AllergyWatch®

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

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Oral Immunotherapy for Peanut Allergy May Be Safe ...

STRICT allergen avoidance is currently the only available treatment for peanut allergy. Studies of subcutaneous immunotherapy have reported high rates of serious adverse reactions. An oral immunotherapy (OIT) regimen was tested for safety and efficacy in children with peanut allergy.

The study included 23 children, median age 5.6 years, with IgE-mediated peanut allergy confirmed by double-blind placebo-controlled food challenge (DBPCFC). All patients received a 7-day OIT rush protocol with roasted peanut. If this did not achieve a protective dose of at least 0.5 g of peanut, the children were started on a long-term buildup protocol, with biweekly dose increases up to the 0.5 g. After an 8-week maintenance phase and a 2-week avoidance period, DBPCFC was repeated.

At the end of the 7-day rush protocol, the median peanut dose tolerated was only 0.15 g. All but 1 of the 23 patients proceeded to the long-term buildup protocol. At a median follow-up of 7 months, the protective 0.5 g dose was reached by 14 patients. The median tolerated dose at DBPCFC increased from 0.19 g before the study to 1.0 g after OIT.

On analysis of more than 6,000 daily doses, the rate of mild to moderate side effects was 2.6%. Pulmonary obstructive symptoms occurred with 1.3% of doses. Four patients (18%) had to stop OIT because of adverse events. Immunologic analyses showed a significant increase in peanut-specific IgG_4 after OIT. There were significant reductions in interleukin (IL)-5, IL-4, and IL-2 in peripheral blood mononuclear cells.

The OIT protocol evaluated in this study appears safe for children with peanut allergy. There is evidence of increased threshold levels and reduced production of peanut-specific Th2 cytokines. Further study will be needed to establish the risk-benefit ratio of OIT for peanut allergy.

COMMENT: *Peanut allergy affects about 1% of the U.S. population and is usually severe and lifelong.* ➤➤

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

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

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There have been multiple efforts to develop a desensitization protocol. This paper reports on the findings of one such program in Germany. A 7-day rush protocol was ineffective. After a long-term (median 7 months) protocol, 14 of 22 subjects reached a target dose that allowed them to tolerate a maintenance dose equivalent to four peanut kernels. Immunologic parameters changed favorably. Four of the 22 had to be withdrawn due to adverse events. These results parallel those reported from U.S. researchers. Although not yet ready for clinical implementation--see the editorial review below--hope remains strong.
R.J.M.
Blumchen K, Ulbicht H, Staden U, et al: Oral peanut immunotherapy in children with peanut anaphylaxis.
J Allergy Clin Immunol. 2010;126:83-91. ♦♦

... But Isn't Yet Ready for Clinical Use

INITIAL studies of peanut oral immunotherapy (OIT) have yielded promising results in terms of raising the threshold dose and clinical desensitization. However, many questions remain--most importantly the risks associated with OIT compared to allergen avoidance. The authors review the current state of clinical research on OIT for peanut allergy.

Trials of OIT suggest that up to 18% of patients will be unable to tolerate the associated side effects. This must be considered in light of the reported 15% rate of accidental ingestions over 4 years' follow-up in children with peanut and tree nut allergy. Although studies have suggested that OIT is safe, it is not risk-free. The rate of adverse reactions to home doses is relatively low, but certain groups of patients may be at higher risk. More data on the safety profile are needed.

The OIT protocols being studied use different dosing regimens, treatment durations, and patient selection criteria. Studies using higher OIT doses may have a better chance of inducing tolerance, but may also have higher risks. In addition, patient management after desensitization is achieved remains to be worked out. There is also the chance that going through OIT will create a false sense of security.

The high time and labor commitment associated with OIT is an issue, as is reimbursement. Although OIT remains a promising therapy for peanut allergy, the authors conclude that it is not yet ready for clinical use in patients with peanut allergy, or other food allergies.

COMMENT: *Food allergy immunotherapy remains an important goal for our specialty and the patients we serve. Peanut allergy represents the most pressing need because of its prevalence (more than 1% in Western countries), severity, and duration (usually lifelong). Other food allergies raise the total to 3.9% of children. While researchers are reporting promising results of OIT, several of them have grouped together to present this editorial emphasizing that there are many unanswered questions to be resolved. Oral immunotherapy for peanut or other food allergens is not ready for general clinical use yet. Patience is advised. Avoidance may remain the treatment of choice for most patients anyway.*
R.J.M.
Thyagarajan A, Varshney P, Jones SM, et al: Peanut oral immunotherapy is not ready for clinical use.
J Allergy Clin Immunol. 2010;126:31-32. ♦♦

Rising Rates of Peanut/Tree Nut Allergy in U.S. Children

RATES of food allergy in the United States appear to be increasing. In two previous population surveys, the authors reported that the prevalence of peanut and tree nut allergy increased significantly between ➤➤

1997 and 2002. They report the findings of a third survey performed in 2008.

A telephone survey was conducted in a random sample of 5,300 U.S. households, comprising 13,534 subjects. Rates of self-reported peanut and tree nut allergy were assessed, with additional questions about sesame allergy.

The participation rate was 42%, lower than in previous surveys. Peanut and/or tree nut allergy was reported by 1.4% of participants, compared to 1.2% in 2002 and 1.4% in 1997. The prevalence of these allergies in adults was 1.3%, similar to previous years.

In children, the prevalence of peanut or tree nut allergy was 2.1%, continuing the previous increase from 0.6% in 1997 to 1.2% in 2002. The prevalence of peanut allergy was 1.4% in 2008, compared to 0.8% in 2002 and 0.4% in 1997. Tree nut allergy was reported by 1.1% of children, compared to 0.5% in 2002 and 0.2% in 1997. The 2008 prevalence of sesame allergy was 0.1%--most of these patients also had peanut or tree nut allergy.

The prevalence of peanut and/or tree nut allergy appears to be increasing in U.S. children. The survey results suggest that greater than 1% of the population--more than 3 million Americans--report peanut or tree nut allergy. This highlights the urgent need for better prevention and treatment approaches.

COMMENTS: *The prevalence of allergy to peanuts and tree nuts seems to be increasing. This report confirms that impression for children but not adults, on the basis of a random survey--the third by this group since 1997. Self-reported allergy to peanuts and tree nuts both increased in the under-18 group by 2- to 5-fold since 1997. There was no attempt to confirm the allergies by testing in any of the three surveys. But the authors point out that nut reactions are usually acute and severe, so the likelihood of false-positive results is low, and the methodology was the same in all three survey years. It appears that some 3 million people in the U.S. have nut allergies, and the number has been increasing for still-unknown reasons.*
R.J.M.

Sicherer SH, Muñoz-Furlong A, Godbold JH, Sampson HA: US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up.
J Allergy Clin Immunol. 2010;125:1322-1326. ♦♦

Recombinant Allergens May Help in Diagnosing Insect Allergy

VENOM immunotherapy is highly effective in preventing allergic reactions to insect stings, but it can be difficult to identify the culprit insect. As for other causes of allergic disease, recombinant allergens may help in making the diagnosis. A panel of recombinant bee and wasp allergens was evaluated for use in diagnosing bee and wasp allergy, including patients with negative skin test results.

The study included serum samples from 43 patients with bee and/or wasp venom allergy, as well as 6 patients with pollen allergy and false-positive IgE reactivity to natural bee and/or wasp extract. Samples were tested for IgE reactivity to recombinant (r) bee and wasp allergens. These included nonglycosylated *Escherichia coli*-expressed rApi m1, rApi m2, rVes v 5, and insect-cell expressed glycosylated rApi m 2. Reactivity to the natural plant glycoproteins Phl p 4 and bromelain was assessed as well.

Patients with insect venom allergy were correctly diagnosed with a combination of *E. coli*-expressed rApi m1, rApi m2, and rVes v 5. Sera from patients with pollen allergy did not react to the recombinant bee and wasp allergens. For 29 insect-allergic patients with negative results on testing with natural allergen extracts, the nonglycosylated allergens correctly identified the sensitizing venom. In the 14 patients who did react to bee or wasp venom extracts, the recombinant nonglycosylated allergens identified the sensitizing venom.

IgE inhibition studies found carbohydrate epitopes in glycosylated Api m 2 that cross-reacted with natural Api m 1 and Ves v 2, as well as with Ph1 p 4 and bromelain. These cross-reactive structures explained why some patients had serologic false-positive results or positive reactions to both bee and wasp extracts.

The nonglycosylated recombinant bee and wasp venom allergens evaluated in this study may have implications for serologic diagnosis of insect allergies. They can identify patients with bee and wasp allergy who have false-negative results on testing with natural extracts and facilitate accurate prescription of venom immunotherapy.

COMMENT: *It is reported that about 30% of patients with systemic reactions to insect stings are (false-) negative on skin testing, and that serologic tests can be false-positive due to venom antigens that cross-react with irrelevant allergens like pollens and latex. This study found that* E. coli*-expressed recombinant antigens more reliably diagnose bee and wasp allergies than possible using natural venom extracts. It remains to be seen if these recombinant allergens will find their way into our commercially available diagnostic tests.*
R.J.M.

Mittermann I, Zidarn M, Silar M, et al: Recombinant allergen-based IgE testing to distinguish bee and wasp allergy.
J Allergy Clin Immunol. 125:1300-1307. ♦♦

Non-Atopic Dust Mite Allergy!

NASAL allergen provocation testing (NAPT) has lent new insights into the mechanisms of allergic rhinitis. A subgroup of patients have been reported to have local allergic rhinitis (LAR), or "entopy," with in situ production of specific IgE (sIgE) and a positive response to NAPT but without atopy. The authors performed a detailed examination of responses to house dust mite in a group of patients with LAR.

The study included 40 adult patients with LAR to dust mite--all with a positive result on NAPT but a negative skin-prick test--plus 50 healthy controls. The ➤➤

response to NAPT was assessed using a nasal symptom scale and acoustic rhinometry. Nasal lavage was performed before and after nasal challenge to measure tryptase, eosinophil cationic protein (ECP), and sIgE.

Positive responses to NAPT were accompanied by a 45% increase in tryptase, a 65% increase in ECP, and a 25% increase in sIgE. Sixty percent of patients with LAR had an immediate response to nasal dust mite challenge, while 40% had a dual response. In the immediate responses, nasal tryptase peaked at 15 minutes, while ECP and sIgE continued to increase from 1 to 24 hours. In dual responders, tryptase remained elevated from 15 minutes to 6 hours after nasal challenge. There were no isolated late responders; controls had no response to NAPT.

Patients with LAR to dust mite may have an immediate or dual response to NAPT. Both patterns are associated rising levels of local sIgE, with evidence of mast cell and eosinophil activation. More study is needed to define the kinetics of sIgE production and to identify the lymphocyte subpopulations and cytokines involved.

COMMENT: *This fascinating study and related review (Powe DG, Bonnin AJ, Jones NS: Clin Exp Allergy. 2010;40:987-997) remind us of the small but well-documented subset of rhinitis sufferers whose symptoms are mediated by local nasal IgE, in the absence of skin test reactivity. They should not be confused with the much larger group of patients who have nonallergic rhinitis (eg, vasomotor, gustatory, etc). The investigators used dust mite nasal allergen challenge and demonstrated that 40% of the "local allergic rhinitis" patients also exhibited a late phase response.*
S.A.T.

López S, Rondón C, Torres MJ, et al: Immediate and dual response to nasal challenge with Dermatophagoides pteronyssinus *in local allergic rhinitis.*
Clin Exp Allergy. 2010;40:1007-1014. ♦♦

Nasal Mometasone May Improve Sleep in Allergic Rhinitis

MANY patients with allergic rhinitis (AR) have impaired sleep, particularly related to morning congestion. Such rhinitis-disturbed sleep (RDS) has a significant impact on patients' lives. This study evaluated the impact of intranasal corticosteroids on nasal congestion and sleep quality in patients with RDS.

The randomized, double-blind trial included 30 adult patients with perennial AR and moderate sleep disturbance symptoms, defined as a score of 2 or higher on the Interference with Sleep Scale. All had at least 5 but no more than 30 apnea and hypopnea events per hour on a home sleep study. In a 2:1 ratio, patients were randomly assigned to receive mometasone furoate nasal spray, 200 µg each morning, or placebo.

The two groups had similar and nonsignficant increases in the apnea-hypopnea index at the end of the study: 0.96/h in the mometasone group and 1.61/h in the placebo group. However, several secondary outcomes improved significantly with mometasone, including morning and evening total nasal symptom scores, morning and evening nasal congestion, daily peak nasal inspiratory flow, and flow limitation index. Mometasone also led to improvements in sleepiness, patient-reported quality of life, work absenteeism, and daily activity level. In the mometasone group, increases in work-related and non-work-related productivity were correlated with reduced nasal symptoms.

Mometasone furoate nasal spray has benefits for patients with sleep problems related to perennial AR. Treatment is associated with reductions in nasal symptoms, daytime sleepiness, and impairment in daily activities, despite the lack of effect on apnea-hypopnea index. Reduced nasal congestion may be the most important contributor to improved sleep quality.

COMMENT: *This was a negative study, as intranasal mometasone did not affect the apnea-hypopnea index. However, as discussed by the investigators, the relationship between nasal congestion and daytime sleepiness was confirmed. The idea of sleep disturbance secondary to rhinitis without meeting criteria for sleep apnea is very interesting, and I think rings true to my clinical experience. Allergists/immunologists need to wake up and look at sleep.*
D.K.L.

Meltzer EO, Munafo DA, Chung W, et al: Intranasal mometasone furoate therapy for allergic rhinitis symptoms and rhinitis-disturbed sleep.
Ann Allergy Asthma Immunol 2010;105:65-74. ♦♦

Oral vs Intravenous Steroids for Acute COPD

SYSTEMIC corticosteroids have been found to improve lung function, among other benefits, in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). However, the best dosage and route of administration are still uncertain. This issue was addressed in a "pharmacoepidemiological cohort study."

The study included 79,985 patients with acute COPD exacerbations treated at 414 U.S. hospitals in 2006 and 2007. All patients received systemic corticosteroids during the first 2 days in the hospital. Rates of treatment failure--defined as starting mechanical ventilation after hospital day 2, death in the hospital, or readmission for COPD within 30 days--were compared for patients receiving intravenous versus oral steroids.

Steroids were initially given intravenously in 92% of patients and orally in 8%. Treatment failure occurred in 10.9% of patients receiving intravenous steroids and 10.3% receiving oral steroids. Rates of in-hospital death were 1.4% and 1.0%, respectively. On adjusted analysis including propensity for oral treatment, treatment failure rates were not significantly different between the two routes of administration.

In contrast, on propensity-matched analysis, the treatment failure rate was lower with oral steroids: odds ratio 0.84. Twenty-two percent of patients who were ➤➤

initially started on oral steroids were later switched to intravenous steroids.

In patients hospitalized for acute COPD exacerbations, low-dose oral steroids produce outcomes similar to or better than high-dose intravenous steroids. Oral steroids are also associated with reduced hospital costs and length of stay. A randomized trial is needed to compare these two routes of systemic corticosteroid administration.

COMMENT: *Much of what we do as clinicians is based upon empiricism or what our senior residents and attendings taught us when we were students or junior residents. Corticosteroid treatment for respiratory exacerbations is certainly characterized by a variety of favorite doses and schedules, without much evidence to show which is preferable. Although this was a study of COPD, the results are likely applicable to asthma. The bottom line is oral and low-dose is as good as intravenous and high-dose.*
D.K.L.

Lindenauer PK, Pekow PS, Lahti MC, et al: Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease.
JAMA. 2010;23:2359-2367. ♦♦

The Latest on Vitamin D

SOME studies have suggested associations between vitamin D status and asthma incidence and morbidity. Vitamin D deficiency is more common among African Americans, particularly in urban settings. Rates of vitamin D insufficiency and deficiency were assessed in inner-city African-American youth with and without asthma.

The study included 92 African American patients with asthma, aged 6 to 20 years, identified at a Washington, D.C., children's hospital. Blood samples for 25-hydroxyvitamin D measurement were available for 85 subjects--levels under 30 ng/mL were classified as vitamin D insufficiency and under 20 ng/mL as vitamin D deficiency. The findings were compared with those of 21 nonasthmatic African American youth.

Vitamin D insufficiency was found in 86% of the asthmatic patients, compared to 19% of nonasthmatic controls: adjusted odds ratio 42. Rates of vitamin D deficiency were 54% vs 5%: odds ratio 20. Analysis of children aged 9 or younger showed a similar pattern.

The study finds high rates of vitamin D insufficiency and deficiency among African American youth with asthma at an urban children's hospital. Together with other recent studies, the results urge consideration of routine vitamin D measurement in urban African American children, particularly those with asthma.

COMMENT: *Researchers each year seem to identify a banner mineral, chemical or compound whose investigation yields substantial medical breakthroughs. Would anyone be surprised if this year's "winner" is vitamin D? We are seeing an expanding body of work that should directly impact our specialty, and hopefully improve the lives of our patients.*

Here is yet more research finding a population of urban children with asthma (n = 92) having significantly reduced vitamin D levels. My primary study critique is the low total number of control subjects (n = 21), who paradoxically have vitamin D levels higher than would be expected from recent population studies....
K.R.M.

Freishtat RJ, Iqbal SF, Pillai, et al: High prevalence of vitamin D deficiency among inner-city African American youth with asthma in Washington, DC.
J Pediatr. 2010;156:948-952. ♦♦

SOME studies, but not all, have suggested that higher maternal intake of dairy products during pregnancy leads to a lower risk of allergic disease in offspring. Data on maternal vitamin D intake are also mixed. A Japanese study assessed the effects of maternal consumption of dairy products, calcium, and vitamin D during pregnancy on allergic disease outcomes in infants.

The prospective cohort study included 763 mother-child pairs, with maternal diet during pregnancy assessed using a diet history questionnaire. When the children were 16 to 24 months old, symptoms of wheeze and eczema were assessed, based on International Study of Asthma and Allergies in Childhood criteria.

Overall rates of wheeze and eczema at follow-up were 22.1% and 18.6%, respectively. Infants born to women with higher total consumption of dairy products during pregnancy were less likely to wheeze: adjusted odds ratio (OR) for women in the highest vs lowest quartile. Similar associations were noted for maternal consumption of milk, OR 0.50; cheese; OR 0.51; and calcium, OR 0.57. No associations were noted for infantile eczema.

The 25th percentile value for maternal vitamin D consumption was 4,309 μg/d. For women with consumption at or above this level, offspring were at reduced risk of both wheeze, OR 0.64; and eczema, OR 0.63.

Higher consumption of calcium and dairy products, except yogurt, during pregnancy may be associated with a lower risk of infantile wheezing in offspring. Higher maternal vitamin D consumption may have a protective effect against eczema as well as wheezing. Confirmatory studies should address the possibility that dairy intake during pregnancy protects against respiratory infections, rather than atopy.

COMMENT: *This study continues to expand our understanding of the critical role of vitamin D in the prevention and treatment of allergic diseases including asthma. As continued research is done, it is hoped this will translate into better-defined dietary guidelines, both for pregnant women and patients suffering from allergic disease.*
B.E.C.

Iyake Y, Sasaki S, Tanaka K, Hirota Y: Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants.
Eur Respir J. 2010;35:1228-1234. ♦♦

SEVERAl lines of evidence suggest that vitamin D might be useful in preventing asthma exacerbations. A previous cross-sectional study, in a limited sample, linked low vitamin D levels to increased markers of asthma severity in children. The relationship between vitamin D status and asthma exacerbation risk was evaluated in children from the Childhood Asthma Management Program (CAMP) study.

The analysis included 1,024 school-aged children with mild to moderate persistent asthma at baseline. In the CAMP study, patients were randomly assigned to budesonide, nedocromil, or placebo (with β-agonists as needed). Baseline 25-hydroxyvitamin D levels were analyzed as a predictor of hospitalization or emergency department visits during 4 years' follow-up.

Vitamin D insufficiency, defined as a 25-hydroxyvitamin D level of 30 ng/mL or less, was found in 35% of children. On average, African American children had the lowest vitamin D levels. Children with vitamin D insufficiency were at higher risk of any hospitalization or emergency department visit, odds ratio 1.5, after adjustment for age, sex, body mass index, income, and treatment group. Vitamin D levels had a significant protective effect in addition to that of inhaled corticosteroid therapy.

More than one-third of North American children with mild to moderate persistent asthma have vitamin D insufficiency. Low 25-hydroxyvitamin D levels identify a group of children at high risk of severe asthma exacerbations over 4 years' follow-up. The authors call for a randomized controlled trial to confirm their findings.

COMMENT: *We've been seeing more press recently about the importance of adequate vitamin D levels in both immune function and asthma management. Using data from the CAMP study, this report confirms that vitamin D insufficiency is associated with increased risk of asthma exacerbations and is relatively common in children with persistent asthma. Although the authors suggest that sufficient vitamin D levels improved asthma control, only one measurement was obtained at the beginning of the program. Future prospective studies will need to monitor vitamin D levels to confirm this relationship.*
S.M.F.
Brehm JM, Schuemann B, Fuhlbrigge AL, et al: Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study.
J Allergy Clin Immunol. 2010;126:52-58. ♦♦

What's New with Exhaled NO?

PATIENTS who have continued asthma symptoms despite stepped-up treatment can be considered to have difficult-to-treat asthma. As an indirect marker of airway inflammation, exhaled nitric oxide (eNO) could help in facilitating patient assessment, helping to avoid overtreatment or undertreatment. Exhaled NO was evaluated as a predictor of which patients would go on to have difficult-to-treat asthma in a guideline-based stepwise treatment approach.

The prospective study included 102 consecutive patients with suboptimally controlled asthma despite minimal maintenance therapy with a long-acting β_2-agonist and high-dose inhaled corticosteroid. After eNO measurement, patients received 1 month of stepwise treatment with a maximal fluticasone/salmeterol combination. Those who still did not have disease control then received 1 month of oral corticosteroid therapy.

This stepwise approach provided disease control in 52% of patients. Disease control was more likely for patients with positive skin test results, a positive bronchodilator test, and peak expiratory flow variability of 20% or greater; and less likely for those with depression.

Higher baseline eNO was also associated with a greater likelihood of disease control. An eNO of 30 ppb or higher predicted disease control with sensitivity of 87.5% and specificity of 90.6%. Baseline eNO was 67 ppb for patients who achieved disease control versus 28 ppb in those who did not.

Among patients with asthma, baseline eNO measurement can aid in identifying those with difficult-to-treat asthma. Patients with eNO of 30 ppb or higher are more likely to respond to increased doses of inhaled corticosteroids or to oral steroid therapy. The findings may be a useful part of new approaches to treatment according to asthma phenotype.

COMMENT: *The use of eNO in this study helps to predict patients who will be responsive to a stepwise approach in difficult-to-treat asthma. Other recent studies have reported similar findings (Dweik R et al: Am J Respir Crit Care Med. 2010;181;1033-1034). This allows for a defined paradigm of stepwise care to optimize asthma control.*
B.E.C.
Pérez-de-Llano LA, Carballada F, Castro Añon O, et al: Exhaled nitric oxide predicts control in patients with difficult-to-treat asthma.
Eur Respir J. 2010;35;1221-1227. ♦♦

NEW approaches are needed to predict which infants and toddlers with wheezing will go on to develop asthma. Exhaled nitric oxide (eNO) is a promising marker of airway inflammation in asthma, but few studies have evaluated its use in infants and young children. A single-breath eNO (SB-eNO) measurement technique was used to evaluate the relationship between eNO, lung function, and later exacerbation risk in infants with recurrent wheezing.

Forty-four wheezy infants and toddlers, mean age 15.7 months, underwent measurement of forced expiratory flows and volumes using the raised-volume rapid thoracic compression technique. As part of this study, SB-eNO was measured at a flow rate of 50 mL/s. The relationship between SB-eNO and lung function and with subsequent exacerbation risk was assessed. Lung function testing was repeated at 6 months' follow-up.

At baseline, mean forced expiratory volume in 0.5 seconds ($FEV_{0.5}$), forced expiratory flow at 25% to 75% of expiration (FEF_{25-75}), and forced expiratory flow at 75% of expiration (FEF_{75}) *z* scores were significantly less than zero, ie, the mean value of published norms. However, SB-eNO was unrelated to initial lung➤➤

function measures. Infants with bronchodilator responsiveness had higher SB-eNO, 46.1 vs 23.6 ppb; in association with reduced lung function at 6 months' follow-up. Each 10 ppb increase in SB-eNO was associated with reductions of about 0.4 point in $FEV_{0.5}$, FEF_{25-75}, and FEF_{75}.

Baseline SB-eNO was higher in infants who went on to have an acute episode of wheezing treated with systemic steroids: 39.3 vs 22 ppb. Baseline SB-eNO was a better predictor of acute wheezing than lung function or bronchodilator responsiveness.

In infants and toddlers with recurrent wheezing, SB-eNO measurement may provide useful information on future lung function changes and risk of wheezing. Baseline SB-eNO is higher in infants with bronchodilator responsiveness. Longer follow-up in larger sample sizes is needed.

COMMENT: *As clinicians we are challenged trying to predict which young children with recurrent wheezing will be early persistent asthmatics or just transient wheezers. These Seattle researchers used a somewhat complicated technique to measure both lung function and eNO in young children with wheezing illnesses. They report that elevated eNO was a better predictor for reduced lung function and recurrent wheezing than baseline pulmonary function tests or bronchodilator responsiveness. We look forward to a follow-up report with a longer interval than 6 months. However, the fact that sedation is required to obtain these measurements suggests that we probably won't have this technique available in the clinic in the near future.*
S.M.F.

Debley JS, Stamey DC, Cochrane ES, et al: Exhaled nitric oxide, lung function, and exacerbations in wheezy infants and toddlers.
J Allergy Clin Immunol. 2010;125:1228-1234. ♦♦

Late Preterm Birth Does Not Increase Asthma Risk

MOST preterm infants in the United States are "late preterm," ie, born at 34 to 36 weeks' gestation. Late preterm infants have higher rates of early respiratory illness than term infants, but it is unclear whether this affects their risk of long-term respiratory problems. Late preterm birth was evaluated as a risk factor for childhood asthma up to age 7.

The study used linked natality files from the Third National Health and Nutrition Examination Survey (1988-94) to identify 537 children born late preterm and 5,650 term infants. At the time of the survey, the children were 2 to 83 months old. Time to diagnosis of asthma was modeled using survival analysis. Cox proportional hazard regression was performed to estimate the association between gestational age and asthma risk, with adjustment for other risk factors.

Rates of physician-diagnosed asthma were about 9% for children born late preterm vs 6% for term children. However, the association between late preterm birth and childhood asthma risk was not significant after adjustment for other factors: hazard ratio 1.3, 95% confidence interval 0.8 to 2.0.

Late preterm birth is not an independent risk factor for the development of early childhood asthma. Efforts to identify a subgroup of late preterm infants at increased risk of long-term respiratory problems should focus on events shortly after birth, with special attention to those with maternal conditions associated with increased risk.

COMMENT: *Risk of early childhood asthma seems to correlate with reduced gestational age, and its associated reductions in birth weight and pulmonary function. But at what point in gestation does this asthma risk plateau? Late preterm infants arguably remain at higher risk of respiratory complications compared to their term counterparts; but in this study, such risk does not extend to asthma. The threshold of gestational age below which asthma risk increases remains imprecise.*
K.R.M.

Abe J, Shapiro-Mendoza CK, Hall LR, Satten GA: Late preterm birth and risk of developing asthma.
Pediatrics. 2010;157:74-78. ♦♦

Early Exposure to Cow's Milk Protein May Reduce Risk of Cow's Milk Allergy

THE reported prevalence, risk factors, and recovery rate for children with cow's milk allergy (CMA) vary widely. Studies in very large patient cohorts are needed to obtain meaningful data. The prevalence, cross-reactivity, and risk factors for CMA were investigated in a large birth cohort.

The prospective study included more than 13,000 infants born at one Israeli hospital over a 2-year period, with detailed information on feeding history. Infants identified with probable adverse reactions to milk underwent clinical examination, including skin prick and oral challenge testing.

A diagnosis of IgE-mediated CMA was made in 0.5% of infants. Mean age at introduction of cow's milk protein (CMP) was 116 days for infants with CMA, compared to 61.6 days for those without CMA. The rate of CMA increased from 0.05% for infants started on regular CMP formula during the first 14 days of life to 1.05% for those first exposed to CMP at 105 to 194 days. For CMP exposure after 14 days, the odds ratio for IgE-mediated CMA was 19.3. None of 66 infants with CMA had confirmed soy allergy.

The 0.5% incidence of IgE-mediated CMA in this large group of Israeli infants is significantly lower than previously reported. Delayed exposure to CMP is associated with a sharply increased risk of CMA. This raises the possibility that early CMP exposure, as a supplement to breast-feeding, could promote tolerance of cow's milk.

COMMENT: *This large prospective non-interventional study raises questions about current recommendations for early infant feedings. Not only did the researchers find a very low prevalence of CMA,* ➤➤

they report that there was no direct correlation with soy allergy and CMA. The most interesting finding was that early exposure to cow's milk protein seemed to have a protective effect against the development of CMA. There is an increasing appreciation of the role of early exposure to dietary proteins in promoting tolerance.
S.M.F.
Katz Y, Rajuan N, Goldberg MR, et al: Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy.
J Allergy Clin Immunol. 2010;126:77-82. ♦♦

Anti-IL-5 Receptor α Therapy Reduces Eosinophils in Asthma

BECAUSE of its role in eosinophil differentiation, proliferation, and activation, interleukin-5 (IL-5) may affect airway inflammation and asthma exacerbation risk. Preliminary studies have reported promising results with humanized anti-IL-5 monoclonal antibodies (mAbs). The humanized mAb MEDI-563, which specifically targets the IL-5 receptor α chain, was evaluated in patients with asthma.

The phase 1, open-label trial included 44 patients with mild atopic asthma. Over 3 to 30 minutes, patients received a single intravenous dose of MEDI-563, 0.0003 to 3.0 mg/kg. The pharmacokinetics and pharmacodynamics of MEDI-563 were evaluated, along with symptom scores, pulmonary function, and adverse events.

Treatment with MEDI-563 produced a dose-dependent decrease in mean peripheral blood eosinophil levels. In 94% of subjects receiving a MEDI-563 dose of 0.03 mg/kg or greater, eosinophil level was reduced to less than 0.01 x 10^3/μL (from a baseline mean of 0.27 x 10^3/μL). This reduction in eosinophils lasted for at least 8 weeks in patients receiving MEDI-563 doses of 0.03 to 0.1 mg kg, and 12 weeks in those receiving doses of 0.3 to 3.0 mg/kg. Eosinophil cationic protein level decreased from 21.4 to 7.0 μg/L.

Common adverse events included decreased white blood cell count, nasopharyngitis, and increased blood creatine phosphokinase. There was more than a 5-fold increase in mean C-reactive protein level at 24 hours after dosing, although this later returned to baseline. Mean IL-6 levels increased from 6 to 12 hours. Dose-proportional pharmacokinetic activity was noted at doses of 0.03 to 3.0 mg/kg.

Treatment with the anti-IL-5 receptor α mAb MEDI-563 produces a significant and persistent reduction in peripheral blood eosinophil level in patients with mild atopic asthma. Safety appears acceptable. It's unclear whether the reduced eosinophil counts will lead to clinical improvements in asthma and other diseases associated with elevated eosinophil levels.

COMMENT: *Recent reports have shown that anti-IL-5 preparations such as mepolizumab and reslizumab, which neutralize IL-5, can have a steroid-sparing effect and reduce exacerbations in asthmatics with eosinophilia. This is the first report of the initial safety and dosing study for MEDI-563, which is specific for the distinct epitope of the α-chain of the IL-5 receptor. After intravenous administration there was quick depletion of peripheral eosinophils, which persisted for 2 to 3 months. This anti-IL-5 α-chain receptor antagonist has an impressive efficacy for sustained blocking of eosinophilia, which may be more effective clinically in our patients with eosinophil-driven lung diseases.*
S.M.F.
Busse WW, Katial R, Gossage D, et al: Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor α antibody, in a phase I study of subjects with mild asthma.
J Allergy Clin Immunol. 2010;125:1237-1244. ♦♦

Immunotherapy Is Safe for Imported Fire Ant Allergy

NOW endemic in the southeastern United States, imported fire ants (IFA) are aggressive insects that can sting repeatedly. Anaphylactic reactions to IFA venom are well-documented, but little is known about how many stings typically lead to systemic reactions (SRs). There is also a lack of data on the safety of IFA subcutaneous immunotherapy (IFA SCIT).

These issues were addressed in a retrospective case-cohort study, which included all 77 patients undergoing IFA SCIT at one center over a 3-year period: 40 females and 37 males, mean age 34 years. Data on the index field reactions were evaluated as well, including the number of stings leading to SRs.

In a total of 1,887 IFA SCIT injections, 7 patients had a total of 8 reactions--a rate of 0.4% per injection and 9.1% per patient. Patients who had an SR in response to diagnostic skin testing were more likely to have an SR to IFA SCIT, odds ratio (OR) 4.75; and large local reactions to IFA SCIT, OR 34.5. There were no other significant risk factors.

On analysis of field reactions, 59% of patients reacted to just one sting while 87% had just one SR before starting IFA SCIT. Of 4 patients who lost consciousness during the index field reaction, 2 required an increased maintenance dose.

This experience supports the safety of IFA SCIT. Although SRs may occur, they are generally mild. The rate of SRs appears higher for patients with SRs during skin testing or large local reactions to previous IFA SCIT injections. Most field reactions to IFA result from a single sting.

COMMENT: *These researchers describe the safety and risk of systemic reactions in a cohort of patients with imported fire ant allergy receiving allergen immunotherapy. It is not surprising that those patients having SRs during allergy skin testing were at significantly increased risk of SR during IFA SCIT. However, it is notable that large local reactions to IFA SCIT also increased the risk of SR. Another finding of interest was that 59% of the patients had a SR from only one fire ant sting. Fortunately for our patients, IFA SCIT is safe and effective.* ➤➤

S.M.F.
La Shell MS, Calabria CW, Quinn JM: Imported fire ant field reaction and immunotherapy safety characteristics: the IFACS study.
J Allergy Clin Immunol 2010;125:1294-1299. ♦♦

On Review, Old Biopsies Show Esophageal Eosinophilia

ESOPHAGEAL eosinophilia (EE) is a newly appreciated disorder that was rarely diagnosed a decade ago. The reasons for this sudden, apparent increase in EE cases are unknown. A retrospective study looked for histopathologic evidence of EE in children diagnosed with esophagitis before 1999.

The investigators reviewed esophageal biopsy specimens obtained at one U.S. children's hospital between 1982 and 1999--the first year EE was diagnosed at the study center. On re-examination, each specimen was classified as having a peak esophageal eosinophil number above or below the cutoff point 15 eosinophils/hpf. The histologic findings and epidemiologic characteristics of these cases were analyzed, along with those of a population-based cohort.

The analysis included 878 biopsy specimens from 666 patients. Of these, 198 patients had a peak esophageal eosinophil number of 15/hpf or greater. Compared to a population-based cohort, the incidence of biopsies with esoinophil counts above this cutoff increased modestly--incidence rate ratio 1.18. However, after correction for the sharp increase in number of endoscopies performed, the proportion of specimens with an eosinophil count of 15/hpf or higher did not significantly increase.

Patients with 15 eosinophils/hpf or greater were more likely to have a chief complaint of dysphagia: 12% versus 2.5%. This was the main clinical difference between groups. On repeated esophagogastroduodenoscopy, patients with as few as 5 eosinophils/hpf were more likely to have persistent esophageal eosinophilia, evidence of basal layer hyperplasia, and lamina propria fibrosis, compared to those with lower eosinophil counts.

This retrospective study shows no change in the incidence of EE in pediatric esophageal biopsy specimens from the 1980s through the 1990s. About 30% of patients diagnosed with reflux esophagitis during this period had esophageal eosinophil counts consistent with EE. Associated histologic abnormalities and persistent esophageal eosinophilia are found in patients with counts as low as 5 eosinophils/hpf.

COMMENT: *Why are we seeing so many more patients with EE now versus 10 years ago? These Cincinnati researchers reviewed 3,817 esophageal biopsies from 1971 to 1999 and concluded that--after correcting for the 40-fold increase in the number of endoscopies--the proportion of biopsies with increased eosinophilia was relatively constant. The fact that histologic features of EE were found in 30% of patients with reflux esophagitis suggests that EE may have been underdiagnosed in the '80s and '90s.*
S.M.F.
DeBrosse CW, Collins MH, Buckmeier Butz BK, et al: Identification, epidemiology, and chronicity of pediatric esophageal eosinophilia 1982-1999.
J Allergy Clin Immunol. 2010;126:112-119. ♦♦

Upper and Lower Airway Patency Are Linked in Children

MANY patients have both allergic rhinitis and asthma, but the nature of this association remains unclear. Data from a birth cohort study were used to examine associations between upper and lower airway patency in children.

The analysis included 221 children of asthmatic mothers, aged 6 years, from the Copenhagen Prospective Study on Asthma in Childhood. All children underwent acoustic rhinometry to assess upper airway patency, before and after treatment with a topical α-agonist. Lower airway patency was assessed by spirometry, performed before and after administration of an inhaled β_2-agonist. Other assessments included blood eosinophil count, nasal eosinophilia, total IgE level, and exhaled nitric oxide.

There was a significant association between post-α-agonist nasal airway patency and post-β_2-agonist FEV_1. For each 1 L increase in post-β_2 FEV_1, there was a 2.85 cm^3 increase in decongested nasal airway patency. The association remained significant on adjusted analysis. Baseline upper and lower airway patency were significantly associated as well. Decongested nasal airway patency was also inversely associated with blood eosinophil count and nasal eosinophilia.

In this sample of 6-year-old children, there is a consistent association between upper and lower airway patency. The link between decongested nasal airway patency with eosinophil levels suggests a possible common pathophysiology. Another possibility is that the association between upper and lower airway patency serves as the physiologic background for the common comorbidity.

COMMENT: *The moniker "unified airway disease" has been applied to allergic rhinitis and asthma due to either a common physiologic or pathologic background. This study adds to the association by demonstrating statistical correlation between upper and lower airway patency as well as nasal and systemic eosinophilia. Treatment of allergic rhinitis has been shown to affect asthma (Adams R et al: J Allergy Clin Immunol. 2002;109:36-42; Crystal-Peters J et al: J Allergy Clin Immunol. 2002;109:57-62; Ribeiro de Andrade C, et al: Respir Med. 2010; 104:1577-1580), although this effect is not confirmed (Suissa S, Ernst P: J Allergy Clin Immunol. 2005;115:714-719.) Further studies, especially in children, are warranted to determine the effect, if any, of treating the most proximal airway and subsequent benefits distally.*
Chawes BLK, Kreiner-Møller E, Bisgaard H: Upper and lower airway patency are associated in young children.
Chest. 2010;137;1332-1337. ♦♦

Does Obesity Increase the Risk of Asthma Misdiagnosis?

OBESE patients appear to be at increased risk of a new diagnosis of asthma, but the link between obesity and asthma severity remains unclear. This study compared the characteristics of obese vs normal-weight patients with physician-diagnosed asthma, including asthma severity, lung function, and comorbid conditions.

The study included a random sample of 496 patients with physician-diagnosed asthma from 8 Canadian cites: 242 obese and 254 normal weight. A serial asthma testing algorithm was followed to confirm or exclude the diagnosis of asthma. The obese and normal-weight groups were compared by logistic regression analysis, including factors associated with asthma misdiagnosis and interactions with obesity.

Sequential testing confirmed the diagnosis of asthma in 346 patients (69.7%). Compared to their normal-weight counterparts, obese asthma patients were more likely to be male and to have a history of hypertension and gastroesophageal reflux disease (GERD). They also had a lower FEV_1. Factors associated with a higher rate of asthma misdiagnosis were older age, male sex, and higher FEV_1.

Obesity did not predict asthma misdiagnosis, but there was a significant interaction with urgent visits for respiratory symptoms. Among patients with urgent visits in the past 12 months, the rate of asthma misdiagnosis was 4 times higher in those who were obese.

Among patients with confirmed asthma, obesity is associated with lower lung function and increased comorbidity, especially hypertension and GERD. Obese patients who make frequent urgent visits for respiratory problems may be at higher risk of asthma misdiagnosis. The authors highlight the need for objective lung function studies to confirm that the diagnosis of asthma is correct.

COMMENT: *Misdiagnosis of disease (eg, asthma) can have significant health care implications socially and individually. This paper presents factors that may contribute to misdiagnosis of asthma in the obese population. The authors present an algorithm to confirm the diagnosis. Strikingly, 30% of obese patients were misdiagnosed. The demographic of this group tended to be older, male, with GERD and a recent diagnosis. Treating patients appropriately starts with correct diagnoses.*

S.F.W.

Pakhale S, Doucette S, Vandemheen K, et al: A comparison of obese and nonobese people with asthma: exploring an asthma-obesity interaction.

Chest. 2010;137:1316-1323. ♦♦

New Data on T Cell Response to Allergens in Atopic Patients

A DEEPER understanding of the immunologic mechanisms leading to allergies, or to allergen tolerance, is needed. There is evidence that suppressive cytokines and CD4+CD25+ regulatory T cells may be involved in allergen-specific responses. The suppressive cytokine response to major grass allergens was compared in allergic vs healthy subjects.

Peripheral blood mononuclear cells (PBMCs) from subjects with and without allergy were stimulated with major grass allergens Phl p 1 or Phl p 5. In PBMC cultures from atopic subjects, the allergens induced production of interleukin-10 (IL-10), which down-regulated proliferation and cytokine production. These responses did not occur in PBMCs from healthy subjects. There was no significant difference in the frequency of CD4+CD25+ T cells between the 2 groups of PBMCs. However, the cells from atopic subjects showed fewer CD4+CD25+CCR4+ cells but more CD4+CD25+CLA+ cells.

In PBMCs from atopic patients, allergen stimulation induces regulatory cytokines that affect the allergen-specific response. The study documents differences in CD4+CD25+ T cell expression of chemokine receptors between atopic vs nonatopic subjects. These differences may affect the balance between effector and regulatory T cells at the site of allergic inflammation.

COMMENT: *Allergen immunotherapy is the procedure of our specialty to effectively modulate the immune response. Ongoing mechanisms to describe tolerance, the role of regulatory T cells, IL-10, and TGF-β suppressive cytokines have been described. This interesting study determined whether major grass allergens induce production of suppressive cytokines in allergic and healthy subjects. Allergen-specific responses of grass-allergic patients, but not nonatopic subjects, were influenced by regulatory cytokines produced in response to the important allergens. The authors believe that differences in CD4+CD25+ T-cell expression of chemokine receptors in allergic compared to nonatopic donors suggests that the homing of CD4+CD25+ T cells could be important for the regulation of allergen-specific responses.*

M.F.

Domdey A, Liu A, Millner A, et al: The T cell response to major grass allergens is regulated and includes IL-10 production in atopic but not in non-atopic subjects.

Int Arch Allergy Immunol. 2010;152:243-254. ♦♦

CLINICAL TIDBITS

Hygiene Hypothesis: Don't Blame Antibiotics

IT has been suggested that early exposure to antibiotics may affect immune responses in a way that increases the risk of childhood asthma, although studies of this issue have been inconsistent. The relationship between antibiotic use and early childhood asthma was assessed, with attention to confounding by indication.

The prospective birth cohort study included 424 children born in Tucson, Ariz., from 1997 to 2003. Parents were interviewed frequently about oral antibiotic ➤➤

use through the first 9 months of life. Asthma, eczema, and allergen-specific IgE levels were assessed through age 5.

Antibiotic exposure during infancy was unrelated to physician-diagnosed eczema or allergen-specific IgE levels. There was a significant, dose-response relationship between antibiotic use and asthma. However, asthma risk was also related to number of physician visits for illness. After adjustment for these visits, the association between antibiotics and asthma was no longer significant.

Early antibiotic exposure does not appear to increase the risk of childhood asthma, this prospective birth cohort association finds. Instead, children who make more office visits for illness receive more antibiotics and are at higher risk of asthma.

APPARENT increases in childhood allergy risk related to antibiotic exposure could reflect greater use of antibiotics in children with early infections. This potential source of confounding by indication was evaluated in a birth cohort study.

The analysis included 3,306 Swedish children enrolled at 2 months and followed up through age 8. Antibiotic use and respiratory infections were assessed at age 1, and evaluated as predictors of allergic diseases at age 4 and 8.

Forty-three percent of children received antibiotics during the first year, while 23% had at least one respiratory infection. Initial analysis suggested that children receiving antibiotics during the first year had higher rates of wheezing, asthma, eczema, and food hypersensitivity at age 4. The associations with wheezing and asthma remained significant after adjustment for respiratory infections in the first year, However; they were nonsignificant on subgroup analysis of children without early allergic signs. Apparent associations with allergic disease at age 8 became nonsignificant after adjustment for respiratory infections.

Early respiratory infections explain at least part of the apparent association between early antibiotic exposure and allergic diseases in childhood. Some types of respiratory infections during infancy may increase allergic disease risk.

COMMENT: *One of the theories used to explain the hygiene hypothesis is that the early use of antibiotics reduces exposure to pathogens that would otherwise prevent the immune system from deviating toward a Th2 pattern. These two studies refute that theory. Su et al analyzed data from the Infant Immune Study in Tucson, showing that after controlling for illness visits in the first year of life, there was no correlation between antibiotic use and either eczema or allergen-specific IgE. In the study by Mai et al, the relationship between antibiotic use in the first year of life and allergic disease appeared to be due to early respiratory infections rather than the antibiotics themselves.*
S.A.T.

Su Y, Rothers J, Stern DA, et al: Relation of early antibiotic use to childhood asthma: confounding by indication? Clin Exp Allergy. 2010;40:1222-1229.

Mai X-M, Kull I, Wickman M, Bergström A: Antibiotic use in early life and development of allergic diseases: respiratory infection as the explanation.
Clin Exp Allergy. 2010;40:1230-1237. ♦♦

Acupuncture Reduces Itching in Eczema

ITCH is a clinically important symptom of eczema. Studies using a histamine-induced itch model have reported a significant antipruritic effect of acupuncture.

In a randomized trial, 30 patients with atopic eczema were assigned to receive active acupuncture, placebo acupuncture, or no acupuncture in random order before and after an allergen (dust mite or grass pollen) skin prick. Given as either prevention or treatment, active acupuncture was associated with significantly lower itch intensity scores than placebo or no acupuncture. As a preventive measure, active acupuncture was also associated with smaller mean wheal and flare size. Significant effects were also noted for skin perfusion, measured using laser Doppler, and a validated itch questionnaire.

Applied correctly, acupuncture reduces allergen-stimulated itching in patients with atopic eczema. Both preventive and treatment effects are observed. Over time, the preventive effect on itch sensation decreases, while the effect in suppressing skin-prick reactions increases.

COMMENT: *Acupuncture is considered a mainstream medical therapeutic option for symptoms such as pain and nausea, but it is not generally on the short list of allergy treatments recognized by board-certified allergists. This randomized, placebo-controlled crossover study showed that eczema patients itch less with acupuncture treatment. Although there remain questions about its mechanism, acupuncture as an allergy treatment (or at least as a treatment for itching) can no longer be referred to as lacking evidence-based investigation.*
S.A.T.

Pfab F, Huss-Marp J, Garri A, et al: Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema a blinded, randomized, placebo-controlled, crossover trial.
Allergy. 2010;65:903-910. ♦♦

Montelukast Doesn't 'Boost' Effects of SIT

TREATMENTS that boost the induction of regulatory T (Treg) cells might further enhance the effectiveness of specific immunotherapy (SIT) for allergic diseases. Although its effects on Treg cell induction are unknown, montelukast has been shown to upregulate interleukin-10 (IL-10) production.

The effects of montelukast on the response to SIT were evaluated in 36 children with asthma and house dust mite allergy. During the 3-month buildup ➤➤

phase of SIT, one group received montelukast 5 mg/d while the other group received placebo. After this phase, inhaled corticosteroid dose was increased as needed to control asthma symptoms.

After 12 months on SIT, patients in the montelukast group needed more ICS to control asthma symptoms. Their median reduction in ICS dose was 33%, compared to 50% for children in the placebo group. Montelukast was associated with impaired production of regulatory T lymphocytes during the maintenance phase. During the buildup phase, several children in the placebo group had to drop out because of increased asthma symptoms.

Rather than increasing the effectiveness of SIT, giving montelukast during the buildup phase may lead to decreased effectiveness. Routine use of montelukast is not indicated in children undergoing SIT for allergic asthma.

COMMENT: *Specific immunotherapy in patients with allergic asthma can be disease-modifying. Montelukast, often used for asthma control, has been shown to upregulate IL-10 production, which should be favorable for SIT results. Unfortunately, in this study the opposite occurred: during early SIT, the montelukast group had reduced clinical and immunologic effectiveness compared to the placebo group. Whether this adverse outcome countermands using montelukast in allergic asthmatics undergoing SIT is up to the clinician, but at least it seems that the promise of "boosting" SIT with montelukast is unrealized.*
R.J.M.

Majak P, Rychlik B, Pułaski Ł, et al: Montelukast treatment may alter the early efficacy of immunotherapy in children with asthma.
J Allergy Clin Immunol, 2010;125:1220-1227. ♦♦

REVIEWS OF NOTE

COMMENT: *The concept of asthma as a multiple-phenotype syndrome is well accepted, but proving proposed pathophysiologic differences between phenotypes has been difficult. This critical review of childhood asthma phenotypes highlights the shortcomings of traditional phenotype descriptions and suggests that a recent "multidimensional approach" has promise.*
S.A.T.

Spycher BD, Silverman M, Kuehni CE: Phenotypes of childhood asthma: are they real?
Clin Exp Allergy. 2010;40:1130-1141. ♦♦

COMMENT: *This is a useful review of a common problem and is a nice companion article to Brad Chipps' review of infants and children with refractory lower respiratory tract symptoms. (See Ann Allergy Asthma Immunol. 2010;104:279-283.)*
D.K.L.

Ramanuja S, Kelkar PS: The approach to pediatric cough.
Ann Allergy Asthma Immunol. 2010;105:3-8. ♦♦

COMMENT: *An herbal treatment that inhibits food anaphylaxis sounds too good to be true--so most likely it is not true. Nevertheless, this internationally recognized group has demonstrated remarkable effects of this herbal product in food-allergic mice, and now there is evidence it is safe in food-allergic humans. Now if the humans will only respond like the mice to food challenge, we will really have something. Time will tell if this is too good to be true.*
D.K.L.

Wang J, Patil SP, Yang N, et al: Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, double-blinded, placebo-controlled, dose escalation, phase 1 study.
Ann Allergy Asthma Immunol. 2010;105:75-84.

COMMENT: *Obesity is a major health problem. Studies of obesity and atopic sensitization have been inconsistent in both children and adults. These authors hypothesized that obesity might increase the likelihood of a Th2 cell immune response, and that adipokines and cytokines secreted by white adipose tissue might result in decreased immunologic tolerance. They examined the associations between body mass index, waist circumference, and atopic sensitization in adults living in a rural community and showed a significant association between obesity atopy. Atopic sensitization, as indicated by a positive skin test result to common aeroallergens, was significantly associated with obesity. Abdominal obesity was associated with an increased risk of atopic sensitization. The mechanisms for atopic sensitization associated with obesity need to be explored.*
M.F.

Chen Y, Rennie D, Cormier Y, et al. Association between obesity and atopy in adults.
Int Arch Allergy Immunol. 2010; 153:372-377. ♦♦