states. Rates of hospitalization for laboratory-confirmed influenza among patients younger than age 18 were estimated over five consecutive influenza seasons. Data on the children's demographic characteristics, medical history, and clinical course were collected from hospital records. Incidence rates were calculated using Census data.

The rate of influenza hospitalization was highest among infants less than 6 months old, with a seasonal range of 9 to 30 per 10,000 children. The rate was lowest for those aged 5 to 17 years, with a range of 0.3 to 0.8 per 10,000. Of 4,015 cases identified by the surveillance system, 58% were diagnosed by rapid diagnostic testing alone. Overall, 40% of the children had underlying medical conditions: asthma in 18%, prematurity in 15% of children less than 2 years old, and developmental delay in 7%.

Twelve percent of children were admitted to the ICU, 5% developed respiratory failure, and 2% had bacterial coinfection. The mortality rate was 0.5%. For infants with confirmed influenza within 48 hours of symptom onset, the rate of treatment with antiviral medications ranged from 37% to 48%.

The results show substantial variations in the rate of influenza hospitalization among U.S. children, by age and by season. Because many children are not tested, the true rate of seasonal influenza is likely even higher. More accurate assessment of disease burden will require further data on the rates of influenza hospitalization and severe outcomes.

COMMENT: *Who among the pediatric population is most frequently hospitalized with seasonal influenza? And which underlying diseases confer greatest risk? This retrospective survey assesses the available data, and the results are not terribly surprising. More concerning is how few of those hospitalized for influenza received antiviral therapy, even in lab-confirmed cases.*

Flu vaccination rates remain low in the pediatric population, regardless of underlying disease. Room for substantial improvement remains, in both prevention and therapy.

K.R.M.

Dawood FS, Fiore A, Kamimoto L, et al: Burden of seasonal influenza hospitalization in children, United States, 2003 to 2008.

J Pediatrics. 2010;157:808-814. ♦♦

Delaying Egg Exposure May Increase Allergy Risk

IT'S still unknown why the rates of serious food allergies in children are increasing. Despite sparse data, delayed introduction of solid foods is commonly recommended to prevent food allergies in high-risk infants. The effectiveness of delaying egg introduction in preventing egg allergy as evaluated in a population-based study.

The analysis included 2,589 Australian infants, aged 11 to 15 months, enrolled in the "HealthNuts" study of pediatric food allergy. Parents provided data on feeding history and potential confounding factors. Skin prick testing for egg white was then performed, with an oral egg challenge offered to sensitized infants. The effects of duration of breast-feeding and age at introduction of solid foods on the rate of confirmed egg allergy were assessed.

Egg allergy was confirmed in 231 infants. Later introduction of egg was associated with an increased risk of egg allergy: compared to infants introduced to eggs at 4 to 6 months, adjusted odds ratios (ORs) were 1.6 for introduction at 10 to 12 months and 3.4 for introduction after 12 months. The association remained significant even among children without other risk factors: OR 3.3 for introduction at 10 to 12 months. Among infants introduced to egg at 4 to 6 months, the risk of allergy was lower for those who were first exposed to cooked egg, compared to egg in baked goods. Egg allergy was unrelated to duration of breast-feeding or age at introduction of solid foods.

Delayed introduction of egg may actually increase the rate of egg allergy in high-risk children. Risk appears lower for children introduced to egg at age 4 to 6 months, compared with 10 to 12 months or later. If confirmed, the findings may have important implications for infant feeding guidelines to reduce the risk of food allergy. ➤➤

COMMENT: *It has been suggested that the delayed introduction of certain allergenic foods may be contributing to the increasing prevalence of food allergy in children. These Australian researchers report that infants who were introduced to egg after 12 months of age were three times more likely to have proven egg allergy at 14 to 18 months compared to those introduced to egg at 4 to 6 months. Interestingly, there was no correlation with either introduction of solid foods or duration of breast-feeding. The paradigm suggesting delayed introduction of allergenic foods to prevent food allergies appears to be shifting.*
S.M.F.

Koplin JJ, Osborne NJ, Wake M, et al: Can early introduction of egg prevent egg allergy in infants? A population-based study.
J Allergy Clin Immunol. 2010;126:807-813. ♦♦

Mite Allergoid SCIT Has Steroid-Sparing Effect in Children with Asthma

THE goal of management for persistent childhood asthma is to achieve disease control at the lowest effective dose of inhaled corticosteroid. Various steroid-sparing approaches have been investigated, but few have examined the possibility of using subcutaneous immunotherapy (SCIT) as "add-on" therapy for asthma. As part of a randomized trial, the effects of SCIT on steroid dose were evaluated in children with asthma and allergy to house dust mite.

The analysis included 65 children with asthma, aged 6 to 17 years, receiving Global Initiative for Asthma treatment levels II and III. During a 5-month baseline period, all achieved good asthma control with inhaled corticosteroids. One group was then assigned to receive 2 years of SCIT using a new high-dose hypoallergenic mite preparation (allergoid), plus fluticasone propionate (FP). Controls received FP only.

During the 2 subsequent winters, the patients underwent steroid dose adjustment according to a predefined protocol. The steroid-sparing effect of SCIT was assessed by between-group comparison of the change in FP dosage and the lowest effective FP dose. Immunologic and functional parameters were compared as well.

The SCIT group had significantly more step reductions in FP dose than the control group. Mean daily dose decreased from 330.3 µg at baseline to 151.5 µg after 2 years on treatment in the SCIT group. In controls, dose decreased from 290.6 to 206.3 µg. The SCIT group also had an improvement in morning peak expiratory flow and increased levels of mite-specific IgG_1 and IgG_4.

The addition of mite allergoid SCIT has a significant steroid-sparing effect in children with asthma and mite allergy. This form of add-on therapy may yield a reduction in FP dose while maintain good asthma control. Ongoing follow-up will determine how well the benefit of SCIT is maintained after the end of treatment.

COMMENT: *A subset of children in the GOAL trial received mite allergoid SCIT for 2 years in addition to their usual ICS fluticasone treatment. Those receiving SCIT benefited with a sustained reduction of their dose of ICS while maintaining guideline-defined asthma control. Therefore SCIT had an impressive steroid-sparing effect for these allergic children with persistent asthma. Parents with steroid-phobia should understand that SCIT has impressive benefits, including steroid-sparing effects that can benefit children with allergic asthma.*
S.M.F.

Zielen S, Kardos P, Madonini E: Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial.
J Allergy Clin Immunol. 2010;126:942-949. ♦♦

Simple Checklist Assesses Exacerbation Risk in Children with Asthma

EXACERBATIONS are a major source of asthma-related morbidity and costs. A reliable tool for identifying asthmatic children at high risk of exacerbations would be useful in primary care. This paper reports the development and validation of a predictive score for asthma exacerbations in children.

Data from a cross-sectional study of Costa Rican children with asthma were analyzed to identify risk factors for exacerbations, defined as any hospitalization, urgent visit, or course of systemic steroid therapy for asthma. Based on the findings, the investigators created a 17-item checklist addressing asthma symptoms, medications, health care services, and history. The checklist was validated using the Costa Rican data, and externally validated using North American data from the Childhood Asthma Management Program.

The Asthma Exacerbation Clinical Score identified groups of children at low risk and high risk of exacerbations: odds ratio 0.2 versus 5.4. Cutoff scores on the 17-item questionnaire were 5 or lower for high-risk and 9 or higher for high-risk. In the external validation dataset, hazard ratios for exacerbation at 1-year follow-up were 0.6 and 1.9, respectively. A similar pattern of results was observed at 2 years. The strongest risk factors for exacerbation were number of physician visits for asthma and number of oral steroid courses in the previous year.

This checklist provides a simple and effective tool for assessing the risk of exacerbations in children with asthma. Consisting of readily assessed clinical factors, the Asthma Exacerbation Clinical Score is well-suited for use in primary care settings. After further validation, the checklist could be evaluated for use in guiding or adjusting asthma treatment.

COMMENT: *The authors validate a simple 17-item checklist to predict exacerbations in Hispanic children. No spirometry or laboratory items were included in this clinical score, and as such it is meant for primary care predominantly. Nevertheless, to generalize, frequent physician visits and steroid bursts are important markers for future exacerbations. This seems obvious to specialists, but one primary care colleague was debating whether to send his pediatric patient after one more steroid burst--his eighth of the year--which, accord-*➤➤

ing to these data, was sure to come sooner rather than later. This predictive score would therefore be helpful. S.F.W.

Forno E, Fuhlbrigge A, Soto-Quirós ME, et al: Risk factors and predictive clinical scores for asthma exacerbations in childhood.

Chest. 2010;138;1156-1165. ♦♦

Visual Feedback May Improve Value of Peak Flow Monitoring

PEAK flow monitoring is commonly used as part of the asthma treatment plan, but reports of its efficacy in promoting disease control are variable. This monitoring technique is useful only to the extent that it can be used by the patient and clinicians to promptly identify worsening asthma and implement early interventions. A new approach to providing visual feedback on the results of peak flow monitoring was evaluated in patients with asthma and their primary care providers.

The CUE intervention provided a standardized visual interpretation of peak flow data for asthma patients and their clinicians. Feedback included color-coded data on peak flow trends: green, "doing well"; yellow, "caution"; and red, "danger." The goal was to cue communications between patients and clinicians, with the goal of controlling asthma and improving outcomes.

In a cluster randomized trial, 139 adults with persistent asthma received either the CUE intervention (68 patients seen by 22 clinicians) or usual care, ie, clinician monitoring (71 patients seen by 21 clinicians). Asthma control outcomes were assessed over 1 year of monitoring, with adjustment for seasonal variations in exacerbation frequency.

Mean log-transformed adherence to prescribed inhaled corticosteroid (ICS) therapy was not significantly different between the intervention and control groups, although the CUE group showed a trend toward improved adherence over time. Visual feedback was associated with a reduction in oral steroid courses during both winter, 9% versus 23%; and spring, 3% versus 17%. During the winter, patients assigned to the CUE intervention had fewer periods of symptom worsening, 65% versus 89%; and fewer urgent care visits, 10% versus 23%. Post hoc analysis suggested that these benefits were related to improved ICS adherence during the winter in the CUE group. The intervention was also associated with a consistent reduction in day-to-day peak flow variability--from 32% to 23%--suggesting reduced airway reactivity.

For asthma patients using peak flow monitoring, visual feedback provided by the CUE intervention appears to improve asthma control outcomes during the period of highest risk: ie, cold/flu season. The results are consistent with improved ICS adherence, leading to reduced need for oral prednisone and fewer periods of worsening asthma symptoms.

COMMENT: *Peak flow meters are distributed quite freely to asthmatic patients. All too frequently, they are relegated to the garage or storage closet, or left in the previous house. Patients receive little positive feedback for their efforts. Using a color-coded printout, patients in this study responded with fewer seasonal exacerbations, although compliance was not improved. Half (or quarter of) a loaf, or just using peak flow meters seasonally, may be all we can expect or need our patients to do.*

S.F.W.

Janson SL, McGrath KW, Covington, JK, et al: Objective airway monitoring improves asthma control in the cold and flu season: a cluster randomized trial.

Chest. 2010;138;1148-1155. ♦♦

Four Years of SLIT Provide Eight Years of Benefit

SUBLINGUAL immunotherapy (SLIT) has emerged as a new treatment option for patients with respiratory allergies. However, there are still many questions about its clinical use, including the optimal duration of treatment and the long-term persistence of the treatment effects. These issues were addressed using 15-year follow-up data on patients enrolled in a randomized trial of SLIT.

The study included four groups of mite-allergic patients, originally enrolled in 1992. Forty-seven patients were assigned to SLIT, with treatment durations of 3, 4, or 5 years. A control group of 12 patients received drug therapy alone, without SLIT. Outcomes were evaluated each winter, including clinical scores, skin test results, methacholine reactivity, and nasal eosinophil counts. The effect of SLIT was considered to persist as long as clinical scores remained at less than 50% of baseline.

By this definition, the clinical effect of SLIT persisted for 7 years in patients assigned to 3 years of treatment, and 8 years in those receiving 4 or 5 years of SLIT. Controls had no significant change in clinical scores and continued to develop new skin sensitizations during follow-up. In contrast, the rate of new sensitizations was significantly lower in patients assigned to SLIT: 21% in the 3-year group, 11% in the 4-year group, and 11% in the 5-year group.

After the clinical effect faded, patients received another course of SLIT. This second course also yielded a significant benefit, which appeared faster than the initial benefit. The SLIT groups also had reductions in bronchial hyperreactivity and nasal eosinophil count.

Depending on the duration of treatment, the clinical benefits of SLIT last for 7 or 8 years, this long-term follow-up study suggests. Based on the results, the authors suggest that 4 years is the optimal duration of SLIT. After the effect wears off, a second course of SLIT provides an even more rapid benefit.

COMMENT: *Does SLIT really have a sustained effect? These Italian researchers followed monosensitized patients with respiratory allergies to dust mites for over 15 years. The SLIT treatment regimens lasted 3, 4, or 5 years, with outcomes compared to an untreated control group. Besides significant improvement in symptoms, the treated groups all had impressive* ➤➤

improvements in sustained clinical benefit and reduced local inflammation.

The results were more impressive in the groups treated for 4 and 5 years compared to those only treated for 3 years, leading the authors to conclude that a 4-year SLIT treatment duration is optimal. One of the most interesting findings is that, regardless of the duration of SLIT, there was an impressive sustained reduction of new antigen sensitivities developing compared to controls. This suggests that SLIT is not only effective but is also disease-modifying and potentially helps prevent new allergies from developing.

S.M.F.

Marogna M, Spadolini I, Massolo A, et al: Long-lasting effects of sublingual immunotherapy according to its duration: a 15 year prospective study.

J Allergy Clin Immunol. 2010;126:969-975. ♦♦

For Asthma Diagnosis, Mannitol Is More Specific ...

SOME studies have suggested that airway hyperresponsiveness (AHR) to mannitol may be more specific for the diagnosis of asthma than AHR to methacholine. Mannitol AHR may also be a better indicator of airway inflammation. This study assessed mannitol and methacholine AHR in subjects with and without asthma, including comparison with exhaled nitric oxide levels.

The study included 238 Danish young adults, randomly selected from the nationwide civil registration list. Of these, 51 had current asthma. All subjects underwent determination of mannitol and methacholine AHR, as well as exhaled nitric oxide. The diagnostic performance of the two AHR measurements was compared, along with their association with exhaled NO.

Of the two AHR tests, mannitol had greater specificity than methacholine: 98.4% vs 80.2%. Positive predictive values were 90.4% versus 48.6%, respectively. However, sensitivity was 58.8% with mannitol versus 68.6% with methacholine. In patients with asthma, mannitol AHR was significantly associated with eNO: median values were 47 ppb for patients with a positive AHR to mannitol vs 19 ppb for those in whom this test was negative. In contrast, eNO was not significantly different for patients with positive vs negative AHR to methacholine: median 37 and 24 ppb, respectively.

Findings in a random population sample confirm that mannitol AHR is more specific for the diagnosis of asthma than methacholine AHR. However, sensitivity is greater with methacholine. Mannitol AHR is more closely associated with eNO, suggesting that it is a better indicator of airway inflammation in asthma.

COMMENT: *Mannitol for inhalation to evaluate AHR has recently been approved for use by the U.S. Food and Drug Administration. This carefully controlled study demonstrates that, although mannitol is more specific for the diagnosis of asthma, methacholine is still more sensitive. The investigators also found that AHR to mannitol is associated with higher eNO, suggesting that mannitol may be better at detecting ongoing airway inflammation.*

S.M.F.

Sverrild A, Porsbjerg C, Thomsen SF, et al: Airway hyperresponsivelness to mannitol and methacholine and exhaled nitric oxide: a random-sample population study.

J Allergy Clin Immunol. 2010:126:952-958. ♦♦

...But Methacholine Is More Sensitive

TESTING of bronchial hyperreactivity (BHR) to mannitol has been reported to have good specificity for asthma diagnosis. In a research letter, the authors report on the diagnostic performance of mannitol vs methacholine challenge in children with suspected asthma.

Thirty children with current asthma-related symptoms, mean age 10 years, underwent bronchial provocation testing using methacholine on their first clinic visit and using mannitol on subsequent visits. Other evaluations included skin prick testing with common aeroallergens, exhaled nitric oxide measurement, and spirometry.

Ninety percent of the children had a positive response to methacholine, geometric mean PC_{20} 0.92 mg/mL. In contrast, only 43% had positive results on testing with mannitol: the geometric mean provocative dose causing a 15% decrease in FEV_1 (PD15) was 184.5 mg. The results of the two bronchial provocation tests were not significantly correlated with each other.

Bronchial provocation with methacholine appears more sensitive than mannitol in demonstrating BHR in children with current asthma symptoms. However, mannitol challenge may still be useful in clinical monitoring; the authors suggest that the two tests are "complementary but not interchangeable."

COMMENT: *Laboratory diagnosis of BHR, as a hallmark of asthma, has been done most often by inhalation of direct stimulants like methacholine or histamine. Indirect stimuli are those that trigger bronchoconstrictor mediators from mast cells. Exercise is such an indirect stimulus. A new indirect agent, mannitol, has been marketed for clinical use. This study of 30 asthmatic children demonstrated that there was no significant correlation between the results from methacholine and mannitol. Methacholine was much more sensitive than mannitol (90% vs 43%).*

R.J.M.

Andregnette-Roscigno V, Fernández-Nieto M, Garcia Del Potro M, et al: Methacholine is more sensitive than mannitol for evaluation of bronchial hyperresponsiveness in children with asthma (letter).

J Allergy Clin Immunol. 2010;126:869-871. ♦♦

Trial Evaluates MPL-Adjuvanted SLIT

SUBLINGUAL immunotherapy (SLIT) has received widespread attention as a possible alternative to subcutaneous immunotherapy for the treatment of ➤➤

allergic rhinitis and rhinoconjunctivitis, and has been studied in asthma. Published data indicate deficiencies and considerable heterogeneity in both design and data interpretation of SLIT studies. In subcutaneous immunotherapy, the toll-like receptor 4 agonist monophosphoryl lipid A (MPL)--an attenuated form of the lipid A component of the lipopolysaccharide of *Salmonella minnesota*--has been used as an immunologic adjuvant to enhance clinical and immunologic efficacy. A trial of MPL as an adjuvant to grass pollen SLIT is reported.

The European double-blind, placebo-controlled phase I/IIa study included 80 grass pollen-sensitive patients, aged 18 to 65 years, with seasonal allergic rhinitis. Patients were assigned to receive 8 weeks of daily SLIT, with or without MPL; a small control group received placebo. Patients underwent grass allergen nasal challenge tests before dosing and at 4 and 10 weeks; grass pollen-specific IgG and IgE antibodies were measured at baseline and prior to dosing at weeks 2, 3, 4, 5, and 10.

Patients assigned to the highest dose of SLIT containing the highest amount of MPL were most likely to have negative nasal challenge tests at 10 weeks: 47% and 44%, respectively, compared to 20% of the placebo group. They also had earlier increases in specific IgG and lesser increases in IgE than patients in other groups. Adverse events were similar in the SLIT and placebo groups.

This clinical trial supports the safety and possible efficacy of grass pollen SLIT adjuvanted with MPL. The tested SLIT preparations are well tolerated and affect immunologic responses to antigen within 3 weeks after the start of treatment. They also produce significant suppression of nasal challenge responses.

COMMENT: *This trial assessed the effects of adjuvant MPL combined with grass pollen SLIT formulations. There was an excellent safety profile, with possible clinical and immunologic effects apparent after a preseasonal course of only 8 weeks. Limitations include the fact that it was a phase 1 study with low subject numbers and not highly robust statistical data.*
M.F.

Pfaar O, Barth C, Jaschke C et al. Sublingual allergen-specific immunotherapy adjuvanted with monophosphoryl lipid A: a phase I/IIa study.
Int Arch Allergy Immunol. 2011;154:336-344. ♦♦

CLINICAL TIDBITS

How Does Theophylline Reverse Corticosteroid Insensitivity?

PATIENTS with chronic obstructive pulmonary disease (COPD) may develop corticosteroid insensitivity, the mechanism of which involves reduction of the nuclear enzyme histone deacetylase-2 (HDAC2). Low concentrations of theophylline can reportedly restore HDAC2 activity in COPD cells, thus reversing corticosteroid resistance. This study investigated the role of phosphoinositide-3-kinase-δ (PI3K-δ)--which is inhibited by theophylline--in the development of corticosteroid insensitivity.

In vitro, peripheral blood mononuclear cells from COPD patients showed reduced corticosteroid sensitivity, compared to smoking and nonsmoking controls. The nonselective PI3K inhibitor LY294002 and low concentrations of theophylline reversed corticosteroid insensitivity and reduced HDAC2 activity. Theophylline selectively inhibited oxidant-activated PI3K-δ, which was upregulated in samples of peripheral lung tissue from COPD patients. In mice exposed to cigarette smoke, corticosteroid-insensitive lung inflammation was blocked by both theophylline and the selective PI3K-δ inhibitor IC87114.

These experiments suggest that PI3K-δ may be a useful target for reversal of corticosteroid insensitivity in COPD. It may be possible to block oxidative stress-activated PI3K-δ using either theophylline or a selective inhibitor such as IC87114.

COMMENT: *The use of theophylline in COPD and patients with refractory asthma has escalated in recent years. This study helps us understand that HDAC2 upregulation is in part mediated by P13K-δ. This is an important mechanism to reverse steroid insensitivity. This finding may allow modulations of this or similar molecules with more favorable side-effect profiles to achieve the goal of reversing corticosteroid insensitivity in COPD patients and smoking asthmatics.*
B.E.C.

To Y, Ito K, Kizawa Y, et al: Targeting phosphoinositide-3-kinase-δ with theophylline reverses corticosteroid insensitivity in chronic obstructive pulmonary disease.
Am J Respir Crit Care Med. 2010;182:897-904. ♦♦

Beta-Blocker for Asthma?

ALTHOUGH acute administration of beta-blockers can produce acute bronchoconstriction, recent studies have shown that chronic beta-blocker therapy has broad anti-inflammatory effects. This research letter reports on the effects of nadolol, a nonselective β_1- and β_2-blocker, in patients with mild asthma not receiving controller therapy.

All patients received nadolol at escalating doses up to 40 mg/d. After 13 weeks, patients showed reduced airway hyperresponsiveness, with geometric mean PC_{20} of 1.04 at baseline vs 3.61 at the final visit. In addition, salbutamol was able to reverse methacholine-induced bronchoconstriction in all patients receiving chronic nadolol therapy.

Treatment with the inverse agonist nadolol may have benefits for patients with asthma. With confirmatory studies, the results may have important implications for asthma pathophysiology and management.

COMMENT: *Contrary to the predicted effect, therapeutic doses of the nonselective β_1- and β_2-blocker nadolol did not cause adverse effects in a mild asthmatic population receiving no controller therapy. To* ➤➤

the contrary, methacholine PC_{20} improved and β-agonist reversed bronchospasm caused by methacholine. These data suggest that nadolol may be used safely in patients with mild asthma and comorbid conditions requiring therapy.
B.E.C.
Hanania NA, Mannava B, Franklin, AE: Response to salbutamol in patients with mild asthma treated with nadolol.
Eur Respir J. 2010;36:963-965. ♦♦

Want to Lose Weight? Get Lots of Sleep

THERE is evidence that inadequate sleep may modify the neuroendocrine response to reduced food intake, making it more difficult to lose weight by dieting. The effects of sleep restriction on diet-related weight loss were evaluated in a randomized trial.

The crossover trial included 10 overweight nonsmoking adults, mean body mass index 27.4. Subjects underwent two 14-day periods of moderate caloric restriction with shorter (5.5 hours) or longer (8.5 hours) nighttime sleep opportunity. Loss of fat mass and fat-free body mass were compared between periods, along with secondary outcomes.

Mean weight loss as fat was 1.4 kg with 8.5 hours of sleep versus 0.6 kg with 5.5 hours of sleep. Loss of fat-free body mass was 1.5 vs 2.4 kg, respectively. Curtailed sleep time was also associated with enhanced neuroendocrine adaptation to calorie restriction, increased hunger, and reduced fat oxidation.

This experimental trial supports the hypothesis that inadequate sleep makes it more difficult to reduce weight by dieting. This effect may occur via enhanced metabolic, neuroendocrine, and behavioral compensation in response to combined sleep and caloric restriction.

COMMENT: *Obesity is a recognized comorbidity of atopic disease, particularly asthma. Poor sleep patterns are associated with asthma and rhinitis due to compromised breathing during sleep. Thus one potential explanation of the association of obesity and atopic disease is sleep disturbance. I am not sure what we can do other than treat our patients appropriately, but this is something to think about and maybe sleep on.*
D.K.L.
Nedeltcheva AV, Kilkus JM, Imperial J, et al: Insufficient sleep undermines dietary efforts to reduce adiposity.
Ann Intern Med. 2010;153:435-441. ♦♦

Add-on Montelukast May Not Be Helpful in Allergic Rhinitis

ONLY about half of patients with allergic rhinitis have an optimal symptom response to intranasal corticosteroids. This trial evaluated the effects of add-on montelukast therapy for this group of patients.

The randomized, double-blind trial included 54 patients with perennial allergic rhinitis who had incomplete symptom relief after 2 weeks on intranasal fluticasone propionate. One group received montelukast while the other group received placebo, both while continuing intranasal fluticasone. On the Rhinitis Quality of Life Questionnaire, intranasal fluticasone was associated with improvement in almost all domains, compared to baseline. During subsequent add-on therapy with montelukast or placebo, there was no further difference in quality of life, nor for nasal symptom scores.

Adding montelukast to intranasal fluticasone does not improve outcomes for patients with perennial allergic rhinitis. Montelukast is probably not the best choice for patients with residual symptoms despite intranasal steroid.

COMMENT: *I often combine oral leukotriene antagonists with nasal topical corticosteroids in patients with persistent rhinitis, particularly if they have troublesome congestion or cough. My impression is that this works--but this study again shows that our perceptions, beliefs and opinions cannot replace well designed, double-blind studies.*
D.K.L.
Esteitie R, deTineo M, Naclerio RM, Baroody FM: Effect of the addition of montelukast to fluticasone propionate for the treatment of perennial allergic rhinitis.
Ann Allergy Asthma Immunol. 2010;105:155-161. ♦♦

Intranasal Ketorolac for Aspirin Desensitization

ASPIRIN desensitization followed by continuous aspirin therapy is a therapeutic option for patients with aspirin-exacerbated respiratory disease (AERD). Intranasal ketorolac, which can also induce reactions in AERD, was investigated as an alternative agent for aspirin desensitization.

A series of intranasal ketorolac challenges was administered to 100 patients with suspected AERD. This was followed by oral aspirin administration as part of the challenge and desensitization process. Outcomes were compared with those of a group of 100 patients who had undergoing standard oral aspirin challenges and desensitization.

The mean percentage decrease in FEV_1 was 8.5% with intranasal ketorolac and modified aspirin challenge, compared to 13.4% with the standard aspirin challenge and desensitization protocol. Intranasal ketorolac was also associated with a lower percentage of extrapulmonary reactions, 23% vs 45%--especially laryngospasm and gastrointestinal reactions. More than 80% of patients completed the new protocol within 48 hours, compared to 20% of the oral challenge group.

Intranasal ketorolac and modified oral aspirin challenge provides a promising new approach to desensitization for patients with AERDS. This approach is effective, safe, and faster than the standard desensitization protocol.

COMMENT: *Aspirin desensitization and regular treatment is beneficial in individuals who have a* ➤➤

history of increased respiratory symptoms. This research group has made major contributions to understanding the desensitization process, and anything that would make it easier and safer is welcome.
D.K.L.
Lee RU, White AA, Ding D, et al: Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease.
Ann Allergy Asthma Immunol. 2010;105:130-135. ♦♦

Good Results with Intranasal Azelastine-Fluticasone Combo

A previous study reported promising results with a combination of commercially available azelastine hydrochloride and fluticasone propionate nasal spray. The azelastine-fluticasone intranasal combination was evaluated for use in a single-delivery device.

The randomized trial included 610 patients with seasonal allergy to Texas mountain cedar causing moderate to severe symptoms. Patients were assigned to treatment with azelastine or fluticasone nasal spray alone, an azelastine-fluticasone combination product, or placebo nasal spray. All active treatments were superior to placebo in reducing nasal symptoms. The azelastine-fluticasone combination provided the greatest improvement in total nasal symptom score: 28.4%, compared to 20.4% with fluticasone, 16.4% with azelastine, and 11.2% with placebo.

An azelastine-fluticasone combination given in a single delivery device is an effective and well-tolerated treatment for seasonal allergic rhinitis. The combination is more effective than either intranasal agent on its own.

COMMENT: *The utilization of combination topical nasal treatment appeals to me, since we have appreciated the effectiveness of this approach with asthma via the inhaled route and with rhinitis using the combination of antihistamine and decongestant. I have been using both medications in persistent rhinitis and it is encouraging to see that in a single delivery system the approach is effective. Combo with one co-pay sounds good to me.*
D.K.L.
Hampel FC, Ratner PH, Bavel JV, et al: Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device.
Ann Allergy Asthma Immunol. 2010;105:168-173. ♦♦

REVIEWS OF NOTE

COMMENT: *This is an up-to-date, critical review of the literature diagnosis and treatment of acute otitis media and therefore is a useful reference. However, nothing has changed much, with the exception of the decline in streptococcal infection with the use of vaccination.*
D.K.L.
Coker TR, Chan LS, Newberry SJ, et al: Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review.
JAMA. 2010;304:2161-2169. ♦♦

COMMENT: *This is the trifecta of immunotherapy reviews, appropriate for the 100th anniversary of allergen immunotherapy. These three articles summarize the mechanism of action, the history, and the future of immunotherapy.*
D.K.L.
Finegold I, Dockhorn RJ, Ein D, et al: Immunotherapy throughout the decades: from noon to now.
Ann Allergy Asthma Immunol. 2010;105:328-337.
Shakir EM, Cheung DS, Grayson MH: Mechanisms of immunotherapy: a historical perspective.
Ann Allergy Asthma Immunol 2010;105:340-347
Finegold I, Oppenheimer J: Immunotherapy: the next 100 years.
Ann Allergy Asthma Immunol. 2010; 105:394-398. ♦♦

COMMENT: *This review focuses on the genetics and pathophysiology of atopic dermatitis, with a summary of completed and current birth cohort studies. Much will be learned from the more comprehensive cohort studies still in progress.*
K.R.M.
Biagini Myers JM, Khurana Hershey GK: Eczema in early life: genetics, the skin barrier, and lessons learned from birth cohort studies.
J Pediatr. 2010;157:704-714. ♦♦

COMMENT: *Decades-old studies have demonstrated the steroid-sparing properties of macrolides in asthma. There are definable anti-inflammatory properties of macrolides. However, their use in treatment of chronic asthma--unless there is documented* Chlamydia *or* Mycoplasma *infection--is not efficacious. Patients with cystic fibrosis, idiopathic bronchiectasis, or chronic obstructive pulmonary disease may benefit.*
S.F.W.
Friedlander AL, Albert RK: Chronic macrolide therapy in inflammatory airways diseases.
Chest. 2010;138;1202-1212. ♦♦

COMMENT: *This is an excellent review of the differential diagnosis of types of VCD, based on an extensive review of the literature. After reading this article, one is comfortable with the clinical presentation and evaluation of VCD. What is missing is an outline for treatment and long-term outcomes.*
S.F.W.
Morris MJ, Christopher CL: Diagnostic criteria for the classification of vocal cord dysfunction.
Chest. 2010; 138:1213-1223. ♦♦

COMMENT: *This is an up-to-date review of the effects of leukotriene modifiers on asthma. While acknowledging that leukotriene modifier efficacy is generally inferior to inhaled corticosteroids, the authors do a good job defining appropriate uses for this class of medication.*
S.A.T.
Montuschi P, Peters-Golden ML: Leukotriene modifiers for asthma treatment.
Clin Exp Allergy. 2010;40:1732-1741. ♦♦

COMMENT: *This is an excellent review of the state of the art regarding drug desensitization, including altering the terminology from "desensitization" to "induction of tolerance." This document complements the recently published updated Drug Allergy Practice Parameter* (**Ann Allergy** 2010;105:259-273).
S.A.T.
Cernadas JR, Brockow K, Romano A, et al: General considerations on rapid desensitization for drug hypersensitivity--a consensus statement.
Allergy. 2010;65:1357-1366. ♦♦