AllergyWatch®

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

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Tiotropium May Be Effective in Poorly Controlled Asthma

SOME patients with asthma don't achieve adequate disease control despite standard inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABAs). The long-acting anticholinergic drug tiotropium is approved for use in chronic obstructive pulmonary disease, but not asthma. Two randomized trials evaluated the effects of add-on tiotropium in patients whose asthma was poorly controlled on ICS plus LABAs.

The PrimoTinA-asthma 1 and 2 trials included a total of 912 adults with poorly controlled asthma despite inhaled ICS (at least 800 µg of budesonide or equivalent) and LABAs. Enrolled patients had at least one severe exacerbation in the previous year, along with persistent symptoms and a postbronchodilator FEV_1 of 80% of predicted or less (mean 62% of predicted).

In addition to ICS plus LABA, the patients were randomly assigned to treatment with tiotropium, total dose 5 µg, or placebo, once daily via soft-mist inhaler. Lung function, asthma exacerbations, and other outcomes were compared through 48 weeks of treatment.

Add-on tiotropium led to greater improvements in FEV_1, compared to placebo. At 24 weeks, the mean difference in peak FEV_1 was 86 mL in trial 1 and 154 mL in trial 2. Mean differences in prebronchodilator FEV_1 were 88 and 111 mL, respectively. Time to first severe exacerbation was 282 days in the tiotropium groups versus 226 days in the placebo groups: hazard ratio 0.79. Asthma and quality of life scores were similar between the two treatments.

The PrimoTinA-asthma 1 and 2 trials replicate previous reports showing benefits of add-on tiotropium for patients whose asthma is uncontrolled despite ICS plus LABAs. Benefits include a reduced rate of severe exacerbations and modest sustained bronchodilation. Adverse effects are consistent with clinical experience with tiotropium; the reasons for inconsistent results between the two studies are unclear. ➤➤

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

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

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

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COMMENT: *Anticholinergics have traditionally played a "stepsister" role in the treatment of asthma. In two replicate trials of 912 patients who remained symptomatic despite the use of moderate-high dose ICS plus LABAs, Kerstjens et al demonstrated that add-on tiotropium not only provided sustained bronchodilation, but also resulted in reduced asthma exacerbations (21%). Although the improvements in* FEV_1 *were relatively small (less than 10%), these patients were already receiving a LABA and had fixed airflow limitation. In an accompanying editorial, Bel (***N Engl J Med.** *2012;367:1257-1259) points out that prior adherence of subjects to ICS plus LABA combination and the ability of the high fine-particle fraction inhaler Respimat to penetrate deeper into the lung might need to be factored in, along with the speculated selectivity of tiotropium in the "COPD-phenotype" of asthma. Cardiovascular safety in patients with underlying heart issues may need to be tested in a separate study.*
C.D.

Kerstjens HAM, Engel M, Dahl R, et al: Tiotropium in asthma poorly controlled with standard combination therapy.
N Engl J Med. 2012;367:1198-1207. ♦♦

In Children, ICS Affects Adult Height by Up to Half an Inch

In prepubertal children with asthma, inhaled corticosteroids (ICS) have been associated with slowing of growth. Although growth velocity returned to normal within a few years, the effects of ICS treatment on final adult height remain unclear. This issue was addressed using long-term follow-up data on patients enrolled in the Childhood Asthma Management Program (CAMP).

The researchers measured final adult height in 943 CAMP patients, representing more than 90% of those enrolled. At age 5 to 13, the patients were randomly assigned to treatment with budesonide 400 µg, nedocromil 16 mg, or placebo; treatment continued for 4 to 6 years. Measurements of adult height, made at an average age of 24.9 years, were compared between treatment groups. The analysis included adjustment for demographic factors, disease characteristics, and baseline height.

Patients assigned to budesonide had a small but significant reduction in adult height: mean difference 1.2 cm, compared to the placebo group. Adult height was not unaffected by nedocromil. Children receiving higher ICS doses had greater reductions in height: each 1 µg/kg increase in daily budesonide dose was associated with a 0.1 cm decrease in adult height.

Most of the final reduction in height was already apparent after 2 years of treatment, and most of the ICS-related reduction in growth velocity occurred among prepubertal children. Other factors associated with shorter adult height included longer time since asthma diagnosis at baseline and positive allergy skin test results.

Long-term ICS therapy for childhood asthma is associated with reductions in final adult height. The reduction is significant though small, and is not "progressive or cumulative." The researchers highlight the need to balance the disease control benefits of ICS versus the effects on growth, and to use the lowest effective dose for symptom control.

COMMENT: *Measurements of adult height were obtained for 943 of the original 1,041 CAMP study participants. More than 96% of measurements were obtained from patients who had attained adult height (women 18 or older, men 20 or older). Contrary to previous, smaller studies, the adjusted mean adult height was 1.2 cm lower in the budesonide group than in the placebo group: 171.1 cm vs 172.3 cm. The deficit in height seemed to occur in the first 2 years of treatment, was seen primarily in prepubertal participants, and was neither progressive nor cumulative. Although factors such as selection of ICS, delivery device, and optimization of ICS dose may help minimize the potential growth deficit, it is heartening that the reduction is a barely perceptible half-inch or less!* ➤➤

C.D.

Kelly HW, Sternberg AL, Lescher R, et al: Effect of inhaled glucocorticoids in childhood on adult height. **N Engl J Med**. 2012;367:904-912. ♦♦

Again, Symptom-Based ICS Use Is Comparable to Daily Use

PATIENTS receiving controller medications, especially inhaled corticosteroids (ICS), need periodic dose adjustments. Various approaches are used in making these adjustments, including physician assessments, biomarker measurements, or patient symptoms. These three approaches to adjusting ICS therapy for asthma were compared in a randomized controlled trial.

In the study, 342 adults receiving low-dose ICS therapy for mild to moderate asthma were assigned to three different dose-adjustment strategies. One group received adjustments based on physician assessment, with ICS dose adjusted ever 6 weeks. In a second group, adjustments were based on measurement of exhaled nitric oxide as an asthma biomarker. In the third group, adjustments were based on asthma symptoms; patients were instructed to take ICS whenever they used rescue albuterol. The main outcome of interest was time to treatment failure, defined as asthma exacerbations or in-home or clinic measurements.

Times to treatment failure were similar across the three strategies, with 9-month Kaplan-Meier failure rates of 22% in the physician assessment group, 20% in the biomarker group, and 15% in the symptom-based group. There was no significant difference for the physician adjustment strategy versus the biomarker or symptom-based strategy. Asthma exacerbations and other secondary outcomes were comparable as well. Monthly ICS use was lower with the symptom-based strategy.

The results support the use of a symptom-based adjustment strategy for ICS dose adjustment for adults with mild to moderate asthma. Treatment failure, exacerbations, and other key outcomes are similar to those achieved with biomarker- or physician assessment-based strategies. The symptom-based approach "may be appropriate in most patients with mild to moderate asthma," the researchers write.

COMMENT: *The Best Adjustment Strategy for Asthma in the Long Term (BASALT) study was a parallel, three-group, placebo controlled, multicenter randomized controlled trial of 342 adults with mild to moderate controlled asthma. Patients were assigned to three approaches to adjusting ICS therapy: physician assessment, biomarker, and symptom-based. For symptom-based adjustment, ICS was taken with each albuterol rescue use; for the others, the ICS dose was adjusted every 6 weeks. Similar to the results of the IMPACT and BEST trials comparing rescue ICS use with symptoms vs other interventions--in patients with mild and mild-moderate persistent asthma, respectively--there were no significant differences in time to treatment failure. Our patients indeed seem to know what is best for them!*

C.D.

Calhoun WJ, Ameredes BT, King TS, et al: Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of ICS therapy in adults with asthma: The BASALT randomized controlled trial. **JAMA**. 2012;308:987-997. ♦♦

Should Pregnant Women Stop Eating Nuts?

THERE is ongoing debate as to whether eating peanuts and tree nuts during pregnancy affects the child's risk of developing allergic disease. Many women reduce nut intake during pregnancy; however, data are limited and some studies suggest that nut intake may promote immunotolerance. Danish registry data were used to explore the association between maternal nut intake and allergic disease in children.

A food frequency questionnaire was used to assess maternal intake of peanuts and tree nuts in 61,908 pregnancies recorded in the Danish National Birth Cohort. Parent-reported childhood asthma symptoms, wheezing symptoms, and recurrent wheezing were evaluated when the children were 18 months old. Physician diagnoses and medication-related diagnoses of asthma at age 7 years were assessed using linked patient registry data.

Eating nuts at least once weekly during pregnancy was associated with a reduced rate of allergic disease in offspring. For asthma at age 18 months, odds ratios were 0.79 for maternal peanut intake and 0.75 for tree nut intake. For maternal intake of peanuts at least once weekly, odds ratios were 0.66 for registry-based and 0.83 for medication-related asthma diagnosis, respectively. Higher consumption of tree nuts during pregnancy was also associated with reduced allergic disease risk: odds ratio 0.81 for medication-related asthma diagnosis and 0.80 for self-reported allergic rhinitis.

This prospective, national birth cohort study finds no evidence that eliminating maternal peanut or tree nut consumption during pregnancy reduces allergic disease risk in children. To the contrary, risk of asthma and other allergic diseases may be lower for children whose mothers ate nuts during gestation. The investigators conclude, "These results do not support avoidance of nuts during pregnancy."

COMMENT: *Some more good news suggesting there's no need to alter the diet in mothers worried about development of atopic disease in their offspring. Data from a Danish birth cohort examining associations between maternal peanut and tree nut intake during pregnancy showed an unexpected inverse association with asthma and wheeze at 18 months. Additionally, higher peanut intake was inversely associated with a registry diagnosis of asthma at age 7 years, although there was weakening of some of the associations when analyzed independent of tree nut intake. Potential weaknesses of the study were its dependence on self-reporting of exposure and outcomes and inability to estimate risk for hidden, processed nut products.*

C.D. ➤➤

Maslova E, Granström C, Hansen S, et al: Peanut and tree nut consumption during pregnancy and allergic disease in children--should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort.
J Allergy Clin Immunol. 2012;130:724-732. ♦♦

Ambient Pollen Counts Affect ED Visits for Asthma

AMBIENT pollen levels have been linked to measures of asthma morbidity. Especially with aeroallergen burdens and asthma prevalence expected to increase worldwide, it is important to understand the population-level associations between pollen levels of asthma. A decade of ambient pollen measurements was evaluated for associations with emergency department (ED) visits for asthma and wheezing.

The study used airborne pollen contractions measured at an Atlanta allergy clinic from 1993 through 2004. Three-day moving averages for selected pollen taxa were analyzed for associations with ED visits for asthma and wheezing in the Atlanta metropolitan area. The analyses were adjusted for covariation in pollen taxa and for ambient air pollutant levels.

Significant associations with ED visits were noted for several pollen taxa. For each standard deviation (SD) increase in *Quercus* species and Poaceae pollen, ED visits for asthma and wheezing increased by 2% to 3%. For days with the highest concentrations of these pollen taxa (top 5%), risk of ED visits was 10% to 15% higher than for days with lower levels (bottom 50%). For Cupressaceae, each SD increase in pollen concentration was associated with a 1% decrease in ED visits.

Children aged 5 to 17 showed the greatest effect of *Quercus* on ED visits. Because of potential confounding by rhinoviruses, it was difficult to assess the impact of *Ambrosia* species pollen on ED visits. Associations for Betulaceae and Pinaceae pollen were not significant after controlling for the effects of *Quercus*.

Ambient pollen levels show significant associations with rates of ED visits for asthma and wheezing. At least in Atlanta, *Quercus* and Poaceae pollen are independently related to asthma morbidity. The authors discuss the implications for management, including aeroallergen surveillance and early warning systems.

COMMENT: *As allergists we have known that when pollen counts increase, our allergic patients have more problems. This is the first epidemiologic study to correlate short-term changes in airborne pollen counts with ED visits for asthma. Using pollen counts--which happened to be reported by our practice's pollen-collecting station over a 12-year period--these Atlanta-based researchers found that ED asthma visits increased by 10% to 15% during the preceding 3 days of the highest concentration pollen days. The association was particularly strong for oak tree and grass pollens. It may be helpful for allergic patients to follow local pollen counts in planning their outdoor activities. This study provides another reason for determining a patient's allergic asthma triggers.*

S.M.F.
Darrow LA, Hess J, Rogers CA, et al: Ambient pollen concentrations and emergency department visits for asthma and wheeze.
J Allergy Clin Immunol. 2012;130:630-638. ♦♦

Egg Allergy Resolves Faster on Baked-Egg Diet

MOST egg-allergic children can tolerate baked foods containing eggs. Baked egg ingestion may lead to immunologic changes similar to those associated with resolution of egg allergy after food oral immunotherapy. Resolution of egg allergy was compared for children who started a baked-egg diet versus egg avoidance.

The follow-up study included egg-allergic children who tolerated baked-egg challenge and subsequently began including baked-egg products in their diet. Immunologic outcomes and the development of tolerance were compared with a group of children who continued on strict egg avoidance.

Intention-to-treat analysis included 79 children with a median follow-up of 37.8 months. Of these, 89% were able to tolerate baked egg and 53% tolerated regular egg. Of 23 children who initially reacted to baked egg, 61% tolerated baked egg and 26% tolerated regular egg at follow-up.

Within the group who initially reacted to baked egg, baseline egg-specific IgE levels were higher in those with persistent reactivity: median 13.5 kU_A/L, compared to 4.4 kU_A/L in those who developed tolerance to baked egg and 3.1 kU_A/L in those who developed tolerance to regular egg. Baked egg ingestion was associated with reductions in egg white-induced skin prick wheals and in egg white-, ovalbumin-, and ovomucoid-specific IgE levels, plus increases in ovalbumin- and ovomucoid-specific IgG_4 levels.

A per-protocol group (excluding children with persistent baked-egg reactivity) was much more likely than the comparison group to develop tolerance to regular egg: hazard ratio 14.6. They also developed tolerance faster, median 50.0 versus 78.7 months.

For egg-allergic children, incorporating baked egg into the diet leads to faster development of regular egg tolerance, compared to strict avoidance. Children with higher baseline egg white-specific IgE levels are more likely to have persistent reactivity to baked as well as regular egg. Those who initially react to baked egg may still develop tolerance.

COMMENT: *It is well known that approximately 80% of children with egg white allergy outgrow their sensitivity and up to 70% with positive AST to egg can tolerate baked egg in their diet. This study provides data to support recommendations for when to consider a supervised oral challenge with baked-egg muffin. Most children with relatively lower egg-specific IgE levels were able to tolerate the challenge. Interestingly, children who tolerated baked egg also had changes in immunologic parameters suggesting accelerated tolerance to regular egg. The article has a flow chart of criteria for egg challenges; the online version includes* ➤➤

a suggested recipe to help patients prepare for the challenge. The muffins even taste good!
S.M.F.
Leonard SA, Sampson HA, Sicherer SH, et al: Dietary baked egg accelerates resolution of egg allergy in children.
J Allergy Clin Immunol. 2012;130:473-480. ♦♦

Can Food Allergy Testing Identify the Cause of EoE?

PATIENTS with eosinophilic esophagitis (EoE) have isolated eosinophilic inflammation in the esophagus. Esophagitis is predominantly triggered by foods, but it can be difficult to identify the causative food. The authors report their experience with an approach to identifying inciting foods in children with EoE.

The retrospective study included 941 patients with EoE seen at a specialized children's hospital center for eosinophilic disorders. Assessments included skin prick and atopic patch testing (SPT/APT) and identification of IgE-mediated food allergies. A food was defined as causative if the esophageal inflammation resolved after elimination, or if EoE recurred when the food was reintroduced. The clinical effects of targeted food antigen elimination were compared with those of other dietary approaches.

A causative food was identified in 33.9% of children with EoE. The most commonly identified foods were milk, egg, wheat, and soy; most of these children reacted to two or more foods. Fifteen percent of patients had IgE-mediated food reactions, ie, urticaria and anaphylaxis. The combination of SPTs and APTs had an average negative predictive value of 92%, although this value decreased to 44% for milk. The average positive predictive value was 44%.

The histologic success rate was 53% both for targeted removal of foods positive on allergy testing and for an empiric six-food elimination diet. Elimination of foods identified by SPT/APT plus empiric milk elimination yielded a resolution rate of 77%.

For children with EoE, an elimination diet based on food allergy tests offers an alternative to empiric food elimination diets. The two approaches provide similar success rates, but the targeted strategy requires elimination of fewer foods. Better methods of testing for children with EoE are needed, particularly for milk.

COMMENT: *There seem to be more patients in our offices with EoE in recent years, but determining which foods should be eliminated from their diet can be problematic. In this retrospective analysis of patients from the Children's Hospital of Philadelphia, the causative food was identified in 319 of the total 941 patients with EoE. Milk, egg, wheat, and soy were most commonly documented, either by immediate allergy skin tests or by patch testing. Removal of the skin test-positive food resulted in histologic improvement in 53% of patients, similar to the improvement in the group who followed an empiric six-food elimination diet. The authors suggest that since most of the children were sensitive to milk, egg and meats, a vegan diet might be helpful and more socially acceptable.*
SMF
Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al: Identification of causative foods in children with eosinophilic esophagitis treated with an elemental diet.
J Allergy Clin Immunol. 2012;130:461-467. ♦♦

Periostin: New Biomarker of Airway Eosinophilia

IN a recent study, the authors identified an asthma subtype defined by expression of genes inducible by Th2 cytokines in the bronchial epithelium. About one-half of patients with asthma have this gene signature, which includes periostin. Serum periostin was evaluated as a systemic biomarker of eosinophilic airway inflammation in patients with severe persistent asthma.

The study included 67 patients with persistent asthma symptoms despite maximal inhaled corticosteroid (ICS) therapy, drawn from the multicenter Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma (BOBCAT). The patients, mean age 46 years, had a mean FEV_1 of 60% predicted with a mean Asthma Control Questionnaire score of 2.7. Exhaled nitric oxide, peripheral blood eosinophils, periostin, YKL-40, and IgE levels were compared with airway eosinophilia. Periostin was measured using a highly sensitive new peripheral blood assay.

Serum periostin was sensitive, but not specific, for airway eosinophilia. At a cutoff of 25 ng/mL, serum periostin identified eosinophil-low and eosinophil-high patients with a positive predictive value of 93%. In a logistic regression model including 59 patients with severe asthma, serum periostin was the single best predictor of airway Th2/eosinophilic inflammation. In this regard, periostin was superior to IgE, blood eosinophil count, exhaled NO, or YKL-40.

The findings suggest that serum periostin could be a useful systemic biomarker of airway eosinophilia in asthmatic patients. This biomarker could be of special value in identifying asthma patients likely to benefit from experimental Th2-targeted treatments.

COMMENT: *What is the most important inflammatory marker for patients with eosinophilic asthma inflammation? Periostin is a matricellular protein that is partially regulated by interleukin-13. It has recently been suggested as a biomarker that can identify airway eosinophilia and the potential response to Th2-directed therapies for asthma. Using data from a subset of patients from the BOBCAT study, these researchers found that serum periostin measurements were more discerning than exhaled NO, blood eosinophils, or YKL-40--another marker of asthmatic inflammation--for monitoring airway eosinophilia. Periostin is not asthma-specific; it is also increased in other conditions, particularly those associated with tissue injury, cellular hyperplasia, and stress. It may be time for another Raft Debate on inflammatory markers at our annual meeting.*
S.M.F. ➤➤

Jia G, Erickson RW, Choy DF, et al: Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients.
J Allergy Clin Immunol. 2012;130:647-654. ♦♦

Risk Factor for Severe Hymenoptera-Induced Anaphylaxis

SKIN involvement is an "early and obvious" sign of anaphylaxis, but hypotension and respiratory symptoms can occur even without skin involvement. Various risk factors for severe anaphylaxis related to Hymenoptera stings have been suggested. The study further examined the indicators of and risk factors for severe anaphylaxis caused by Hymenoptera field stings.

The retrospective analysis included 657 consecutive patients referred to the authors' department for venom immunotherapy from 2003 to 2010. Of these, 26.2% had severe, grade III anaphylactic sting reactions. Patient-specific factors and details related to the sting reaction were analyzed for associations with the severity of reactions. Baseline serum tryptase (BST) was measured in subgroups of patients with moderate to severe anaphylaxis.

Elevated BST was associated with severe anaphylaxis. Other significant factors were lack of urticaria or angioedema during the anaphylactic reaction, symptoms developing less than 5 minutes after the sting, and older age. Absence of urticaria/angioedema and elevated BST were significantly related to each other. In contrast to previous reports, comorbid illnesses and use of beta-blockers or angiotensin-converting enzyme (ACE) inhibitors were not significantly related to severity of anaphylaxis.

This large cohort study suggests steps for individual assessment of risk of severe Hymenoptera-sting induced anaphylaxis. Severe reactions are more likely in patients with elevated BST and in older adults. Absence of urticaria or angiodema is also a significant indicator of severe anaphylaxis, and possibly mastocytosis, and is an indication for BST measurement. The study finds no evidence that concurrent cardiovascular medications aggravate sting-induced anaphylaxis.

COMMENT: *Our current understanding about anaphylaxis is that the most common symptom is skin involvement with urticaria and pruritus. In this German study of 657 patients who were candidates for venom immunotherapy, elevation of BST, absence of urticaria or angioedema during anaphylaxis, rapid onset of symptoms after the sting, and older age were the main four indicators and risk factors for anaphylaxis after Hymenoptera stings. Interestingly, the authors report that cardiovascular medications such as beta-blockers or ACE inhibitors were not a significant risk factor in these patients. This study suggests that we should consider obtaining tryptase levels in our older patients who have had anaphylaxis following Hymenoptera stings, particularly if they have not had urticaria.*
S.M.F.
Stoevesandt J, Hain J, Kerstan A, et al: Over- and underestimated parameter in severe Hymenoptera venom-induced anaphylaxis: cardiovascular medication an absence of urticaria/angioedema.
J Allergy Clin Immunol. 2012;130:698-704. ♦♦

Cutaneous Reactions to Systemic Steroids--16 Cases

ALLERGIC hypersensitivity to corticosteroids is common, with delayed reactions seen more often than immediate reactions. Sensitization and subsequent elicitation of reactions generally occurs via the skin. This study reports on 16 patients with contact dermatitis occurring as a reaction to systemic corticosteroids.

The 16 cases were identified from a series of 315 patients with delayed-type hypersensitivity reactions to corticosteroids, seen at the authors' dermatology department over an 18-year period. All patients developed skin reactions followed systemic administration of corticosteroids--including intra-articular injections. All but 2 had previously been exposed to the same molecule via the skin.

All patients developed generalized eruptions within hours or days after the first corticosteroid dose; three also had "flare-up" reactions at previously involved skin sites. Eleven patients reacted to corticosteroid molecules from all three groups of the recently reappraised classification. Methylprednisolone and other group 1 molecules were the most frequently involved corticosteroids.

"Systemic contact dermatitis" reactions to oral or parenteral corticosteroids can occur. In most such cases, the patient has been sensitized to previous topically applied corticosteroids. Many patients will react to any type of corticosteroid molecule, underscoring the need for individualized evaluation of their sensitization/tolerance profile.

COMMENT: *Corticosteroid allergy is a relatively rare but well-accepted form of allergic contact sensitivity. This large retrospective chart review identified 16 cases, out of 15 confirmed with corticosteroid contact allergy, who reported cutaneous symptoms hours to days after systemic administration of corticosteroids, suggesting apparent "systemic contact dermatitis." All had previously experienced local symptoms after topical administration of corticosteroid. This underscores the importance of considering corticosteroid allergy in patients reporting symptoms after topical steroid use.*
S.A.T.
Baeck M, Goossens A: Systemic contact dermatitis to corticosteroids.
Allergy. 2012;67:1580-15850. ♦♦

Are Beer-Allergic Patients Allergic to All Beers?

IgE-mediated allergy to beer is an uncommon but well-documented condition. Most reported cases are ➤➤

associated with hypersensitivity to the nonspecific lipid transfer protein (LTP). However, since brewing processes vary widely, affected patients may not be allergic to all beers. Allergy tests and oral challenges with many different beers were performed in a patient with beer allergy.

The patient was a 45-year-old man with repeated episodes of urticaria, facial angioedema, oral mucosa swelling, and dyspnea after drinking beer. Skin prick testing (SPT) showed hypersensitivity to grass pollen, cat dander, and *Alternaria tenuis*, along with weak skin reactivity to corn.

Further testing included SPTs with 36 different brands of beer, followed by open challenge with beers with negative SPT results. Immunoblot studies were performed using two SPT-positive and two SPT-negative beers as well as barley, wheat, and maize extracts; these tests included patient serum as well as a maize LTP-specific polyclonal antibody from rabbit.

The patient had positive SPT results to 30 out of 36 beers. Immunoblot tests showed IgE reactivity at about 10 kDa--corresponding to the molecular weight of LTP--for the two SPT-positive beers and for maize. This was so for both the patient's serum and the polyclonal anti-LTP rabbit serum; no such reactivity was noted for the SPT-negative beers or barley extract. The immune-reactive LTP from one beer was isolated, and was found to co-migrate with purified maize LTP. The patient was advised to drink only the beers that he tolerated on challenge testing, and had no further allergic reactions.

The results show that patients with beer allergy may not react to all types of beer. Testing may identify brands of beer that the patient can tolerate without risk of reactions. The authors note that their patient was able to tolerate other corn products; they speculate that alcohol in beer may have enhanced intestinal absorption of the allergen.

COMMENT: *We all have patients who report symptoms after consuming certain kinds of beer, especially during the Oktoberfest season. However, relatively little is known about the components of certain beers that are likely to cause symptoms. This study, which excluded metabisulfite allergy, performed both beer skin tests and immunoblot studies. The results showed variations in skin test reactivity that correlated with oral challenge results. Although much is still unknown about this condition, the study shows there is hope on the horizon for our beer-loving patients who have had allergic problems with their beverage of choice.*
S.A.T.

Quercia O, Zoccatelli G, Stefanini GF, et al: Allergy to beer in LTP-sensitized patients: beers are not all the same.
Allergy. 2012;67:1186-1189. ♦♦

Free Light Chains May Play a Role in Nasal Polyposis

INCREASED free light chain (FLC) concentrations are seen in various inflammatory disorders, in which they may act by mediating mast cell-dependent immune responses. Mast cells may be involved in chronic rhinosinusitis with nasal polyposis (CRSwNP), which is associated with a local Th2 inflammatory response. Free light chains were evaluated as a possible mast cell-activating factor in patients with CRSwNP.

The study included 41 CRSwNP patients, along with 46 CRS patients without nasal polyps and 25 controls. Immunohistochemistry was used to measure expression of FLCs in nasal polyp specimens. The effects of treatment with methylprednisolone, doxycycline, anti-interleukin-5 (mepolizumab), and placebo on levels of FLC in serum and nasal secretions were examined as well.

Both groups of CRS patients--especially the CRSwNP group--showed increased FLC concentrations in nasal secretions and nasal mucosal tissue specimens. Immunohistochemical studies confirmed diffusely increased FLC concentrations in nasal polyp tissue. Patients with CRSwNP showed decreased systemic FLC concentrations in response to methylprednisolone, and decreased local FLC concentrations in response to mepolizumab.

The study documents expression of FLCs in CRS patients with or without nasal polyps. Free light chains may thus play a role in mediating the local immune reaction. The response to mepolizumab in CRSwNP patients suggests a possible role of interleukin-5 in the production, effects, or function of FLC.

COMMENT: *In recent years we have realized that immunoglobulins play many roles beyond specific binding to antigens. In allergy, for example, monoclonal anti-IgE may be more potent in disrupting the regulatory roles of the IgE molecule than in reducing the effects of mast cell activation from allergen recognition. This study demonstrates that lambda and kappa light chains are not only found in nasal polyp tissue, but may play a role in perpetuating this Th2 inflammation, independent of atopic status.*
S.A.T.

Groot Kormelink T, Calus L, De Ruyck N, et al: Local free light chain expression is increased in chronic rhinosinusitis with nasal polyps.
Allergy. 2012;67:1165-1172. ♦♦

Going to the Dogs: Exposure May Reduce Early Respiratory Infections, Too

RECENT studies suggest that exposure to dogs in early life may reduce innate immune responses. Information on the relationship between pet exposure and respiratory tract infections during early childhood may lend insights into the factors affecting maturation of immune responses. This study looked for associations between home pet exposure and respiratory tract infections during the first year of life.

The researchers analyzed data on dog and cat exposure and frequency of respiratory symptoms in a birth cohort of 397 Finnish children. On multivariate analysis, children exposed to dogs at home had fewer respiratory tract symptoms or infections. The adjusted ➤➤

odds ratio for remaining healthy (ie, no respiratory symptoms or infections) was 1.31 for children exposed to dogs.

Home dog exposure was also associated with a significant reduction in otitis, odds ratio 0.56, along with a trend toward less need for antibiotics. A univariate analysis suggested lower respiratory morbidity for children who had more weekly and yearly contact with dogs and cats. The risk of respiratory tract symptoms or infections was lowest for children who lived in houses where dogs spent only part of the day indoors--less than 6 hours.

Early exposure to pets, particularly dogs, seems to influence the risk of respiratory infections during the first year of life. The findings add to the evidence that animal contacts in early life may strengthen resistance to childhood respiratory illnesses.

COMMENT: *Numerous studies have focused on the presence of cats and dogs in childhood homes, as related to subsequent development of allergic disease. But drilling down further, perhaps a reduction in respiratory infections is another byproduct of the "bacterial diversity" which seems to be largely associated with dogs. Reverse causality-- from atopic families avoiding animals altogether--could not be completely discounted in this prospective study.*
K.R.M.

Bergroth E, Remes S, Pekkanen J, et al: Respiratory tract illnesses during the first year of life: effect of dog and cat contacts.
Pediatrics. 2012;130:211-220. ♦♦

Controversies in Management of Pediatric Asthma

THERE are significant differences among different sets of "evidence-based" recommendations for managing pediatric asthma. The "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) methodology was developed to provide a structured and transparent approach to assessing evidence and arriving at recommendations. The authors applied the GRADE approach to three areas of controversy in clinical management of pediatric asthma.

The 3 topics included in the analysis were: treatment for "step 3" asthma that is not controlled by standard-dose inhaled corticosteroids (ICS), use of leukotriene receptor antagonists for viral wheezing, and the clinical role of extra-fine-particle aerosols. After performing systematic literature reviews on each topic, the researchers used GRADE methods to rate the quality of the evidence and the strength of recommendations. Final recommendations were developed with consideration of benefits versus harms, preferences and values, and resource use.

Using this approach, the researchers made recommendations for all three problems that differ from those of current international guidelines. For step 3 pediatric asthma, doubling the dose of ICS was preferred over adding a long-acting β-agonist. Inhaled corticosteroids were preferred over leukotriene receptor antagonist for initial treatment of wheezing in preschoolers, while extra-fine-particle ICS products were not recommended for initial treatment of childhood asthma. However, all three recommendations were regarded as weak, based on low-quality evidence for some important patient outcomes.

This analysis, following a systematic and transparent approach to assessing the research evidence, leads to different recommendations for three current controversies in pediatric asthma management. Further efforts using the GRADE approach may be helping in updating recommendations, improving implementation of practice guidelines, and defining important but unanswered research questions.

THERE is ongoing debate over the best therapeutic option for "step 3" children with asthma that is not controlled with inhaled corticosteroids (ICS): increasing the ICS dose or adding a long-acting β_2-agonist. The authors report a systematic review of randomized trials addressing this issue.

A literature search identified nine randomized controlled trials of LABAs versus increased ICS dose for children or adolescents with uncontrolled persistent asthma. The studies, including a total of 1,641 patients, were performed between 1996 and 2012. A meta-analysis compared the two strategies for their effects on asthma exacerbations requiring systemic corticosteroids. A wide range of secondary outcomes were analyzed as well.

The meta-analysis found no significant difference in the primary outcome between LABA plus ICS versus increased doses of ICS: odds ratio 0.76, 95% confidence interval 0.48 to 1.22. In a subgroup analysis to examine the effect of ICS dose, exacerbation risk was lower with LABA plus ICS versus higher than a doubled dose of ICS: odds ratio 0.48, 95% confidence interval 0.28 to 0.82. Some secondary outcomes favored LABA plus ICS, including peak expiratory flow, rescue medication use, and short-term growth.

This review and meta-analysis of recent randomized trials finds no significant difference between the two strategies for management of uncontrolled persistent asthma in children. However, exacerbation risk appears lower with ICS plus LABA compared to higher than double doses of ICS.

COMMENT: *The GRADE approach is a method for developing clinical guidelines and practice parameters. Using GRADE, Boluyt et al conclude that increasing ICS over LABA at step 3 of the NHLBI guidelines is most appropriate (based on the literature through June, 2010), among other interesting findings using this approach.*

The exact same question--what to do at step 3--yields a completely different answer in the meta-analysis by Castro-Rodriguez et al (based on the literature through January 2012). Recent data linking ICS to (slight) permanent growth reduction might tip the scales further toward LABA, of course dependent on the quality of that evidence. Kudos to Pediatrics *for publishing* ➤➤

these studies sequentially, highlighting the controversy!
Boluyt N, Rottier BL, de Jongste JC, et al: Assessment of controversial pediatric asthma management options using GRADE. **Pediatrics**. 2012;130:e658-e668.
Castro-Rodriguez JA, Rodrigo GJ: A systematic review of long-acting β2-agonists versus higher doses of inhaled corticosteroids in asthma.
Pediatrics. 2012;130:e650-e657. ♦♦

The FDA Weighs in on Whey Partially Hydrolyzed Formula

THE U.S. Food and Drug Administration is required to authorize certain types of health claims made on the labeling of foods and dietary supplements. Authors from the FDA's Office of Nutrition, Labeling, and Dietary Supplements discuss their review of a health claim that 100% whey-protein partially hydrolyzed infant formula (W-PHF) can reduce the risk of atopic dermatitis (AD).

The FDA was petitioned to review a qualified health claim that W-PHFs can reduce AD risk in healthy infants with a family history of allergy who are not exclusively breast-fed, and that protection would continue up to 3 years of age. Reports of 20 intervention studies were evaluated. No scientific conclusions could be drawn from 16 studies for various reasons--most commonly the lack of definitive diagnosis of AD cases.

Of the remaining four studies, only two showed an association between W-PHF consumption during the first four months of life and a reduced risk of AD through the first year. Just one of these studies was a large, high-quality intervention; this was the only study to report a continuously reduced risk throughout the first year and up to 3 years.

Based on its review, the FDA concludes that there is "very little credible evidence" for the claim that W-PHF can reduce AD risk in infants. The conclusion also requires a statement, in boldface type, that these products should not be fed to infants with milk allergy. Further scientific data related to this claim or possible safety concerns will be evaluated as they become available.

COMMENT: *Potential health claims by infant formula manufacturers require rigorous scrutiny by the FDA, before any marketing. This summary reviews the FDA decision-making process that found little evidence of a qualified health claim for use of whey partially hydrolyzed formula to reduce the risk of atopic dermatitis. Further, concern regarding possible confusion for parents of milk-allergic infants is elaborated.*
K.R.M.
Chung CS, Yamini S, Trumbo PR: FDA's health claim review: Whey-protein partially hydrolyzed infant formula and atopic dermatitis.
Pediatrics. 2012;130:e408-e414. ♦♦

Cow's Milk Allergy-- Natural Course and Persistence

COW'S milk allergy (CMA) resolves in most patients, but is more likely to be persistent in infants with IgE-mediated reactions (IgE-CMA). A population-based cohort of infants with CMA was studied to examine the course of disease and to identify factors associated with an increased risk of persistence.

From a prospective follow-up study of more than 13,000 Israeli children, the researchers identified 54 infants with IgE-CMA. The diagnosis was made using data on patient history and the results of skin-prick testing and oral food challenge. Families were regularly contacted during follow-up and asked about the child's recent exposures to milk. At age 48 to 60 months, oral food challenge was performed to evaluate resolution of CMA. Infants with persistent versus resolved IgE-CMA were compared in terms of clinical characteristics and skin-prick test and oral food challenge results.

During follow-up, IgE-CMA resolved in 57.4% of children. In 70.9% of these cases, recovery occurred within the first 2 years. On multivariate analysis, persistent IgE-CMA was more likely for children who reacted to less than 10 mL of milk on oral food challenge; who had a larger wheal size on skin-prick testing; and who were 30 days old or less at the time of their first reaction.

The results confirm that most infants with IgE-CMA "outgrow" their allergy. It also identifies clinical and allergy test factors associated with an increased risk of persistence. The researchers believe these risk factors "may reflect a more severe underlying immune reactivity" to cow's milk protein.

COMMENT: *This small prospective population study highlights what we often see in clinical practice: that in a number of children with IgE-mediated cow's milk allergy, the problem persists to school age. Knowing which children are at greater risk of persistence is helpful as we counsel parents about prognosis and determine which patients should have oral food challenges. Unfortunately, the researchers didn't obtain data regarding cow's milk-specific IgE levels.*
K.R.M.
Elizur A, Rajuan N, Goldberg MR, et al: Natural course and risk factors for persistence of IgE-mediated cow's milk allergy.
J Pediatr. 2012;161:482-487. ♦♦

Is There a Best Time of Year for Exercise Challenge Tests?

EXERCISE challenge tests can be helpful in making the diagnosis of exercise-induced bronchoconstriction (EIB). Asthma morbidity varies seasonally, being lowest in the summer months. The study looked at seasonal effects on the results of EIB performed during the summer or outside the patient's personal "asthma season."

Forty-nine Israeli military recruits with suspected asthma underwent exercise challenge testing (ECT) ➤➤

on two occasions: at baseline and again 6 months later. Tests were considered positive in patients with at least a 10% drop in postexercise FEV1. The diagnosis of EIB was made if either of the two tests were positive. The effects of season, including the patient's self-reported asthma season, on the diagnostic sensitivity of ECT were evaluated.

The ECT positivity rate was 14.3% for patients tested in summer versus 33.8% for those tested in other months. Among patients with confirmed EIB, the sensitivity of ECT was 25% in summer compared to 76% in other seasons. Similarly, the positivity rate was 10.0% for ECT performed outside the patient's personal asthma season versus 37.1% for tests performed during personal asthma season: sensitivity 27% versus 74%. Patients with two positive ECT results had a greater mean drop in postexercise FEV_1, compared to those with one positive test: 34.5% versus 16.3%.

The sensitivity of ECT is lower when the test is performed at times of year with lower asthma activity. Test sensitivity is reduced by about one-third when ECT is performed during the summer or at times other than the patient's personal asthma season. The authors discuss the implications for scheduling testing for suspected EIB.

COMMENT: *This study looked at the use of the exercise challenge test for the diagnosis of EIB. Not surprisingly, the authors found that the study was most sensitive during the time of year during which the patients with suspected asthma have symptoms. Since not every patient had a particular season that correlated with asthma symptoms, the authors recommend not performing the test during the summer months. This may be particularly important in some patient populations--such as the military recruits included in the study, or competitive athletes--in which accurate diagnoses are essential.*

V.H.-T.

Goldberg S, Mimouni F, Joseph L, et al: Seasonal effect on exercise challenge tests for the diagnosis of exercise-induced bronchoconstriction.

Allergy Asthma Proc. 2012;33:416-420. ♦♦

Vitamin D Affects Lung Function Response to ICS

PREVIOUS studies have linked low vitamin D levels to asthma and decreased airway responsiveness. Evidence suggests that vitamin D supplementation may increase the anti-inflammatory effects of corticosteroids in patients with asthma. This prospective study examined vitamin D's effects on lung function in asthmatic children taking inhaled corticosteroids (ICS).

The study included 1,024 children with asthma enrolled in the Childhood Asthma Management Program. At baseline, 65% of the children were vitamin D sufficient, with 25-hydroxyvitamin D levels greater than 30 ng/mL; 25% were vitamin D insufficient, levels of 20 to 30 ng/mL; and 10% were vitamin D deficient, less than 20 ng/mL. Associations of vitamin D status with prebronchodilator $FEV_1$1, bronchodilator response, and responsiveness to methacholine during treatment with ICS, nedocromil, or placebo were assessed. The analysis was adjusted for covariates, including age, treatment, sex, body mass index, race, history of emergency department visits, hospitalizations, and season of vitamin D measurement.

Vitamin D deficiency was more likely for patients who were older, African American, and with a higher body mass index. Among children treated with ICS, the increase in prebronchodilator FEV_1 from baseline to 12 months was 140 mL for patients with vitamin D deficiency, 330 mL for those with vitamin D insufficiency, and 290 mL for those with vitamin D sufficiency. The change in pre-bronchodilator FEV_1 percent predicted was a 1.5% decrease in the vitamin D-deficient group, compared to increases of 6.1% in children who were vitamin D insufficient and 5.2% in those who were vitamin D sufficient.

For asthmatic children with vitamin D deficiency, inhaled corticosteroid treatment yields less improvement in prebronchodilator FEV_1, compared to those who are vitamin D sufficient. "These findings support the hypothesis that vitamin D supplementation may enhance the antiiflammatory function of corticosteroids in patients with asthma," the researchers write. They suggest vitamin D monitoring and/or supplementation during inhaled corticosteroid therapy for asthma.

COMMENT: *Our knowledge of vitamin D continues to expand. Previous data published by Panettieri and Sutherland are supported by this study. Patients who are deficient in vitamin D (levels less than 20 ng/mL) are at much higher risk for poor response to inhaled corticosteroid. These data support the important recommendation that vitamin D levels be measured in all patients with asthma. See the accompanying editorial by Kreindler* (**Am J Respir Crit Care Med**. 2012;186:470-472).

B.E.C.

Wu AC, Tantisira K, Li L, et al: Effect of vitamin D and inhaled corticosteroid treatment on lung function in children.

Am J Respir Crit Care Med. 2012;186:508-513. ♦♦

Childhood BHR Predicts Adolescent Asthma

BRONCHIAL hyperresponsiveness (BHR) is a characteristic but not specific feature of asthma. Bronchial hyperresponsiveness to methacholine and exercise challenge in children was evaluated as a predictor of active asthma in adolescence.

The investigators performed methacholine challenge and exercise-induced bronchoconstriction (EIB) tests in 530 ten-year-old children from a Norwegian birth cohort. The presence of BHR was assessed according to the methacholine dose causing a 20% reduction in FEV_1 and the reduction in FEV_1 in response to exercise challenge. On follow-up examination when the children were 16 years old, the presence of active asthma was assessed, based on physician diagnosis, asthma symptoms, and/or asthma treatment in the past year (two out of three criteria). ➤➤

Both PD_{20} and EIB at age 10 were associated with an increased risk of active asthma at age 16. Values were β = 0.94 per μmol of methacholine and β = 1.10 per percent of EIB, respectively. Methacholine PD_{20} explained 10% of the risk of active asthma while EIB explained 7% of the risk. Together, these two variables explained 14% of the risk of active asthma in adolescence.

As PD_{20} decreased and EIB increased, the predicted probability of active asthma in adolescence increased. Areas under the receiver operating characteristic curve were 0.69 and 0.60, respectively.

Test results showing BHR at age 10 are associated with a small but significant increase in the risk of active asthma at age 16. The methacholine PD_{20} is a stronger predictor than the presence of EIB.

COMMENT: *This very important study and follow-up editorial by Dr. Malcolm Sears* (**Am J Respir Crit Care Med**. 2012;186:469-470) *reiterates the clear association between allergic disease, early-onset intense airway hyper-responsiveness, and persistence of asthma. These data give us a better understanding of the role of inhalation challenge testing in the characterization of the allergic childhood asthma phenotype and aid in predicting persistence of wheezing.*
B.E.C.
Riiser A, Hovland V, Carlsen K-H, et al: Does bronchial hyperresponsiveness in childhood predict active asthma in adolescence?
Am J Respir Crit Care Med. 2012;186:493-500. ♦♦

CLINICAL TIDBITS

Can We Use Mannitol Challenge to Screen for Asthma?

MANNITOL challenge kits are now approved and marketed for bronchial reactivity testing. This study assessed the value of mannitol provocation testing, compared to classical histamine challenge in children.

The study included 22 adolescents, mean age 15 years, with known asthma and a histamine $PC_{20}FEV_1$ of less than 4 mg/mL. All underwent mannitol provocation testing, followed a day or two later by histamine challenge, as routinely performed in the study clinic.

The percentage of positive results was 72.7% with mannitol provocation, compared to 100% with histamine challenge. Most patient coughed when inhaling dry mannitol powder, although drinking water relieved this symptom in most cases. One patient had to discontinue the mannitol test because of severe coughing.

Static electricity between the inhaler and capsules caused problems with delivery of consecutive mannitol doses. The decrease in FEV_1 associated with bronchial provocation was 70.3% of resting value with mannitol, compared to 81.6% with histamine. The provocative doses of histamine and mannitol were not significantly correlated with each other.

The study points out some problems with the use of mannitol challenge testing, including cough and problems related to static electricity. Although mannitol provocation can be used as a clinical screening test, the patient may still have bronchial hypperresponsiveness even if the results are negative.

COMMENT: *In previous studies, mannitol challenge was not sufficiently sensitive to detect mild asthma and there was no consensus on its use as a gold standard for exercise-induced bronchoconstriction. This study suggests that mannitol can be used as a "screening test" in clinical practice, although a negative result cannot rule out bronchial hyperresponsiveness. Mannitol is limited in its utility by frequent cough and the impact of static electricity on the administration of subsequent doses. The practicing allergist should know that, given mannitol's limitations, it is probably not an adequate screening test for EIB and that there is no consensus on a gold-standard diagnostic test for EIB.*
C.C.R.
Świebocka EM, Siergiejko G, Siergiejko Z: Mannitol does not confirm bronchial hyperreactivity in some histamine-responsive asthmatic children.
J Asthma. 2012;49:817-821. ♦♦

Does Corticosteroid Timing Affect ED Length of Stay for Children with Asthma?

FOR children with asthma seen in the emergency department (ED), early administration of oral corticosteroids reduces the risk of hospital admission. This study evaluated the effects of early corticosteroid treatment--within 60 minutes--on length of ED stay for children with asthma.

The retrospective analysis included 882 children and adolescents with acute asthma exacerbations seen at a children's hospital ED during 2007. Length of ED stay was compared for children who received oral corticosteroids within 60 minutes, compared to those with later administration. Children who did not receive oral corticosteroids in the ED were excluded, as were those with current or recent (1 week) oral corticosteroid treatment and those with significant comorbidity.

Patient characteristics, including insurance status and disposition, were similar for children treated within 60 minutes versus later. Mean length of ED stay was 157 minutes for children receiving oral corticosteroids within 60 minutes, compared to 182 minutes for those treated at 61 minutes or later: a difference of 25 minutes. The difference was greater, 38 minutes, for children with moderately severe asthma exacerbations.

For children with asthma seen in the ED, early administration of oral corticosteroids is associated with reduced ED length of stay. Although oral corticosteroids don't reach their peak effect until 4 to 6 hours, clinical benefits may occur much earlier. A randomized trial is planned.

COMMENT: *Changing the paradigm of pediatric emergency care for asthma by early administration of oral steroids changes the length of stay for children in the ED. The authors demonstrate that the admin-*➤➤

istration of corticosteroids within 1 hour of triage leads to a 25-minute mean decline in length of stay. Early intervention with oral steroids can enhance recovery from asthma exacerbations. It also improves ED efficiency, cumulatively and for each child with asthma.
C.C.R.
Davis SR, Burke G, Hogan E, Smith R: Corticosteroid timing and length of stay for children with asthma in the emergency department.
J Asthma 2012;48:862-867. ♦♦

Some Adults with Lactose Intolerance Have CMA

LACTOSE intolerance due to hypolactasia is a common condition. In adults reporting adverse reactions to cow's milk, physicians may not consider or test for the possibility of cow's milk allergy (CMA).

The authors tested for CMA in 46 adult patients with confirmed lactose intolerance who were having continued symptoms despite a lactose-free diet. Skin-prick tests were positive to whole cow's milk in 69.5% of patients, alpha-lactalbumin in 36.9%, beta-lactoglobulin and caseins in 56.5% each, goat's milk in 54.3%, and soy in 50%. Immunoblot testing for specific IgE was positive for alpha-lactalbumin in 21.7% of patients, beta-lactoglobulin in 63%, caseins in 67.3%, and bovine serum albumin in 2.1%.

Many adult patients with lactose intolerance may also have IgE-mediated sensitization to milk proteins. Testing for CMA should be considered in lactose intolerance that is refractory to a lactose-free diet.

COMMENT: *This thought-provoking study investigated adults with lactose intolerance who remained symptomatic despite following a lactose-free diet. Most patients with symptoms had positive skin-prick tests to cow's milk. Some also had positive tests to other milk proteins; in contrast, patients who tolerated cow's milk had negative results to all milk proteins on skin testing. The authors recommend consideration of testing to cow's milk proteins in patients whose symptoms persist despite a lactose-free diet. Although the patients may not be truly allergic to cow's milk, sensitization was seen in these patients; this additional information may improve their quality of life.*
V.H.-T.
Olivier CE, Lorena SLS, Pavan CR, et al: Is it just lactose intolerance?
Allergy Asthma Proc. 2012;33:432-436. ♦♦

REVIEWS OF NOTE

COMMENT: *This systematic review summarizes research data on the cost-effectiveness of immunotherapy. It concludes that immunotherapy is likely cost effective for allergic rhinitis, but possibly not for asthma.*
S.A.T.
Simoens S: The cost-effectiveness of immunotherapy for respiratory allergy: a review.
Allergy. 2012;67:1087-1105, ♦♦

COMMENT: *What points can we glean from this retrospective analysis of a relatively large number (261) of near-fatal and fatal asthma episodes admitted to pediatric ICUs? African-American children are disproportionately represented, with thankfully a majority of patients recovering fully. Lack of consistency or guidelines regarding critical asthma management remains a central issue.*
K.R.M.
Newth CJL, Meert KL, Clark AE, et al: Fatal and near-fatal asthma in children: The critical care perspective.
J Pediatr. 2012;161:214-221. ♦♦

COMMENT: *This review addresses the use of biomarkers in patients with eosinophilic esophagitis. Since invasive procedures are needed to make the diagnosis and monitor the response to treatment, the use of biomarkers may be a practical way to follow these patients. Eotaxin-3 and interleukin-13 appear to best correlate with disease activity. This article reminds us that biomarkers are a promising tool in our ability to monitor disease response to treatment in atopic patients and in eosinophilic esophagitis--an oftentimes challenging disease.*
V.H.-T.
Bhardwaj N, Ghaffari G: Biomarkers for eosinophilic esophagitis: a review.
Ann Allergy Asthma Immunol. 2012;109:155-159. ♦♦