AllergyWatch®

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

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Do Statins Lead to Worse Asthma Control?

WIDESPREAD use of the cholesterol-lowering statin drugs has altered the primary and secondary prevention of coronary artery disease. Recent studies have suggested that these medications have an important immunomodulatory effect, including down-regulation of the Th1 response and upregulation of the Th2 response. This raises questions about the possible effects of statins on Th2-driven diseases such as asthma.

This question was addressed in a retrospective study of 759 patients with asthma. Medical records were used to identify 24 patients with extrinsic asthma who were prescribed statins at their initial asthma evaluation, along with 26 controls who did not receive statins. Asthma outcomes were compared through up to 2 years' follow-up, including change in FEV_1, asthma medications, and office visits.

Most patients had mild persistent asthma. At baseline, mean body mass index was 32.2 for patients in the statin group compared to 29.0 in controls. Throughout follow-up, statin-treated patients had significant worsening of FEV_1--by a median of 5% at 6 months, 4% at 12 months, and 3% at 24 months--compared to no change or a small increase in control patients. By 6 months, 67% of patients in the statin group had increased maintenance medication, compared to 27% of controls. Statins were associated with more frequent use of albuterol, 75% versus 12%; and increased nighttime awakenings, 33% versus 0%. By 6 months, 38% of patients in the statin group had made an office visit for acute asthma, compared to 4% of controls.

Although preliminary, the study is the first to suggest that treatment with cholesterol-lowering statin drugs may adversely affect asthma control. Because of the widespread use of statins and the increasing prevalence of asthma, more study is needed to clarify this possible interaction.

COMMENT: *Interesting concept that statins may influence allergic inflammation--but also very concerning if a drug class so commonly used could worsen asthma. The small size of the study population, the*➤➤

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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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increased body weight of the study population compared to controls, and the lack of control groups with other respiratory conditions make these observations preliminary but worthy of notice. As stated by the authors, clearly more data are needed.
D.K.L.
Ostroukhova M, Kouides RW, Friedman E: The effect of statin therapy on allergic patients with asthma.
Ann Allergy Asthma Immunol 2009;103:463-468. ♦♦

Rise in Peanut Allergy May Be Leveling Off

IN Europe as in the United States, peanut is the most common cause of severe food allergy. Previous studies reported an increased prevalence of peanut sensitization and allergy among two cohorts of children born 6 years apart in the Isle of Wight, United Kingdom. This study extended the analysis to a third cohort of children.

Rates of peanut sensitization and clinical allergy at age 3 to 4 were compared for three birth cohorts of children. Cohort A included 2,181 children born in 1989; cohort B, 1,273 children born between 1994 and 1996; and cohort C, 891 children born between 2001 and 2002.

Based on skin prick tests, the rate of peanut sensitization increased from 1.3% in cohort A to 3.3% in cohort B, then decreased to 2.0% in cohort C. The prevalence of peanut allergy, based on clinical history or oral food challenge, showed a similar pattern: 0.5% in cohort A, 1.4% in cohort B, and 1.2% in cohort C. Overall atopy rates were 12.3%, 15.0%, and 11.7%, respectively. The trends in peanut sensitization and overall atopy were significant.

These data on successive birth cohorts of British children suggest that the rate of peanut sensitization has decreased for children born in 2001-02, compared to those born in 1994-96. The prevalence of clinical peanut allergy may also have decreased slightly or stabilized during this time.

COMMENT: *By all accounts, the prevalence of peanut allergy in the United States and Europe has more than doubled in the past 20 years. In this study, researchers in England compared three cohorts of children born roughly 5 years apart who were evaluated for peanut sensitization when they were 3 or 4 years old. As expected, the 3-year-olds born in 1989 had a lower prevalence of peanut sensitization than 3-year-olds born later. Interestingly, children born in 2001 or 2002 did not have an increased prevalence of peanut sensitization compared to those born around 1995. This may signal a leveling of the peanut allergy epidemic, at least in England.*
S.A.T.
Venter C, Arshad SH, Grundy J, et al: Time trends in the prevalence of peanut allergy: three cohorts of children from the same geographical location in the UK. **Allergy**. 2010;65:103-108. ♦♦

Grass-Pollen SLIT Shows Long-Term Efficacy

GRAZAX is an SQ-standardized grass allergy immunotherapy tablet approved in Europe for the treatment of grass pollen-induced rhinitis and conjunctivitis. The 3-year results of a randomized controlled trial of sublingual immunotherapy (SLIT) in patients with rhinoconjunctivitis caused by grass pollen allergy are reported.

The phase III trial study included 257 adult patients with moderate to severe grass pollen-induced rhinoconjunctivitis who continued to have troublesome symptoms despite medications. They were randomly assigned to 3 years of daily treatment with Grazax, *Phleum pratense* 75,000 SQ-T/2,800 BAU; or placebo tablets. Clinical outcomes were rhinoconjunctivitis symptom and medication scores, quality of life, and percentage of symptom-➤➤

free and medication-free days. Immunologic and safety outcomes were evaluated as well.

Active SLIT was associated with significant improvement in efficacy outcomes throughout the 3-year treatment period, as well as at 1 year after the end of treatment. Mean average daily rhinoconjunctivitis symptom score was 26% lower in patients assigned to Grazax, compared to the placebo group. There was also a 29% reduction in rhinoconjunctivitis medication score. Quality of life was also improved with SLIT.

Immunologic studies showed progressive improvement in IgG4 and IgE-blocking factor in the active SLIT group, beginning at 2 months and continuing through follow-up. Adverse events were infrequent and not serious.

Grazax SLIT for grass pollen-induced allergic rhinoconjunctivitis yields significant clinical and immunologic improvement, compared to placebo. The benefits persist through 1 year after the end of treatment, consistent with a disease-modifying effect.

COMMENTS: *This is the first large double-blind, placebo-controlled study showing sustained efficacy of grass pollen SLIT in grass-allergic patients. Although there was some reduction in immunologic parameters after stopping active SLIT, statistical significance of improvement was sustained. It will be of interest to see if future reports from these SLIT-treated patients demonstrate persistent benefit and whether SLIT is truly a disease-modifying therapy.*
S.M.F.
Durham SR, Emminger W, Kapp A, et al: Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet.
J Allergy Clin Immunol. 2010;125:131-138. ♦♦

Biphasic Reactions to Immunotherapy: How Often and How Severe?

QUESTIONS remain about the incidence of and risk factors for biphasic systemic allergic reactions. In one large study, 5% of anaphylactic reactions after allergen immunotherapy had a biphasic pattern. The incidence, risk factors, and outcomes of biphasic reactions were evaluated in a large group of patients receiving allergen immunotherapy.

The prospective follow-up study included all patients undergoing immunotherapy at an Israeli hospital allergy clinic over a 2-year period. When anaphylactic reactions occurred, all treatments were recorded and the patient was asked to keep a 3-day diary, including symptoms and peak expiratory flow (PEF) measurements. Biphasic reactions were defined as those in which PEF decreased by more than 20% at 3 hours or longer after resolution of the initial anaphylactic reaction.

In a total of 1,040 visits by 453 patients--including 21,022 immunotherapy injections--there were 131 anaphylactic reactions (incidence 1.3% per visit). Of these, 11 met the criteria for a biphasic reaction, incidence 10.9%. All anaphylactic reactions, including the biphasic reactions, occurred in patients being treated for allergic rhinitis (who made up two-thirds of all patients). Patients experiencing biphasic reactions were more likely to have a low baseline PEF and to have asthma accompanying allergic rhinitis. All of the biphasic reactions were mild, resolving without treatment or with oral antihistamines.

In this large clinical series, about 10% of anaphylactic reactions are biphasic. Biphasic reactions appear more common in patients with low baseline PEF or asthma. The reactions are generally mild and do not require emergency treatment; thus a short observation period should be adequate in most patients.

COMMENT: *These results are similar to our group's experience with biphasic reactions to immunotherapy, some of which has been published. Perhaps the rapid treatment of anaphylaxis or the milder form of most allergen immunotherapy systemic reactions reduces the likelihood of a late-phase response. Regardless of the reason, it is reassuring that there is likely a reduced risk of delayed reactions and less need to keep patients under prolonged observation after a systemic reaction in clinic.*
D.K.L.
Confino-Cohen R, Goldberg A: Allergen immunotherapy-induced biphasic systemic reactions: incidence, characteristics, and outcome: a prospective study.
Ann Allergy Asthma Immunol. 2010;104:73-78. ♦♦

Immunotherapy Saves Money

ALLERGIC rhinitis (AR) in children is associated with impaired health and quality of life, and thus with increased health care utilization and high costs. Despite the benefits of allergen immunotherapy, most patients receive symptomatic drug treatment. This study assessed the impact of immunotherapy on health care utilization and costs in children with AR.

The retrospective analysis used Florida Medicaid claims data on children (under 18) who had newly diagnosed AR and no previous immunotherapy. All received at least two immunotherapy treatments after diagnosis and had at least 18 months of follow-up data. They were matched for age, sex, race/ethnicity, and other diagnoses (asthma, conjunctivitis, or atopic dermatitis) to control children with newly diagnosed AR who did not receive immunotherapy after diagnosis.

Health care utilization and costs were compared for 2,985 cases who received immunotherapy and 176,202 controls who did not. Of all children newly diagnosed with AR during the 10-year study period, only 2.5% received de novo immunotherapy.

Median total health care costs per patient over 18 months were about $3,250 in immunotherapy-treated cases versus $4,900 in controls. Most of the difference reflected reduced outpatient costs, independent of immunotherapy care: $1,100 vs $2,600, respectively. Pharmacy costs were $1,110 vs $1,300; there was no difference in inpatient costs. The cost savings became significant within 3 months after the start of immunotherapy. ➤➤

Immunotherapy leads to substantial reductions in health care costs for children with AR. In the 18 months after diagnosis, total health care costs are 33% lower for patients receiving immunotherapy. Increasing the use of indicated allergen immunotherapy would not only improve clinical outcomes but also reduce direct medical expenditures.

COMMENT: *Health care reform is largely a result of increased costs as well as limited access to care for some. Allergen immunotherapy pays for itself, and with the long-term benefits, there is no rationale to limit this therapy and increase pharmacologic treatment. We should be shouting this from the rooftops.*
D.K.L.
Hankin CS, Cox L, Lang D, et al: Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study.
Ann Allergy Asthma Immunol. 2010;104:79-85. ♦♦

Low Rate of Epinephrine Use in Pediatric Food Challenges

ORAL food challenges (OFCs) play an important role in diagnosis and follow-up of patients with food allergies. There are few data on the risks of anaphylactic reactions, biphasic reactions, and reactions requiring epinephrine use during OFCs in children. This issue was addressed in a large series of pediatric allergy patients undergoing OFCs.

The referral center series included 1,273 OFCs performed in children over a 7-year period. The incidence of reactions requiring single or multiple doses of epinephrine were analyzed, along with possible risk factors. The rate of biphasic reactions was assessed as well.

There were a total of 436 positive food challenges, a rate of 34%. Epinephrine was required in 50 challenges: 3.9% of OFCs overall and 11% of positive challenges. Epinephrine treatment was more likely to be needed in older children, median age 7.9 vs 5.8 years; and to be caused by peanut challenge. Risk was unaffected by presence of asthma, previous history of anaphylaxis, specific IgE level, skin prick responses, or amount of food given.

Three reactions required 2 doses of epinephrine; the foods were wheat, cow's milk, and pistachio. One reaction was biphasic, but there were no life-threatening reactions.

Epinephrine treatment is required in about 11% of positive OFCs in children. Such reactions are more likely to occur in older children and those receiving peanut OFC. Very few reactions are biphasic or require two doses of epinephrine. The findings support the safety of OFC in children, when performed for appropriate indications by experienced practitioners.

COMMENT: *This study reaffirms the relative safety of controlled OFCs in patients with food allergy. Nevertheless it is still essential that we instruct our food-allergic patients on the necessity of having two doses of epinephrine available for self-administration in the event of accidental ingestion of the food allergen.*
S.M.F.
Järvinen K, Amalanayagam S, Shreffler WG, et al: Epinephrine treatment is infrequent and biphasic reactions are rare in food-induced reactions during oral food challenges in children.
J Allergy Clin Immunol. 2009;124:1267-1272. ♦♦

Response to Steroids Affects Esophageal Remodeling in EE

PATIENTS with eosinophilic esophagitis (EE) may develop subepithelial fibrosis, which has been linked to expression of transforming growth factor (TGF)-β and vascular cell adhesion molecule-1 (VCAM-1). It is unclear whether the subepithelial remodeling is reversible by topical oral corticosteroid treatment, and whether this is affected by the epithelial eosinophil response.

Sixteen children with EE underwent esophageal biopsies before and after at least 3 months of treatment with swallowed budesonide. Changes in the degree of lamina propria remodeling were assessed, along with effects on measures of vascular activation, including VCAM-1 expression; and TGF-β_1 activation, including TGF-β_1 levels and phosphorylated Smad2/3.

Budesonide treatment was followed by decreased epithelial eosinophilia in 9 of the 16 patients. Treatment responders (those with residual eosinophil counts of 7 or fewer eosinophils per hpf) had evidence of decreased esophageal remodeling, including decreased fibrosis, decreased vascular activation, and fewer TGF-β_1- and Smad2/3-positive cells. A pilot analysis suggested that budesonide responders were more likely to have a CC genotype at the -509 position of the TGF-β_1 promoter.

In children with EE, an epithelial response to topical oral budesonide is also associated with decreased esophageal remodeling. This effect may involve a reduction in TGF-β_1 activation and vascular activation in the esophagus. More study is needed, including phenotype/genotype identification of EE patients at increased risk for esophageal remodeling and stricture formation.

COMMENT: *Eosinophilic esophagitis is increasing in prevalence. In some patients, EE results in subepithelial fibrosis, which previous studies suggest involves TGF-β. This retrospective study examined biopsy specimens from 16 children with EE before and after 3 months of oral budesonide treatment. The investigators found that patients whose eosinophilia decreased following oral budesonide also had reduced esophageal remodeling. This may be due in part to a polymorphism in the promoter region of the TGF-β gene.*
S.A.T.
Aceves SS, Newbury RO, Chen D: Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids.
Allergy. 2009;65:109-116. ♦♦

Parasitic Worms Prevent Allergen Sensitization

PREVIOUS studies have suggested that infection with helminth parasites may be associated with reduced rates of allergic disease and allergic skin sensitization. The mechanism of this effect may involve helminth-induced inflammatory cytokines, particularly interleukin IL-10. This raises the possibility that public health interventions to eradicate these parasitic infections might increase allergic disease risk.

This hypothesis was tested in a rural area of Vietnam where hookworm is endemic. A total of 1,566 schoolchildren were randomly assigned to treatment with anti-helminthic medications or placebo. Clinical allergic disease outcomes were assessed, along with allergen skin sensitization and immunologic variables.

There was no significant difference in allergic disease outcomes, including exercise-induced bronchoconstriction, wheezing or rhinitis, or flexural dermatitis. However, children assigned to anti-helminthic therapy had a higher rate of allergen skin sensitization, adjusted odds ratio (OR) 1.31. For children infected with roundworm (*Ascaris lumbricoides*) at baseline, the OR increased to 4.90. Sensitization risk was inversely associated with hookworm-specific IL-10 at baseline, OR 0.76. None of the cytokine levels tested, including IL-10, changed significantly in response to anti-helminthic therapy.

For children in an area where hookworm is endemic, anti-helminthic therapy is associated with an increased risk of allergic skin sensitization. This effect does not appear to be explained by changes in immunologic parameters, and is not accompanied by any increase in clinical allergic disease. More research is needed to clarify the possible association between helminth infection and allergic disease.

COMMENT: *It is well known that allergic diseases are much less common in rural parts of developing countries. Parasitic infection has been proposed as a possible explanation. In this prospective, randomized, placebo-controlled study, the authors treated over 1,500 schoolchildren with anti-helminthic therapy or placebo for 12 months. They found that this therapy was associated with an increase in inhalant allergen skin test positivity. There was no difference between treated and untreated subjects for any of the clinical endpoints measured. Although the clinical relevance is unclear, this important study suggests that there indeed is a relationship between helminth infection and allergic sensitization.*
S.A.T.

Flohr C, Tuyen LN, Quinnell RJ, et al: Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam.
Clin Exp Allergy. 2009;40:131-142. ♦♦

Good 1-Year Results with Bronchial Thermoplasty

BRONCHIAL thermoplasty (BT), using controlled thermal energy to decrease the mass and contractility of airway smooth muscle, has been proposed as a treatment for severe asthma. Previous studies of BT have reported a decreased long-term rate of asthma exacerbations and other favorable outcomes. A large sham-controlled trial of BT for adult patients with severe persistent asthma is reported.

The study included 288 adults with severe asthma and continued symptoms despite high doses of inhaled corticosteroids and long-acting β_2-agonists. In a 2:1 ratio, patients were randomly assigned to BT or a sham control procedure, both carried out in three bronchoscopies. The main outcome of interest was the change in Asthma Quality of Life Questionnaire (AQLQ) scores from baseline to 12 months. Secondary efficacy and safety outcomes were evaluated as well.

Mean change in AQLQ score was 1.35 in patients assigned to BT vs 1.16 in those assigned to the sham procedure. On intention-to-treat analysis, 79% of BT patients had a clinically significant 0.5-point improvement in the AQLQ, compared to 64% in the placebo group. Patients in the BT group were more likely to be hospitalized up to 6 weeks after the procedure. Thereafter, they had fewer severe exacerbations, emergency department visits, and missed work/school days.

For adult patients with severe asthma, BT yields improved disease-specific quality of life, compared to a sham procedure. There are also associated reductions in severe exacerbations and health care use. Benefits persist for at least 1 year, outweighing the increase in short-term risks.

COMMENT: *This is one of the largest sham-controlled intervention trials in the history of pulmonary medicine. Bronchial thermoplasty is directed toward a very small percentage of patients who have not responded to any currently available intervention strategies. Although the objective changes were not significant, there were fewer exacerbations, fewer days missed from work, and improved quality of life. This procedure should be reserved for special centers and highly selected patients.*
B.E.C.

Castro M, Rubin AS, Laviolette M, et al: Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial.
Am J Respir Crit Care Med. 2010;181:116-124. ♦♦

New Data on Effects of Environmental Exposures on Asthma

THERE is evidence that pesticide exposure may contribute to asthma among farmers, but only a few studies have examined the effects of individual pesticides. Because of the higher rate of nonatopic asthma among farmers, it is important to consider atopy ➤➤

separately when evaluating asthma risk factors. Data from a large study of farmers were used to assess the relationship between pesticide use and allergic and nonallergic asthma.

The analysis included 17,704 male farmers in Iowa and North Carolina enrolled in the prospective Agricultural Health Study. The men provided data on lifetime use of 48 pesticides and on physician-diagnosed asthma after age 20. In the absence of atopy testing, subject reports of eczema or hay fever were used to classify asthma cases as allergic or nonallergic. Associations with pesticide exposure were analyzed, controlling for age, state, smoking, and body mass.

Men with events of unusually high pesticide exposure had a twofold increase in both allergic and nonallergic asthma. Twelve pesticides were individually associated with allergic asthma and four with nonallergic asthma. Pesticides associated with allergic asthma and showing odds ratios of greater than 2 were coumaphos, heptachlor, parathion, 80/20 mix, and ethylene dibromide. Each showed a significant exposure-response trend. The associations were not confounded by current farm activities, including animal handling.

Pesticides may have an important effect on the risk of adult-onset asthma in farmers. Twelve different pesticides are linked to allergic asthma risk. Episodes of high exposure to pesticides may be a risk factor for both allergic and nonallergic asthma.

COMMENT: *We continue to increase our understanding of the significant impact of outdoor air pollution on the development of asthma in adults. Exposure of farm workers to 12 pesticides was associated with significant increases in allergic asthma. Given the lack of commonality among the pesticides, it seems unlikely that these findings are due to uncontrolled confounding factors and that the development of allergy was not the major driving factor.*
B.E.C.
Hoppin JA, Umbach DM, London SJ, et al: Pesticide use and adult-onset asthma among male farmers in the Agricultural Health Study.
Eur Respir J. 2009;34:1296-1303. ♦♦

EXPOSURE to ambient fine particulate matter ($PM_{2.5}$) in air pollution has been linked to asthma exacerbations and other asthma outcomes. However, little is known about how exposure to specific types of fine-particle pollutants--including carbon and elemental metals--affects children's respiratory health. This issue was addressed in a birth cohort study of infants in New York City.

The study included 687 children born between 1998 and 2006; about two-thirds were Dominican and one-third African American. Parents completed respiratory symptom questionnaires every 3 months through the first 2 years of life. Data on ambient pollutant levels were gathered from monitoring sites within the study area (Northern Manhattan and South Bronx). Average exposures to nickel, vanadium, zinc, elemental carbon, and total $PM_{2.5}$ were calculated for each 3-month symptom reporting period. Associations were adjusted for sex, ethnicity, passive tobacco smoke, and calendar time.

Children with higher exposure to ambient nickel and vanadium had increased rates of wheezing. Higher exposure to elemental carbon was associated with increased cough during cold/flu season. Total $PM_{2.5}$ exposure was not significantly related to either wheezing or cough. The strongest and most consistent association was that between nickel and wheezing.

Specific components of $PM_{2.5}$ pollution are related to respiratory symptoms in infants and younger children. Significant associations are noted for nickel, vanadium, and elemental carbon, but not for total $PM_{2.5}$. The findings suggest that regulatory efforts should be directed at specific sources of pollution, or at levels of specific types of particulate pollutants.

COMMENT: *This study--which collected data at 3-month intervals for the first 24 months of life in an inner-city cohort--shows that exposure to elemental metals and carbon are significant risk factors for the development of asthma. The findings again reinforce the important reasons for control of air pollution in our environment.*
B.E.C.
Patel MM, Hoepner L, Garfinkel R, et al: Ambient metals, elemental carbon, and wheeze and cough in New York City children through 24 months of age.
Am J Respir Crit Care Med. 2009;180:1107-1113. ♦♦

QUESTIONS remain about the associations between air pollution and asthma. In mice, co-exposure to diesel exhaust particles and endotoxin has a synergistic effect on production of reactive oxygen species. This study evaluated the effects of co-exposure to traffic-related particulate pollution and endotoxin on wheezing in young children.

The analysis included 624 children with atopic parents, drawn from the Cincinnati Childhood Allergy and Air Pollution Study. Exposure to traffic-related particles was estimated from pollution monitoring data, using a previously described regression model. Indoor endotoxin exposure was assessed from household dust samples collected during the first year of life. The main health outcome of interest was persistent wheezing at age 3.

Children with high exposure to traffic-related particulate pollution during the first year of life were more likely to have persistent wheezing at age 3, odds ratio 1.75. There was evidence of a synergistic effect of co-exposure to endotoxin and traffic exposure: among children with high exposure to endotoxin, the prevalence of persistent wheezing was 11% for those with low traffic exposure vs 36% for those with high traffic exposure. With adjustment for covariates, the odds ratio for persistent wheezing in children with high traffic/high endotoxin exposure was 5.85, compared to low traffic/low endotoxin exposure.

Early life exposure to high levels of traffic-related particulate pollutants and high levels of endotoxin appears to have a synergistic effect on the risk of persistent wheezing at age 3. The findings are consistent with the results of previous animal and human experimental studies. More research will be needed to clarify the effects of early vs later exposure to traffic-related pollution. ➤➤

COMMENT: *This study is particularly important as it links indoor exposure to endotoxin and outdoor exposure to traffic-related particles to an increased risk of persistent wheezing at 3 years of age. The probable mechanism is the synergistic action of reactive oxygen species with co-exposure to diesel exhaust particles and endotoxins. This again supports the need for very strict control of the indoor and outdoor environments.*
B.E.C.
Ryan PH, Berinstein DI, Lockey J, et al: Exposure to traffic-related particles and endotoxin during infancy is associated with wheezing at age three.
Am J Respir Crit Care Med. 2009;180:1068-1075. ♦♦

Timing of Solid Foods Affects Risk of Sensitization

CURRENT advice to prevent allergic disease in children is to breast-feed exclusively for the first 6 months before introducing solid foods. However, studies of this issue have yielded conflicting results. Data from a large birth cohort study were used to assess the relationship between age at introduction of solid foods and the risk of allergic sensitization at age 5.

The study included 994 children with HLA-conferred susceptibility to type 1 diabetes mellitus, participating in the Finnish Type 1 Diabetes Prediction and Prevention nutrition study. All had available data on duration of breast-feeding, age at introduction of solid foods, and allergen-specific IgE levels at age 5.

The overall median duration of exclusive breast-feeding was 1.8 months. On logistic regression analysis, introduction of certain foods at certain times was directly associated with the risk of sensitization to food allergens. Risk was increased when potatoes were introduced after 4 months, oats after 5 months, rye after 7 months, wheat after 6 months, meat after 5.5 months, fish after 8.2 months, and eggs after 10.5 months.

Children with delayed introduction of potatoes, rye, meat, and fish were more likely to be sensitized to any inhalant allergen. In models including all dietary variables, the foods with the greatest effects on sensitization to food allergens were eggs, oats, and wheat. For sensitization to inhalant allergens, potatoes and fish were the most important foods. Analyses including parental allergic diseases found no evidence of reverse causation.

Contrary to current advice, delaying introduction of solid foods may increase the risk of allergic sensitization to allergens at age 5. Certain foods appear to affect the risk of sensitization to food vs inhalant allergens. The results add to recent evidence that delaying solid foods does not prevent the development of allergic diseases.

COMMENT: *Here is more evidence suggesting that the traditional advice to atopic parents regarding the feeding of their (potentially atopic) infants--specifically, lengthening duration of breast-feeding and delaying introduction of solid foods--might not confer an advantage. In the current study, withholding solid foods until later actually increased the risk of specific serum IgE positivity at age 5, to a variety of allergens. One would correctly argue that such positivity does not constitute a "diagnosis" of allergy, as no physician evaluation was included, and thus may not accurately reflect disease risk.*

Reverse causation is ever a potential problem with these types of studies: are the authors identifying those infants who may genetically be at higher risk for allergy, in the population of infants selected by their parents for later introduction to solid foods? Or does the delay itself actually increase the risk? Regardless of methodologic issues in the current study, "conventional wisdom" has certainly been challenged by evidence from a number of longitudinal population studies in the last several years.
K.R.M.
Nwaru BI, Erkkola M, Ahonen S, et al: Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years.
Pediatrics. 2010;125:50-59. ♦♦

Food Allergy Trends among U.S. Children

SOME studies have suggested a rising incidence of food allergy in children, particularly peanut allergy. However, few reports have been based on nationally representative data. Four national databases were used to estimate the prevalence of food allergies among American children.

Data were drawn from the National Health Interview Survey, 1997-2007; National Health and Nutrition Examination Survey, 2005-06; National Hospital Ambulatory Medical Care Survey and National Ambulatory Medical Care Survey, 1993-2006; and National Hospital Discharge Survey, 1998-2006. The analysis suggested that the prevalence of food allergy in U.S. children increased by 18% from 1997 through 2007. Overall prevalence in 2007 was 3.9%.

The estimated prevalence of serum IgE antibodies to peanut was 9% in 2005-06. Increases were seen in both sexes and all racial/ethnic groups; black children were most likely to have detectable IgE antibodies, but Hispanic children showed the largest increase.

Ambulatory care visits for food allergies nearly tripled from 1993 to 2006, from about 116,000 to 317,000 visits per year. From 1998-2000 to 2004-06, the number of hospitalizations with a recorded diagnosis of food allergy increased from 2,600 to 9,500 discharges per year. (This may have reflected increased use of food allergy V codes.)

Available data from nationally representative databases suggest a rising prevalence of food allergies in U.S. children. Health care visits for food allergy appear to be increasing as well. It is unclear how much of these increases are related to increased awareness.

COMMENT: *Practicing allergists would guess that the prevalence of food allergy among children has been increasing in the United States, in all populations, based on the number of office visits in recent years. But exactly how much of an increase has been noted?* ➤➤

This study attempts to provide a glimpse. Study limitations include reliance on parental reporting of food allergy, and use of specific serum IgE testing for food allergens to assess overall prevalence, in the absence of physician diagnosis. While these methodological concerns have the potential to overestimate the results, the findings here are remarkably consistent with other studies using physician diagnoses of food allergies.
K.R.M.
Branum AM, Lukacs SL: Food allergy among children in the United States.
Pediatrics. 2009;124:1549-1555. ♦♦

Food Allergy Knowledge among Primary Care Doctors: Good But Could Be Better

FOOD allergy is a common in children, and is an unpredictable condition with the potential for life-threatening anaphylaxis. Pediatricians and family physicians play a critical role in diagnosis and follow-up of children with food allergies. These primary care physicians were surveyed regarding their knowledge of food allergy.

A national sample of practicing pediatricians and family physicians were invited to take a validated, Web-based survey evaluating food allergy knowledge, attitudes, and beliefs. The analysis included responses from 407 physicians; more than 80% were pediatricians.

Nearly all respondents said they had children with food allergies in their practice. The rate of correct responses to knowledge-based items was 61%--higher for pediatricians than family physicians. More than 80 percent of respondents knew that egg-allergic children should not receive flu vaccine, that the number of children with food allergies is rising, and that there is no cure for this condition. However, less than one-fourth were aware that food challenges are used in diagnoses or that yogurt or cheese produced from milk are unsafe for children with IgE-mediated milk allergy. Only 12% knew that chronic nasal symptoms are not a sign of food allergies. Less than one-third of the physicians felt comfortable interpreting diagnostic tests for food allergy or well-prepared to care for children with this condition.

The survey identifies gaps in primary care physicians' knowledge regarding food allergies in children. These physicians are aware of limitations in their clinical ability to manage food allergy. The authors discuss opportunities to improve this situation.

COMMENT: *If there was ever an area where allergists/immunologists could serve as an educator for their colleagues, this is certainly an important one. The responses of pediatricians and family physicians caring for food-allergic children in this study are rather informative: most did not identify the oral food challenge as the "gold standard" for diagnosis. Rather, a large proportion identified specific serum IgE results as the definitive diagnostic test. And another large percentage erroneously linked chronic rhinitis symptoms with food allergy. We as a specialty have work to do!*
K.R.M.
Gupta RS, Springston EE, Kim JS, et al: Food allergy knowledge, attitudes, and beliefs of primary care physicians.
Pediatrics. 2010.125;126-132. ♦♦

How Stressful Are Food Allergies?

CHILDREN with food allergies may experience psychosocial stressors, such as social isolation or anxiety regarding accidental exposures. The psychologic distress associated with food allergies is unclear, as are the associated risk and resilience factors. The parents' responses can also affect the child's adjustment.

Standard measures of psychologic distress were administered to 141 mothers of children with food allergies, aged 2 to 7. Another 69 food-allergic children and adolescents, aged 8 to 17, completed measures of anxiety and depression, social stress, and attitudes toward food allergy. Levels of psychologic distress associated with food allergy were analyzed, along with associated factors.

On both the parent-report and self-report measures, scores for anxiety, depression, and social stress fell within the average range. In most cases, rates of psychologic distress were similar to the norm, or sometimes lower. However, child-reported anxious coping and symptoms of separation anxiety were higher than the norm. The mothers' ratings of child stress were higher than the children's ratings. In the older children, distress was significantly related to negative attitudes toward food allergy among the children and to higher anxiety levels among the mothers.

In general, children with food allergies score in the average range on measures of psychologic distress. Mothers may report their children's anxiety as higher than the children do. This study identifies factors associated with distress in children with food allergies, which may be amenable to intervention.

COMMENT: *The diagnosis of food allergy can be life-altering in more ways than one. Certainly those with severe allergy can be saved from severe outcomes. But the diagnosis of food allergy is commonly misapplied by primary care doctors--and some allergists--sometimes based on nothing more than a slightly elevated specific IgE level on a screening blood test. Child and parental anxiety is sure to follow in either case, and will follow a bell-shaped curve of severity. It behooves all clinicians to carefully consider and address the anxieties of children and parents as a routine part of the follow-up of these cases. This article suggests some helpful strategies.*
R.J.M.
LeBovidge JS, Strauch H, Kalish LA, Schneider LC: Assessment of psychological distress among children and adolescents with food allergy.
J Allergy Clin Immunol. 2009;124:1282-1288. ♦♦

Omalizumab as Add-On Therapy for Children with Asthma

SOME children have poor asthma control despite recommended controller therapies. Anti-IgE therapy with omalizumab has proven beneficial as add-on treatment for inadequately controlled moderate to severe asthma in adolescents and adults, and in one study of children. This randomized trial evaluated the benefits of omalizumab for children with inadequately controlled asthma.

The study included 627 children, age 6 to less than 12, with IgE-mediated asthma and perennial allergen sensitivity. All experienced asthma exacerbations and symptoms despite medium- or high-dose inhaled corticosteroids. In a 2:1 ratio, they were assigned to receive omalizumab, 75 to 375 mg sc, every 2 or 4 weeks; or placebo. Treatment continued for 52 weeks, with 24 weeks on a fixed dose of steroids followed by 28 weeks on an adjustable dose.

Efficacy analysis included 576 children. Omalizumab was associated with a 31% reduction in the rate of clinically significant asthma exacerbations during the fixed-dose steroid phase, compared to placebo: 0.45 versus 0.64. Throughout the 52-week study, there was a 43% reduction in exacerbation rate with omalizumab, along with a reduced rate of severe exacerbations. Both the patients' and physicians' global ratings favored omalizumab. There was no difference in the overall rate of adverse events.

For children between 6 and 12 with inadequately controlled asthma, omalizumab is safe and effective as add-on therapy. It reduces the rate of clinically significant exacerbations, as well as the risk of severe exacerbations. Omalizumab provides an important new addition to the limited treatment options for this group of patients.

COMMENT: *In this study, omalizumab was compared with placebo in children 6 to 12 years of age who had moderate to severe asthma and who were already on high-dose inhaled corticosteroids. Clinically significant exacerbation rates were greatly reduced in the omalizumab-treated group, supporting its use as an add-on treatment. Since omalizumab is expensive, it would have been very interesting to see a pharmacoeconomic analysis of the benefit. Perhaps the authors can provide that later.*
R.J.M.

Lanier B, Bridges T, Kulus M, et al: Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma.
J Allergy Clin Immunol. 2009;124:1210-1216. ♦♦

Asthma Patients 'Catch Up' in the Years after Delayed Therapy

CURRENT guidelines emphasize early diagnosis and treatment for asthma, although there are few data on how early treatment affects long-term outcomes. This issue was addressed in a long-term follow-up study of adult asthma patients previously assigned to early vs delayed treatment with inhaled corticosteroids (ICS).

In the original study, early ICS therapy for adults with recently diagnosed asthma was associated with significant improvements in lung function and bronchial responsiveness to histamine at 3 years. For the current study, an additional 10 years of follow-up data were obtained for 90 of the original 103 patients. All patients had their ICS dosage and other treatments adjusted at the end of the trial.

At long-term follow-up, lung function parameters were within the normal range for patients assigned to early treatment or delayed treatment. Both groups had improved bronchial responsiveness, compared to baseline. All clinical and functional outcomes were similar for patients assigned to early vs delayed ICS. However, the neutrophil count was higher in the delayed therapy group, as were the eosinophil cationic protein and myeloperoxidase concentrations in induced sputum. Patients assigned to delayed ICS did use more asthma medications and had more hospital days.

At long-term follow-up, outcomes are similar for adult asthma patients assigned to early ICS therapy compared to a 2-year delay in treatment. With individualized therapy over the subsequent decade, the two groups have similarly good functional asthma control. However, some differences in airway inflammation and rates of optimal disease control may still persist.

COMMENT: *In an oft-cited 1991 study from Finland (*N Engl J Med. *1991;325:388-392), a 2-year delay in use of ICS was associated with poorer outcomes at 3 years of study. This paper reports on the same patients 10 years later. The delayed-start group had had more hospital days over those 10 years, and somewhat more β-agonist use in the most recent year, but none of the differences was statistically significant. Lung function measures were not different. It seems that early users of ICS get off to a better start, but delayed users catch up.*
R.J.M.

Haahtela T, Tamminen K, Kava T, et al: Thirteen-year follow-up of early intervention with an inhaled corticosteroid in patients with asthma.
J Allergy Clin Immunol. 2009;124:1180-1185. ♦♦

New Data on Anticholinergic Safety

RECENT reports have raised concern that the inhaled anticholinergic drug ipratropium bromide may be linked to an increased risk of cardiovascular disease and mortality. A large Veterans Affairs database was analyzed to assess the relationship between ipratropium use and cardiovascular events (CVEs) in patients with chronic obstructive pulmonary disease.

The study included 82,717 patients initially diagnosed with COPD between 1999 and 2002. Patients were followed up to 2004 for CVEs--including acute coronary heart syndrome, heart failure, or cardiac dysrhythmia or death. The association between cumulative anticholinergic exposure and CVE risk was assessed, with adjustment for COPD severity, cardiovascular risk factors, and other potential confounders. ➤➤

A total of 6,234 CVEs were identified, most commonly heart failure. Patients with any exposure to anticholinergics within the past 6 months were at increased risk of CVEs, compared to those with no exposure over the past year. Hazard ratios were 1.40 for patients with four or more 30-day equivalents of inhaled anticholinergics and 1.23 for those with less than four 30-day equivalents. Anticholinergic use more than 6 months previously did not appear to affect CVE risk.

In this large sample of patients with COPD, exposure to inhaled anticholinergics is associated with an increased rate of CVEs. The findings add to previous concerns about the safety of ipratropium bromide.

THERE are conflicting data as to the cardiovascular safety profile of the inhaled anticholinergic drug tiotropium. This study updates the available data on safety outcomes in patients taking tiotropium, including results from a recent randomized trial.

The updated database included 19,545 patients with COPD, drawn from 30 trials: 10,846 were assigned to tiotropium and 8,699 to placebo. All studies were randomized, double-blind trials lasting at least 4 weeks. The risk of cardiovascular events and cardiac death was compared for patients taking tiotropium vs placebo.

Cumulative exposure was 13,146 patient-years for tiotropium and 11,095 patient-years for placebo. The incidence rate for death from any cause was lower with tiotropium: 3.44 vs 4.10 per 100 patient-years, relative risk 0.88. The rate of a composite outcome of cardiovascular events and cardiovascular death was also lower with tiotropium: 2.15 vs 2.67 per 100 patient-years, relative risk 0.83. The relative risk of death from cardiovascular causes was 0.77 with tiotropium. There were no significant differences in total myocardial infarction, cardiac failure, or stroke.

In patients with COPD, tiotropium is associated with a lower risk of adverse cardiovascular outcomes, compared to placebo. Based on a large analysis of pooled clinical trial data, the rates of cardiovascular events, cardiovascular death, and all-cause mortality are all significantly lower with tiotropium.

COMMENT: *There is an ongoing debate regarding cardiac safety in COPD patients treated with anticholinergics. Although there is no pharmacologic reason for increased cardiac adverse events with short-acting compared to long-acting anticholinergics, there appears to be evidence to support this. These studies add to the debate. One article reviews a large database of patients treated with ipratropium and the other analyzes 30 placebo-controlled trials with tiotropium. As with previous reports, there was less overall and cardiac risk in tiotropium-treated subjects and greater risk with short-acting ipratropium. The accompanying editorial (*Chest *2010;137:1-3) states that the longer-acting, more expensive anticholinergic is the drug of choice. This class of medications has little role in the treatment of asthma. However, there may be patients with mixed disease for whom these findings are relevant.*
S.F.W.

Ogale SS, Lee TA, Au DH, et al: Cardiovascular events associated with ipratropium bromide in COPD.
Chest. 2010;137:13-19.
Celli B, Decramer M, Leimer I, et al: Cardiovascular safety of tiotropium in patients with COPD.
Chest. 2010;137:20-30. ♦♦

Intranasal Steroids Don't Help in Otitis Media with Effusion

OTITIS media with effusion is a common problem in children that can lead to hearing loss, especially when both ears are affected. Watchful waiting is the established clinical recommendation, but many patients receive off-license treatment with topical intranasal corticosteroids.

The efficacy of this treatment was evaluated in a randomized controlled trial including 217 children, aged 4 to 11, seen by their general practitioner for persistent bilateral otitis media. One group received topical intranasal mometasone furoate 50 µg once daily, while the other group received a placebo spray.

After 1 month of treatment, the tympanometrically confirmed cure rate was not significantly different between groups: 41% with mometasone and 45% with placebo. There was still no difference in this primary outcome after adjustment for clinical severity, atopy, age, and season, or at 3 months' follow-up. There was also no difference in symptoms and no harms of treatment. The problem resolved naturally between 1 and 3 months in most cases.

For children with persistent bilateral otitis media, treatment with intranasal corticosteroids does not lead to improved outcomes. Active monitoring appears to be a feasible strategy for use in primary care.

COMMENT: *Since there is no systemic effect, I have always wondered why our ENT and pediatric colleagues tend to treat serous otitis media with topical nasal steroids. Perhaps the high spontaneous resolution makes them feel there is beneficial drug effect. This primary care study seems to refute this treatment; the only effect of nasal steroids for treatment of serous otitis media is on cost.*
S.F.W.

Williamson I, Benge S, Barton S, et al: Topical intranasal corticosteroids in 4-11 year old children with persistent bilateral otitis media with effusion in primary care: double blind randomised placebo controlled trial.
BMJ. 2010;340:b4984. ♦♦

Smoking Doesn't Reduce Response to ICS

IN patients with asthma, smoking may not only adversely affect on lung function, but may also be associated with reduced efficacy of inhaled corticosteroid (ICS) therapy. The "inhaled Steroid Treatment As Regular Therapy" (START) study was a randomized, placebo-controlled trial of early intervention with➤➤

low-dose budesonide for patients with newly diagnosed persistent asthma. Data from this trial were used to compare the response to ICS in asthmatic smokers vs nonsmokers.

In the START study, adult patients with newly diagnosed mild persistent asthma were stratified for smoking status before being assigned to budesonide or placebo. The current analysis compared 3-year outcomes for 492 smokers and 2,432 nonsmoking patients with asthma.

Within the placebo group, the 3-year decline in postbronchodilator FEV_1 was -263.9 mL for smokers vs -180.8 mL for nonsmokers. In contrast, patients assigned to budesonide had a significant increase in postbronchodilator FEV_1, whether or not they smoked. The difference between budesonide and placebo was 71.5 mL in smokers and 46.5 mL in nonsmokers. The differences in prebronchodilator FEV_1 were 118.1 and 72.9 mL, respectively. Budesonide's effect on the risk of a first severe asthma-related event were similar for smokers and nonsmokers.

For patients with mild persistent asthma, 3-year declines in pulmonary function are greater in smokers than nonsmokers. In terms of preventing decreased lung function, early treatment with inhaled budesonide is similarly effective in smokers and nonsmokers. The authors point out that, in the absence of a placebo group, their data would have erroneously suggested that smokers were less responsive to budesonide than nonsmokers.

COMMENT: *This paper reports another post hoc analysis of the START study, a large, multinational project initially designed to assess the effects of early intervention with ICS on the natural course of newly diagnosed asthma. In contradistinction to pivotal trials, smokers were not excluded from this long term-trial. Inhaled budesonide had similar salient effects on asthmatics who smoked or didn't. Untreated nonsmoking asthmatics had statistically less decline in lung function than untreated smokers. For asthmatic smokers, inhaled steroids are good and smoking is bad.*
S.F.W.

O'Byrne PM, Lamm CJ, Busse WW, et al: The effects of inhaled budesonide on lung function in smokers and nonsmokers with mild persistent asthma.
Chest. 2009;136;1514-1520. ♦♦

CLINICAL TIDBITS

Exposure to Other Children in Toddler Years Reduces Asthma Risk in Teens

PREVIOUS studies have suggested that daycare attendance during early childhood may reduce the risk of asthma and allergic disease. A large study providing detailed information on early child care exposure was used to assess the long-term effects of exposure to other children on asthma risk.

The study included data on 939 children enrolled in the National Institute of Child Health and Development Study of Early Child Care and Youth Development. The number of other children to whom the child was exposed as an infant (up to 15 months) and toddler (16 to 36 months) was evaluated as a risk factor for late-onset or persistent asthma, with follow-up to age 15.

The number of children in the child care setting as an infant was unrelated to asthma risk. However, children exposed to a higher number of children as a toddler were at lower risk of persistent or late-onset asthma by age 15. The probability of asthma continued to decrease as the number of children increased, up to 9 other children. Risk appeared to increase for toddlers exposed to 10 or more children. The association was significant after adjustment for respiratory tract illnesses and other risk factors.

Being exposed to more children as a toddler may be associated with a reduced risk of persistent or late-onset asthma through adolescence. The mechanism of this effect is unknown, but is apparently not explained by number of respiratory illnesses.

COMMENTS: *Parents are concerned about the burden of illness placed on toddlers in daycare, and frequently wonder whether such early childhood exposures impact subsequent asthma risk. What is interesting in this study is that a particular level of exposure (as measured by number of other children) is identified as protective--in this case, exposure to 9 other children conferred greatest benefit. The protective effect for risk of teenage asthma diminished when the toddler exposure was either less than 8 or greater than 10 children. Such findings do support the hygiene hypothesis, and should help to answer the questions we receive from parents regarding long-term effects of early viral exposure.*
K.R.M.

Gurka MJ, Blackman JA, Heymann PW: Risk of childhood asthma in relation to the timing of early child care exposures.
J Pediatr. 2009;155:781-787. ♦♦

SCID: Improved Outcomes with Early Bone Marrow Transplants

PREVIOUS studies have reported on the immunologic outcomes after bone marrow transplantation in infants with severe combined immunodeficiency (SCID), but not the clinical outcomes. The authors present the long-term clinical outcomes of related-donor bone marrow transplantation in 161 patients with SCID.

Only 10% of the patients had HLA-identical donors. Data on long-term outcomes were available for 111 of 124 survivors. Overall survival was 77%, increasing to 94% for 48 infants who were transplanted during the first 3.5 months of life (compared to 70% for those transplanted later). Three-fourths of deaths were caused by viral infections that were present at the time of SCID diagnosis. Although most of the survivors had at least some clinical problems over the past 2 years, 86% were considered healthy by their families.

The results show good long-term outcomes with related donor bone marrow transplantation for infants with SCID. Survival and other outcomes appear particularly good when transplantation is performed before age 3.5 months. ➤➤

COMMENT: *Neonatal screening for SCID should be implemented, given compelling evidence from Duke University that bone marrow transplant recipients less than 3.5 months of age with SCID fare the best over time. Some of these children are leading remarkably healthy lives, after transplantation. The innate severity of SCID, combined with the need for immediate intervention, makes these disorders ideal for targeted screening in the neonatal period. Another study (***J Pediatr***. 2009;155:829-833) raises hopes that widespread neonatal screening for SCID may be achievable in the near future!*
K.R.M.
Railey MD, Lokhnygina Y, Buckley RH: Long-term clinical outcome of patients with severe combined immunodeficiency who received related donor bone marrow transplants without pretransplant chemotherapy or post-transplant GVHD prophylaxis.
J Pediatr. 2009;155:834-840. ♦♦

REVIEWS OF NOTE

COMMENT: *Hypereosinophilic syndrome (HES) is a heterogeneous disorder, the manifestations of which can be in many organs (especially skin, lung, and gastrointestinal tract). Most cases are idiopathic. This is a retrospective review of clinical features of HES and the treatment options. Corticosteroids are effective for most patients but are limited by toxicity. Other options are discussed.*
R.J.M.
Ogbogu PU, Bochner BS, Butterfield JH: Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy.
J Allergy Clin Immunol. 2009;124:1319-1325. ♦♦

COMMENT: *This is an updated review of angioedema due to angiotensin-converting enzyme inhibitors, including a thorough discussion of its mechanism.*
S.A.T.
Hoover T, Lippmann M, Grouzmann E, et al: Angiotensin converting enzyme inhibitor induced angio-oedema: a review of the pathophysiology and risk factors.
Clin Exp Allergy. 2009;40:50-61. ♦♦

COMMENT: *This is a useful summary and the authors include a brief review of monoclonal mast cell activation syndrome.*
D.K.L.
Bains SN, Hsieh FH: Current approaches to the diagnosis and treatment of systemic mastocytosis.
Ann Allergy Asthma Immunol 2010;104:1-10. ♦♦

COMMENT: *This is an excellent review of primary ciliary dyskinesia, covering diagnosis, clinic course, comorbid conditions, and treatment.*
B.E.C.
Barbato A, Frischer T, Kuehni CE, et al: Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children.
Eur Respir J. 34:1264-1276. ♦♦

COMMENT: *The unique perspective relevant for the practicing allergist-immunologist is that costimulatory molecules characterized by an acute Th2 polarization are involved in promotion or prevention of allergic immune responses and are potential targets for the development of novel therapeutic agents for allergic airway disease. This excellent review focuses on current understanding of the relationship between allergic diseases and costimulatory molecules in the six B7 families (CD80, CD86, PD-1, ICOS, and CTLA-4) and six tumor necrosis factor receptor families (OX40, CD30, 4-1BB, Fas, CD27, and CD40), along with a description of antigen-presenting effector cells and a list of their functions and characteristics.*
M.F.
Lombardi V, Singh AK, Akbari O: The role of costimulatory molecules in allergic disease and asthma.
Int Arch Allergy Immunol. 2010;151:179-189. ♦♦

COMMENT: *Some practicing allergists-immunologists and pulmonologists are not convinced on the concept of airway remodeling in allergic asthma. This excellent review focuses on the potential cooperative link between mast cells and basophils in promoting angiogenesis during allergic inflammation and the multifaceted roles of mast cells and basophils as a source and target of proangiogenic mediators.*
M.F.
Crivellato E, Travan L, Ribatti D: Mast cells and basophils: A potential link in promoting angiogenesis during allergic inflammation.
Int Arch Allergy Immunol 2010;151:89-97. ♦♦

COMMENT: *This article is recommended reading for those who contemplate celiac disease in their pediatric differential diagnosis. Diagnosis patterns of celiac disease have changed with the widespread availability of serologic testing. The authors also offer a brief review of the spectrum of presentations of this disease.*
K.R.M.
McGowan KE, Castiglione DA, Butzner JD: The changing face of childhood celiac disease in North America: impact of serologic testing.
Pediatrics. 2009;124:1572-1578. ♦♦