AllergyWatch®

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

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New Findings on β_2-Receptor Polymorphisms

VARIATIONS in the β_2-adrenergic receptor gene (*ADRB2*) might help to explain the heterogeneous response to β_2-agonist therapy in asthma patients. Recent studies indicate that asthma patients who are homozygous for arginine at position 16 of *ADRB2* might be less responsive to long-acting β_2 agonists. This study analyzed the effects of *ADRB2* genotype on the response to inhaled β_2-agonists plus inhaled corticosteroids.

The researchers analyzed data from two previous randomized trials of combined inhaled β_2-agonist and inhaled corticosteroid therapy for asthma exacerbations. In the first study, 2,250 patients received budesonide plus formoterol maintenance and reliever therapy, fixed-dose budesonide plus formoterol, or fixed-dose fluticasone plus formoterol. In the second study, 405 patients received adjustable or fixed-dose budesonide plus formoterol, or fixed-dose fluticasone plus salmeterol. Patients were stratified by *ADRB2* genotype to assess severe asthma exacerbations and other treatment outcomes.

In the first study, the rate of severe exacerbations was similar for patients with differing Gly16Arg genotypes: 12% with Gly/Gly, 11% with Gly/Arg, and 9% with Arg/Arg. Other outcomes were similar as well, including FEV_1, peak expiratory flow, use of as-needed medications, and nighttime awakenings. The *ADRB2* haplotype was unrelated to patient outcomes.

The second study also showed no difference in frequency of asthma exacerbations by Gly16Arg genotype: 8% to 9% across groups. Secondary outcomes were also unaffected.

For patients with asthma, the Gly16Arg genotype does not appear to affect the therapeutic response to inhaled β_2-agonist and inhaled corticosteroid therapy. Thus *ADRB2* genotype should not be used to guide therapy asthma exacerbations.

COMMENT: *This post hoc analysis of severe exacerbations in subjects treated with relatively high* ➤➤

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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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doses of inhaled corticosteroids and long-acting β-agonists gives comfort to current guidelines recommending long-acting β_2 agonists as add-on therapy in patients with moderately severe uncontrolled asthma. There was no predictive genotype for severe exacerbations. It is possible that high-dose inhaled corticosteroids are protective in patients with specific genotypes. Differently designed studies would be necessary to explore this.
S. F. W.
Bleecker ER, Postma DS, Lawrance RM, et al: Effect of ADRB2 *polymorphisms on response to long acting β_2-agonist therapy: a pharmacogenetic analysis of two randomised studies.*
Lancet. 2007;370:2118ñ2125. ♦♦

FOCUS ON FOOD ALLERGIES

Delaying Solid Foods Doesn't Reduce Childhood Atopy

RECENT recommendations call for delaying the introduction of solid foods for the first 4 to 6 months of life to reduce the risk of childhood allergic diseases. However, there has been little scientific support for this recommendation. Data from a German population-based cohort study were used to evaluate the protective effect of delaying solid foods on the development of atopy and allergic diseases in children.

The analysis included 2,073 children from the Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood study. All were healthy term infants at birth in 1997-99 Parental questionnaire responses provided detailed information on feeding history, including when solid foods were introduced. Multivariate logistic regression analysis was performed to assess whether delaying solid foods past 4 to 6 months had any protective effect against eczema, asthma, allergic rhinitis, and sensitization to food and inhalant allergens at age 6 years. To account for reverse causality, a separate analysis was performed including children with no skin or allergic symptoms from birth to 6 months.

Delaying the introduction of solid foods did not reduce the odds of any of the allergic diseases evaluated, or of allergic sensitization. To the contrary, delaying solid foods beyond 4 months was associated with an increased rate of food sensitization, especially in children without early skin and allergic symptoms. There was no consistent association between the timing of solid foods and childhood eczema. Later introduction of solid foods or a less-diverse diet within the first 4 months had no effect on allergy outcomes. However, among children without early skin and allergic symptoms, those with a more diverse diet during the first 4 months had a higher rate of eczema.

In contrast to recent recommendations, delaying the introduction of solid foods beyond the first 4 to 6 months of life does not reduce the risks of asthma, allergic rhinitis, or allergic sensitization by age 6 years. The relationship between solid food introduction and eczema remains unclear. Despite the observed positive association, the authors consider it unlikely that late introduction of solid foods truly increases the risk of food sensitization.

COMMENT: *This study is the most recent of a series arguing against conventional wisdom on the subject of delaying solid food introduction in infants. In addition to having no protective effect on subsequent atopic disease, delayed introduction of solids increased the tendency for serum IgE food sensitization in this population, statistically significant for peanut only. (Clinical food allergy was, unfortunately, not documented.) Once a concept is accepted as "common wisdom" in the medical community, the more rigorously that idea should be tested using an evidence-based approach.*
K. R. M.
Zutavern A, Brockow I, Schaaf B, et al: Timing of solid food introduc-➤➤

tion in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. **Pediatrics**. 2008;121:e44-52; DOI: 10.1542/peds.2006-3553. ♦♦

Peanut-Allergic Patients Are Getting Younger

THE prevalence of peanut allergy among children appears to be increasing, as does public awareness of the problem. Clinicians report that they are seeing children with peanut allergy at younger ages. A referral center reviewed its experience to assess the age at first exposure reaction among children evaluated for peanut allergy.

The analysis included 140 children diagnosed with peanut allergy at a university clinic between 2000 and 2006. Most had other allergic diagnoses as well, including atopic dermatitis in 82%, asthma in 62%, and allergic rhinitis in 57%. Median age at the time of first peanut exposure was 14 months, while age at first reaction was 18 months. These ages were significantly younger than in a comparable group of patients seen between 1995 and 1997: 22 and 24 months, respectively.

For children born before 2000, median age at first exposure was 19 months and age at first reaction was 21 months. For those born after 2000, the ages were 12 and 14 months, respectively. Fifty-three percent of the children with peanut allergy were also sensitized to eggs, 26% to cow's milk, 20% to tree nuts, 11% to fish, 9% to shellfish, 7% to soy, 6% to wheat, and 6% to sesame seeds.

Children referred for evaluation of peanut allergy are being seen at younger ages. This trend appears to be related to earlier initial exposure to peanut. Egg and sesame are among the other important food allergens in this group of patients.

COMMENT: *Despite increasing public awareness about peanut allergy, peanuts are, paradoxically, being introduced into children's diets at earlier ages. However, in this study, a majority of peanut-allergic children reacted to an initial ingestion, suggesting that delaying introduction would not have affected the outcome or overall incidence. Among coincident food allergies, we should all take note that 6% of these patients are allergic to sesame seeds, statistically equivalent to wheat allergy!*
K. R. M.
Green TD, LaBelle VS, Steele P, et al: Clinical characteristics of peanut-allergic children: recent changes. **Pediatrics**. 2007;120:1304-1310. ♦♦

High QOL Impact of Food Hypersensitivity

LIMITED data suggest that food allergies can have a major impact on children's lives. One study reported that children with peanut allergy had a lower health-related quality of life (HRQOL) than those with insulin-dependent diabetes. A validated instrument was used to assess HRQOL in children with food hypersensitivity.

The Child Health Questionnaire Parental Form 28, plus additional questions specific to food hypersensitivity, was administered to the parents of 1,378 nine-year-old children enrolled in a Swedish birth cohort. The cohort included 212 children with food hypersensitivity, as well as 221 with other allergic diseases. The HRQOL impact of food hypersensitivity was assessed, including the effects of symptom severity and levels of food-specific IgE antibodies.

Children with food hypersensitivity had lower scores on a number of subscales, including physical functioning, role/social limitations-physical, and general health. Food-related lower airway symptoms were associated with lower scores for self-esteem, parental impact-time, and family cohesion. Subscale scores were not related to sensitization, although children with higher specific IgE antibody levels had lower scores for mental health and general health. Scores were unrelated to a physician's diagnosis of food allergy.

The results show the high HRQOL impact of food hypersensitivity in school-age children. The effects are especially large for children with lower airway symptoms or high levels of food-specific IgE antibodies. Clinicians should be aware of the impact of food hypersensitivity on HRQOL, not only for the children themselves but for the entire family.

COMMENT: *Although objectively documenting HRQOL has become an important part of describing how asthma and rhinitis impact patients, relatively few studies have measured HRQL in patients with food allergy. This study, the first population-based evaluation of quality of life in food allergy patients, involved administering a validated HRQOL instrument to parents of 9-year-old Swedish children with food allergy. Not surprisingly, impairment in HRQOL was more striking in children with more severe food allergy.*
S. A. T.
Östblom E, Egmar A-C, Gardulf A, et al: The impact of food hypersensitivity reported in 9-year-old children by their parents on health-related quality of life. **Allergy**. 2008;63:211-218. ♦♦

New Data on Natural History of Egg Allergy

EGG allergy is a very common problem that can have a major impact on patients. Parents are often told that most patients "outgrow" egg allergy in early childhood. A large cohort of children with egg allergy were assessed to clarify the natural history of this disorder. ➤➤

The retrospective analysis included 881 patients evaluated for egg allergy at a referral clinic. The patients, 68% boys, were followed up for a median of nearly 6 years. The children had a high rate of other allergic diseases, including an 81% rate of eczema and a 93% rate of other food allergies. Follow-up data were analyzed to assess the development of egg tolerance, based on the response to concentrated egg.

On Kaplan-Meier analysis, egg allergy was predicted to resolve by age 4 in 4% of patients, age 6 in 12%, age 10 in 37%, and age 16 in 68%. Persistent egg allergy was associated with higher egg IgE levels throughout follow-up; most children with a peak egg IgE level of 50 kU/L did not become tolerant by age 18. In addition to the highest recorded egg IgE level, risk factors for persistent egg allergy included other atopic diseases and other food allergies.

Most children with egg allergy do outgrow the problem over time. However, development of egg tolerance may take longer to occur than previously thought. At least in this referral population, egg IgE level is a strong predictor of the resolution of egg allergy.

COMMENT: *This chart review of 881 patients reports that children don't "grow out of" their egg allergy as quickly as previously thought. Specific egg IgE greater than 50 kU/L predicts children with persistent sensitivity. Interestingly, 81% of the children also had eczema and over 90% had other food sensitivity as well.*
S. M. F.
Savage JH, Matsui EC, Skripak JM, Wood RA: The natural history of egg allergy.
J Allergy Clin Immunol. 2007;120:1413-1417. ♦♦

Gene Variants Modify Protective Effect of Farm Milk

DRINKING farm milk may contribute to the lower rate of asthma and allergies among children who grow up on farms. Previous studies have suggested that variations in the innate immunity receptor *CD14* might interact with environmental risk factors in the development of allergic disease. The effects of *CD14* polymorphisms on the relationship between farm milk consumption and allergic disease outcomes were analyzed.

The study included data on farm and non-farm children from two European studies. A subsample of 222 children underwent measurement of *CD14* expression in peripheral blood leukocytes.

There was a significant interaction between the *CD14/-1721* polymorphism and farm milk consumption. Adjusted odds ratio for the association between farm milk and asthma was 0.18 for children homozygous for the A allele, 0.47 for AG heterozygotes, and 0.98 for GG homozygotes. Comparable associations were noted for allergic rhinoconjunctivitis and pollen sensitization. The *CD14/-1721* polymorphism also influenced the relationship between farm milk and *CD14* gene expression, with adjusted geometric means ratios of 1.61 for the AA genotype, 1.11 for AG, and 0.76 for GG.

The *CD14/-1721* polymorphism modifies the protective effect of farm milk consumption against allergic diseases. The effect is stronger among children with the AG and especially the AA genotypes of *CD14/-1721*, compared to GG homozygotes. These genetic variations also influence gene expression of *CD14*, which might therefore mediate the effect of farm milk consumption against asthma and allergies.

COMMENT: *It is fascinating when research supports the hygiene hypothesis. These investigators suggest that the biologic effects of differential gene expression of* CD14 *might mediate the effect of farm milk on the development of allergic disease. Could the probiotic bacteria found in non-pasteurized farm milk be providing the benefit for those children with this allele?*
S. M. F.
Bieli C, Eder W, Frei R, et al: A polymorphism in CD14 modifies the effect of farm milk consumption on allergic diseases and CD14 gene expression.
J Allergy Clin Immunol. 2007;120:1308-1315. ♦♦

Risk Factors for Persistent Airflow Limitation in Severe Asthma

PATIENTS with asthma may develop chronic, persistent airflow limitation (PAFL). However, the course of asthma is variable, and the characteristics predisposing to PAFL are unclear. Data from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study were used to assess factors predicting the development of PAFL in asthma patients.

The analysis included 1,017 adult patients with severe or difficult-to-treat asthma. Those with chronic obstructive pulmonary disease, possible obesity-related lung function abnormalities, or more than a 30 pack-year history of smoking were excluded. Sixty percent of patients developed PAFL, defined as a postbronchodilator FEV_1/FVC ratio of 70% or less at two consecutive annual visits. Multivariate analysis was performed to identify variables independently associated with this outcome.

Demographic factors associated with PAFL were older age, odds ratio (OR) 1.4 per 10 years; male sex, OR 4.5; and black ethnicity, OR 2.2. Independent clinical risk factors were current smoking, OR 3.9; past smoking, OR 1.6; aspirin sensitivity, OR 1.5; and longer duration of asthma, OR 1.6 per 10 years. Factors associated with a lower risk of PAFL included Hispanic ethnicity, higher education, family history of atopic dermatitis, household pets, and dust sensitivity. Patients without PAFL generally had more comorbid allergic conditions and more asthma triggers.

These TENOR data show a high prevalence of PAFL among patients with severe or difficult-to-treat asthma, even after exclusion of patients with comorbid conditions that could contribute to airflow obstruction. The demographic and clinical risk factors identified suggest at least two distinct patterns of asthma progression in this group of patients. The results may aid in identifying patients at high risk of PAFL, as well as the factors that increase or reduce the risk of progression to predominantly irreversible airflow obstruction. ➤➤

COMMENT: *The FEV_1/FVC is increasingly used to assess lung function, supplanting peak flow rates in current guidelines. The authors used postbronchodilator FEV_1/FVC of 70% or less as a marker of persistent airway obstruction. Demographic associations included male sex, duration of asthma, smoking, aspirin sensitivity, and black race. These findings help define which patients are at risk for PAFL and the factors that may prevent or reduce progression into a predominantly irreversible form.*
S. F. W.
Lee JH, Haselkorn T, PhD, Borish L, et al: Risk factors associated with persistent airflow limitation in severe or difficult to-treat asthma: insights from the TENOR study.
Chest. 2007;132:1882-1889. ♦♦

Exhaled NO Increases, Lung Function Drops after Montelukast Withdrawal

IN children with asthma, treatment with montelukast reduces fractional exhaled nitric oxide (FENO). One report has described increases in FENO after montelukast withdrawal in asthmatic children, but the effects on lung function are unknown. This issue was addressed in a randomized controlled trial.

Twenty-six children with mild persistent asthma were randomly assigned to receive 4 weeks of treatment with oral montelukast, 5 mg/d, or placebo. At a follow-up visit 2 weeks after the end of treatment, the patients underwent pulmonary function testing and FENO measurement.

Pretreatment FENO levels were similar between groups. During montelukast treatment, FENO was reduced by 17%. After exclusion of 3 children exposed to seasonal allergens during treatment, this figure increased to 35%.

Two weeks after montelukast withdrawal, FENO had increased again to baseline levels. This change was accompanied by significant reductions in pulmonary function measures, including absolute FEV_1, FEV_1 percentage of predicted, FEV_1/FVC, and forced expiratory flow at 25% to 75% of FVC. None of these changes occurred in placebo-treated children.

Montelukast treatment reduces FENO in children with asthma, especially without exposure to relevant allergens. However, montelukast withdrawal is associated with rising FENO concentrations, along with worsening lung function. Larger studies are needed to clarify the effects of montelukast withdrawal in asthmatic children.

COMMENT: *This very small study demonstrated increased FENO after montelukast withdrawal in children with mild asthma after 2 weeks. Concomitantly, lung function decreased. Exhaled NO may be used to monitor inflammation in children withdrawing from montelukast.*
S. F. W.
Montuschi P, Mondino C, Koch P, et al: Effects of montelukast treatment and withdrawal on fractional exhaled nitric oxide and lung function in children with asthma.
Chest. 2007;132:1876-1881. ♦♦

Health Care Use in Childhood Asthma Predicts Persistence into Adulthood

PATTERNS of childhood asthma seem to predict long-term outcomes--when asthma is persistent in childhood, it is more likely to continue into adulthood. Knowledge of risk factors for persistent asthma in early childhood would aid in targeting children for continued asthma management and follow-up. A longitudinal cohort study was performed to identify factors associated with persistence vs resolution of childhood asthma.

From a cohort of 123,707 infants born in Ontario during 1994, the analysis included 34,216 infants (27.7%) diagnosed with asthma before age 6. The study definition of early childhood asthma was one asthma hospitalization or two asthma-related physician claims within the 3-year period before age 6. Follow-up to age 11 included data on health care utilization and hospitalizations. Patterns of resource utilization within 1 year after asthma diagnosis were analyzed as predictors of remission or persistent asthma, defined as continued asthma events from age 6 to 11.

Within the year after diagnosis, 54.4% of the children had additional health care encounters for asthma. By age 11, asthma was considered in remission for 48.6% of patients. Children hospitalized for asthma during the first year after diagnosis were three times more likely to have persistent asthma at age 11. A similar increase in risk was noted for children with at least four physician visits during the first year, odds ratio 2.6. The associations were unaffected by age at diagnosis.

For young children with asthma, the intensity of health resource utilization during the year after diagnosis is associated with an increased risk of persistent asthma. Patients with hospitalizations and/or frequent physician visits for asthma should be targeted for close follow-up, disease management, and asthma education.

COMMENT: *More than a fourth of the babies born in Ontario in 1994 developed asthma by 6 years of age. When asthma was diagnosed during a hospitalization, the children were twice as likely to have another hospitalization for asthma in the next 6 years, and had a threefold risk of persistent asthma by age 12 years. This study reaffirms the importance of close follow-up and monitoring of preschool children after their initial diagnosis of asthma.*
S. M. F.
To T, Gershon A, Wang C, et al: Persistence and remission in childhood asthma: a population-based asthma birth cohort study.
Arch Pediatr Adolesc Med 2007;161:1197-1204. ♦♦

Immunotherapy For Allergic Rhinitis Reduces Costs

ALLERGY immunotherapy (IT) improves outcomes in children with allergic rhinitis, including a reduced risk of new-onset asthma. However, there are few data on the use and cost-benefits of IT for U.S. children with allergic rhinitis. Patterns of IT care among children with allergic rhinitis were analyzed, including the effects on health resource use and costs.

Florida Medicaid claims were reviewed to identify 102,390 children and adolescents newly diagnosed with allergic rhinitis between 1997 and 2004. Demographic and clinical characteristics associated with IT use were identified, along with subsequent patterns of care. Health services use and costs were compared for the 6 months before starting IT and the 6 months after discontinuation.

Just 3% of the children with newly diagnosed allergic rhinitis received IT. Factors associated with higher use of IT included male sex, Hispanic ethnicity, and concomitant asthma. Patients who received IT had lower use of health resources over the subsequent 6 months, including pharmacy claims, outpatient visits, and hospitalizations. Costs in all three areas were also lower in the IT group, including the cost of IT itself. Weighted cost savings over 6 months averaged $401 per patient. However, just 16% of patients completed a 3-year course of IT.

These Medicaid data suggest that IT for children with newly diagnosed allergic rhinitis is associated with reductions in resource utilization and costs. Only a minority of patients are started on IT, and most of these do not complete treatment. Increasing access to and continuation of IT might increase the benefits of therapy.

COMMENT: *Despite the fact that most patients prematurely discontinued their IT, there was still a substantial reduction of health care expenses in those allergic rhinitis patients receiving IT. One could only speculate how much more of a reduction in health care costs and how much better the patients might have been if they had been more compliant.*
S. M. F.

Hankin CS, Cox L, Lang D, et al: Allergy immunotherapy (IT) among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs.
J Allergy Clin Immunol 2008;121:227-232. ♦♦

What's the Optimal Dose of SLIT for Allergic Rhinitis?

IN Europe, sublingual immunotherapy (SLIT) has become a popular alternative to subcutaneous immunotherapy for treatment of allergic rhinitis in adults. However, in the absence of data on optimal dosing, the use of SLIT remains controversial. A randomized controlled trial was conducted to assess the efficacy, safety, and optimal dose of grass-pollen SLIT for allergic rhinoconjunctivitis.

The multicenter trial included 628 patients with moderate to severe seasonal allergic rhinoconjunctivitis, drawn from 42 centers in 10 European countries. Grass pollen allergy was confirmed by skin prick testing and specific IgE measurement. Patients were randomly assigned to SLIT or placebo. Patients assigned to SLIT received one of three daily doses of a standardized five-grass pollen tablet: 100 index of reactivity (IR), 300 IR, or 500 IR. Treatment began 4 months before the predicted start of grass pollen season and continued throughout the season. Symptom scores, rescue medication use, quality of life, and safety outcomes were assessed.

Mean Rhinoconjunctivitis Total Symptom Score was 3.58 in the 300 IR SLIT group and 3.74 in the 500 IR group--significantly lower than the means of 4.93 in the placebo group and 4.70 in the 100 IR group. Individual symptom scores, rescue medication use, and quality of life assessments also supported the efficacy of the two higher SLIT doses. Treatment was generally well-tolerated, although the higher doses were associated with higher rates of discontinuation because of adverse events. There were no serious side effects.

This randomized trial confirms the safety and efficacy of grass pollen SLIT for seasonal allergic rhinoconjunctivitis. The 5-grass pollen tablet evaluated in this study is effective at both 300 and 500 IR doses. Based on a lower rate of adverse events, the 300 IR dose appears optimal for clinical practice.

COMMENT: *Publicity about SLIT is increasing here in the United States. It is critical that the proper dose is utilized for effective improvement in symptoms. These European researchers show that there is a minimal dose that is efficacious, but when that dose is exceeded, the incidence of side effects becomes intolerable. As we wait for approval of this emerging therapy, it is important that we understand the risks vs benefits.*
S. M. F.

Didier A, Malling H, Worm M, et al: Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis.
J Allergy Clin Immunol. 2007;120:1338-1345. ♦♦

Rituximab Shows Benefits in Severe Atopic Eczema

SEVERAL characteristics of atopic eczema suggest that B cells may play a major role in pathogenesis. The monoclonal anti-CD20 antibody rituximab, developed for treatment of B-cell malignancies, has shown benefits in patients with autoimmune diseases. This pilot study evaluated the use of B-cell depletion therapy for patients with severe atopic eczema.

The open-label trial included 6 patients with severe atopic eczema: 4 women and 2 men, average age 39 years. All received two treatments with rituximab, 1,000 mg IV, given 2 weeks apart. Within 4 to 8 weeks, all patients had significant improvement in skin symptoms: the mean eczema area and severity index decreased from 29.4 before treatment to 8.4 at 8 weeks. ➤➤

Pruritus scores and topical corticosteroid use decreased as well.

The clinical improvements were accompanied by improvement in histologic findings, including spongiosis, acanthosis, and dermal infiltrate, with reductions in both T-cell and B-cell infiltration. Skin B cells were reduced by about 50%, while blood B cells fell to undetectable levels. Treatment was also followed by reduced expression of interleukin-5 and interleukin-13. Total IgE level decreased somewhat, but allergen-specific IgE was unaffected.

The preliminary results suggest that treatment with rituximab yields striking improvement in patients with severe atopic eczema. This effect supports the involvement of B cells in the pathogenesis of atopic eczema. Placebo-controlled trials are needed to establish the safety and efficacy of this therapy.

COMMENT: *Rituximab is a monoclonal anti-CD20 antibody that has been effective in B-cell malignancies and certain autoimmune disorders. In this pilot study, rituximab was remarkably effective for patients with severe atopic eczema. The authors speculate that the reduction of B-cells in eczematous skin resulted in reduced T-cell activation as well. Future studies could confirm the benefits of rituximab for patients with this frustrating condition.*
S. M. F.

Simon D, Hösli S, Kostylina G, et al: Anti-CD20 (rituximab) treatment improves atopic eczema.
J Allergy Clin Immunol. 2008;121:122-128. ♦♦

Inhaled Ciclesonide and Linear Growth

CONCERNS about growth suppression may limit the use of inhaled corticosteroids for children with asthma. Ciclesonide is a new inhaled corticosteroid with low oral bioavailability, rapid elimination, and high plasma protein binding. This randomized trial evaluated the effects of ciclesonide on linear growth velocity in asthmatic children.

The study included 661 children with mild, persistent asthma, aged 5.0 to 8.5 years. After a 6-month run-in period, patients received once-daily morning treatment with ciclesonide, 40 or 160 µg, or placebo. Linear growth velocity was estimated by linear regression, based on four stadiometer measurements. Adverse events and urinary free cortisol levels were assessed as well.

During the run-in period, mean linear growth velocity was similar across groups, ranging from 6.20 to 6.49 cm/y. During study treatment, growth velocity was not significantly different for children receiving ciclesonide vs placebo: mean differences were -0.02 cm/y in the 40 µg dose group and -0.15 cm/y in the 160 µg dose group. There were no significant differences in adverse events, or in 10-hour overnight or 24-hour urinary free cortisol levels.

Even at a once-daily dose of 160 µg, inhaled ciclesonide does not cause any significant reduction in linear growth velocity in asthmatic children. This finding may help to reduce concerns about systemic adverse events, and promote appropriate use of inhaled corticosteroids in asthmatic children.

COMMENT: *In this industry-sponsored study, inhaled ciclesonide was found to have a reassuring safety profile with regard to linear growth in children, over the course of 1 year. No active comparisons were made with other inhaled corticosteroids, so it is unknown whether ciclesonide is superior to other products, in its lack of growth suppression. One always wonders whether the patients actually receive all of the prescribed medication in such studies--here, compliance was measured using patient diaries and canister weights.*
K. R. M.

Skoner DP, Maspero J, Banerji D, and the Ciclesonide Pediatric Growth Study Group: Assessment of the long-term safety of inhaled ciclesonide on growth of children with asthma.
Pediatrics. 2008;121:e1-e14. ♦♦

Strategies for Reducing Pediatric ED Return Visits for Asthma

FOR children receiving emergency department (ED) care for acute asthma exacerbations, the rate of unscheduled return visits is high--up to 10% within 14 days. Although risk factors have been identified, few studies have evaluated interventions to prevent such relapses. This study sought to identify interventions associated with a lower rate of return visits by children receiving ED care for asthma.

Administrative data were used to identify 2- to 17-year-old patients receiving asthma care at all 152 EDs in Ontario between 2003 and 2005. The 32,966 children represented more than 9% of all pediatric asthma patients in Ontario. Hospital surveys were used to collect data on the asthma care strategies used. In a risk-adjusted model, the effects of the various strategies on unscheduled return visits to any ED within 72 hours were analyzed.

More than two-thirds of the ED visits analyzed were triaged as high acuity. Ninety-seven percent of EDs used at least one asthma management strategy and 74% used three or more strategies. The overall rate of unscheduled return visits was 5.6%. On logistic regression analysis, strategies associated with a lower rate of return visits included preprinted order sheets and having a pediatrician available for consultation. At 11 EDs where both strategies were used, return visits were reduced by 36%. There was no significant advantage of being seen directly by a pediatrician or pediatric emergency medicine physician, or of routine peak flow monitoring for children aged 7 or older.

The study documents the wide range of strategies used by EDs to manage acute asthma exacerbations in children. Preprinted order forms and the availability of pediatricians are associated with significant reductions in unscheduled return visits. The findings support previous research showing that tools to standardize care can lead to improvement in care processes. ➤➤

COMMENT: *We are lacking evidence-based medicine regarding which specific strategies reduce return ED visits for asthma. This large retrospective Canadian study attempts to clarify the data. While standardized asthma order forms are found helpful, it remains unclear which component resulted in improvement; one would suspect early corticosteroid use would factor highly. In the case of pediatric consultants, having a pediatrician immediately available would be helpful, but may not be feasible in smaller, community hospitals. Peak flow monitoring continues to factor prominently in asthma guidelines, but was notably not found to be helpful in reducing return ED visits.*
K. R. M.

Guttmann A, Zagorski B. Austin PC, et al: Effectiveness of emergency department asthma management strategies on return visits in children: a population-based study.
Pediatrics. 2007;120:e1402-e1410. ♦♦

Mannitol AHR Reflects Airway Inflammation in Asthma

AIRWAY hyperresponsiveness (AHR) to indirect stimuli depends on the presence of inflammatory cells and the mediators they release, in addition to a responsive muscle. Airway hyperresponsiveness to mannitol has been linked to measures of asthma disease activity; a mannitol test kit is now commercially available. The relationship between AHR to mannitol vs methacholine was assessed, including comparison with airway inflammatory markers and other asthma measures.

The study included 53 nonsmoking adult asthma patients not taking inhaled corticosteroids. All underwent provocation testing with mannitol, up to 635 mg, and methacholine, up to 8 µmol. The results were related to measures of airway inflammation, ie, sputum eosinophils and exhaled nitric oxide (eNO); peak flow; and quality of life.

Mannitol and methacholine AHR were both associated with increased measures of airway inflammation: eNO was greater than 20 ppb for 83% of subjects with AHR to mannitol and 88% with AHR to methacholine. Percentage of patients with more than 1% eosinophils in sputum was 70% and 77%, respectively. Compared with AHR to methacholine, AHR to mannitol was more closely correlated with sputum eosinophil percentage and with eNO. The response to mannitol was also positively correlated with variation in peak flow and with quality-of-life score.

At least in non-steroid-treated asthma patients, AHR to mannitol is a better indicator of airway inflammation than AHR to methacholine. In addition to airway inflammation, asthma patients with AHR have signs of poor asthma control, including decreased quality of life and significant variation in peak flow. More study is needed to assess responses to mannitol in a more general population of asthma patients.

COMMENT: *As we search for conveniently obtainable surrogate measurements of airway inflammation in asthma, there is increasing interest in standardized bronchoprovocation testing using inhaled mannitol. This test offers practical advantages over methacholine challenge and induced sputum eosinophil measurement because it takes only 15 minutes, involves a kit with premeasured doses, and requires no equipment other than a spirometer. In this study, compared with methacholine challenge, "mannitol challenge" results more closely correlated with induced sputum eosinophilia and eNO levels. Stay tuned, mannitol challenge may soon be in our offices.*
S. A. T.

Porsbjerg C, Brannan JD, Anderson SD, Backer V, et al: Relationship between airway responsiveness to mannitol and to methacholine and markers of airway inflammation, peak flow variability and quality of life in asthma patients.
Clin Exp Allergy. 2007;38:43-50. ♦♦

Low Childhood Cholesterol Predicts Atopy (But Don't Head to McDonald's!)

LIMITED data have suggested that low serum cholesterol is linked to atopic disease. It has been suggested that this may reflect alterations in dietary fat intake, thus contributing to the increase in allergic diseases in the industrialized world. Serum lipid levels in infancy were evaluated as predictors of allergic disease in childhood and adolescence.

The analysis was based on a prospective nutritional study including 200 unselected newborns followed up from 1981 to 2002. Serial measurements of total cholesterol were made throughout the first year of life. At ages 5, 11, and 20, the subjects were re-evaluated for allergic symptoms, skin prick test results, total IgE levels, and total, high-density lipoprotein, and low-density lipoprotein cholesterol.

Cholesterol levels in infancy were significantly lower for children who had allergic symptoms at age 5, compared to symptom-free children. The difference was not significant in cord blood but became apparent at age 2, when 94% of the subjects were exclusively breast-fed. Lower cholesterol levels in infancy were also related to atopic dermatitis and higher total IgE levels. Cholesterol concentrations were also inversely related to total IgE at age 11 and to atopic disease manifestations at age 20.

Children and adolescents with atopy and allergic disease appear to have lower cholesterol levels during infancy and afterward, compared to non-allergic children. Given the high rate of exclusive breast-feeding in this study, the difference does not appear to be diet-related. Decreased cholesterol may play a role in the early development of allergic sensitization.

COMMENT: *Refuting prior suggestions that a low-fat diet in infancy increases atopy, this study conducted a 20-year follow-up of a birth cohort. Indeed, there was an inverse relationship between atopy and serum lipids during infancy. However, this relationship preceded any dietary influence because all of the infants* ➤➤

were exclusively breast-fed at the time the lipids were measured. This suggests that the lipid profiles in infancy are independent of environmental influence.
S. A. T.
Pesnonen M, Ranki A, Siimes MA, Kallio MJT: Serum cholesterol level in infancy is inversely associated with subsequent allergy in children and adolescents.
Clin Exp Allergy. 2007;38:178-184.

♦♦

Real-World Diesel Exposure Reduces Lung Function in Asthma Patients

DIESEL exhaust is the main source of particulate air pollution in urban environments. Exposure chamber studies have found that breathing diesel exhaust causes changes in airway resistance and bronchial inflammation. This study examined the respiratory effects of real-world exposure to diesel traffic in asthma patients.

Sixty adult patients with mild or moderate asthma were studied before and after 2-hour walks in two areas of London: a busy street where only diesel-powered vehicles were allowed (Oxford Street) and a traffic-free park (Hyde Park). Particulates and other pollutants were monitored as the participants walked. The effects of the two exposures on lung function, symptoms, and lung inflammatory markers were assessed.

The subjects were exposed to significantly higher levels of fine and ultrafine particles, elemental carbon, and nitrogen dioxide on the busy street than in the park. After exposure to diesel traffic, FEV_1 decreased by up to 6.1% and forced vital capacity by up to 5.4%, despite a lack of symptoms. The changes were larger among patients with moderate asthma. Walking on Oxford Street was also associated with increases in sputum myeloperoxidase, a marker of neutrophilic inflammation; and airway pH. The latter changes were more closely related to ultrafine particles and elemental carbon than to particulates.

Even short-term exposure to diesel traffic leads to significant reductions in lung function among patients with mild to moderate asthma. The findings support epidemiologic data linking diesel exposure to increased asthma symptoms and severity.

COMMENT: *Multiple studies of the effect of isolated diesel particles on lung function have not provided consistent evidence of an effect. This study exposed mild and moderate asthmatics to a real-world diesel-only street in London and found significant effects on spirometry and surrogate measures of inflammation. Perhaps it's the entire pollutant "soup," not just the diesel particles, that affects asthma.*
R. J. M.
McCreanor J, Cullinan P, Nieuwenhuijsen MJ, et al: Respiratory effects of exposure to diesel traffic in persons with asthma.
N Engl J Med. 2007;357:2348-2358.

♦♦

Platelet-Activating Factor Reflects Anaphylaxis Severity

PLATELET-activating factor (PAF) has been shown to be involved in many of the manifestations of anaphylaxis. In animal models, PAF-receptor antagonists prevent fatal anaphylaxis. This study sought to clarify the role of PAF--and the PAF-inactivating enzyme PAF acetylhydrolase--in human anaphylaxis.

Serum PAF levels and PAF acetylhydrolase activity were prospectively measured in 41 patients with anaphylaxis. Mean serum PAF level was 805 pg/mL, compared with 127 pg/mL in 23 controls. Elevated PAF levels were found in 20% of patients with grade 1 anaphylaxis, 71% with grade 2 anaphylaxis, and 100% with grade 3 anaphylaxis, compared to 4% of controls. Platelet-activating factor levels were inversely correlated with PAF acetylhydrolase activity; patients with more severe anaphylaxis had lower PAF acetylhydrolase activity.

The study also included a retrospective analysis of serum samples from 9 patients who died of anaphylaxis. Mean PAF acetylhydrolase activity was significantly lower than in five control groups, including 24 patients with nonfatal anaphylaxis, 10 children who died of other causes, 15 children with life-threatening asthma, 19 children with non-life-threatening asthma, and 63 children with mild peanut allergy. The lowest values were found in patients who died of anaphylactic reactions to peanut. Activity of PAF acetylhydrolase activity was normal in both groups of asthmatic controls.

Serum PAF level and PAF acetylhydrolase activity are indicators of anaphylaxis severity. More severe anaphylaxis is associated with higher serum PAF and lower PAF acetylhydrolase activity. The findings suggest that selective PAF blockers might be useful as rescue therapy in acute anaphylaxis, and for prevention in patients at high risk.

COMMENT: *Every now and then, yesterday's news becomes newly relevant today. So it is with PAF, a mast cell mediator whose existence has been known for about 30 years. This study shows that PAF levels are correlated with the severity of anaphylaxis, and that its natural enemy, PAF acetylhydrolase, is inversely correlated. Thus are we provided with another biomarker of anaphylaxis that may be superior to tryptase and histamine.*
R. J. M.
Vadas P, Gold M, Perelman B, et al: Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis.
N Engl J Med. 2008;358:28-35.

How Does RSV Affect Cytokine Responses in Atopic Adults?

QUESTIONS remain as to how respiratory viral infections and allergic sensitization interact in patients with allergic asthma. Respiratory syncytial virus (RSV), recognized as an important cause of lower respiratory infection in children, may also be➤➤

important in adults. There may be differences in immune responses to RSV, with children showing a Th2-skewed response. Responses to RSV were evaluated in adults sensitized to a common aeroallergen.

Experiments were performed using peripheral blood mononuclear cells (PBMCs) from 9 adult patients sensitized to house dust mite and 11 nonatopic controls. The cells were exposed to live or ultraviolet-inactivated RSV, then incubated with or without mite allergen. Cytokine responses were measured using enzyme-linked immunosorbent assay and reverse transcriptase-polymerase chain reaction.

In PBMCs from atopic subjects, mite allergen induced significantly increased production of interleukin (IL)-5. In both atopic and control PBMCs, RSV was associated with increased production of interferon-γ (IFN-γ), although levels were higher for atopic cells. Production of IL-5 by atopic PBMCs was significantly reduced by allergen stimulation after live RSV infection. Production of allergen-specific IL-10 by atopic cells was increased in response to inactivated but not live RSV. Interleukin-12 was undetectable in these experiments.

Respiratory syncytial virus infection does not result in an enhanced allergen-specific Th2 response in adults sensitized to mite, the results suggest. In atopic adults, allergic inflammation of the airways may be affected by IFNγ induced by live RSV and by IL-10 induced by RSV protein.

COMMENT: *In addition to the role of RSV in childhood respiratory disease, it can be an important agent in adults. These investigators from Japan evaluated the effects of RSV infection in adults previously sensitized to mite allergens in vitro with PBMCs exposed to live or UV-inactivated RSV. Interestingly, live RSV infection with mite allergen did not enhance Th2 responses, which might reflect immune differences between adults and neonates. Inactivated RSV enhanced allergen specific IL-10 in cells from atopic patients. The authors stated that a critical limitation could be that protease activity in the mite allergen might have affected cytokine production.*
M. F.
Hirose H, Matsuse H, Tsuchida T et al. Cytokine production from peripheral blood mononuclear cells of mite allergen-sensitized atopic adults stimulated with respiratory syncytial virus and mite allergen.
Int Arch Allergy Immunol. 2008:146:149-155. ♦♦

Cystatin A Blocks Keratinocyte Responses to Mite Allergen

DESPITE the importance of mite allergen exposure in allergic disease, questions remain as to the route of exposure leading to sensitization. Cystatin A is the dominant inhibitor of proteolytic activity of the major dust mite allergens, Der f 1 and Der p 1, in skin--it blocks upregulation of interleukin-8 (IL-8) release from allergen-stimulated keratinocytes. Granulocyte-macrophage colony-stimulating factor (GM-CSF) plays several important roles in allergic disease, including atopic dermatitis (AD). The effects of mite allergen stimulation on release of GM-CSF by keratinocytes were assessed, along with the possible blocking activity of cystatin A.

Experiments were performed using the human keratinocyte cell line HaCaT, as well as normal human keratinocytes. The effects of stimulation with recombinant group 1 allergens were assessed, in the presence and absence of cystatin A.

Both HaCaT cells and normal keratinocytes in culture with high calcium levels showed upregulation of GM-CSF release on stimulation with recombinant group 1 allergens. In both types of cells, GM-CSF release was inhibited by cystatin A. Cystatin A was not digested by allergens with proteolytic activity. Incubation with keratinocytes, with or without preactivation by *L*-cysteine, led to partial restoration of the proteolytic activity of recombinant Der f 1.

In cultured keratinocytes, the proteolytic activity of recombinant mite allergen leads to upregulation of GM-CSF and IL-8 release. The findings may be relevant to mite sensitization via the skin, and to the perpetuation of skin responses in AD. The results also suggest that cystatin A may play a homeostatic role in controlling inflammation of the skin.

COMMENT: *Inhibition of proteolytic activity of Der f 1 and Der p1 by cystatin A is known to block the upregulation of IL-8 from human keratinocytes in the presence of allergen. These investigators from Japan analyzed Der f 1/Der p 1-stimulated keratinocytes for IL-8 and GM-CSF, which is involved in atopic dermatitis. Proteolytic activity of recombinant forms of Der f 1/Der p 1 upregulated both IL-8 and GM-CSF. The results suggest that skin sensitization and perpetuation of AD occurs, in addition to supporting a role of cystatin A in inhibiting cutaneous inflammation*
M.F.
Ogawa T, Takai T, Kato T, et al: Upregulation of the release of granulocyte-macrophage colony-stimulating factor from keratinocytes stimulated with cysteine protease activity of recombinant major mite allergens, Der f 1 and Der p 1.
Int Arch Allergy Immunol. 2008; 146:27-35 ♦♦

No Benefit of Anti-IL-5 Therapy in Persistent Asthma

INTERLEUKIN-5 (IL-5) is thought to play a key role in eosinophil involvement in allergic inflammation. Animal studies suggest that strategies targeting IL-5 can reduce allergen-induced airway eosinophilia. This randomized trial evaluated the clinical effects of mepolizumab, a monoclonal antibody specific for human IL-5, in patients with persistent asthma.

The multicenter study included 362 patients with persistent asthma symptoms despite inhaled corticosteroid at doses of up to 1,000 of beclomethasone or equivalent. After a 4-week run-in period, patients were randomly assigned to receive three infusions of mepolizumab, 250 or 750 mg, or placebo at monthly intervals. Follow-up continued for 8 weeks after the end of treatment. A wide range of asthma outcome measures were assessed. ➤➤

Mepolizumab had no significant effect on the main efficacy variable, change in morning peak expiratory flow. There were also no differences in response in terms of FEV_1, β_2-agonist use, asthma symptoms, or quality of life. This was despite significant reductions in blood and sputum eosinophils at both doses of mepolizumab. There was a trend toward a reduced frequency of exacerbations at the 750 mg dose of mepolizumab, but this was also nonsignificant.

Anti-IL-5 therapy with mepolizumab does not improve clinical outcomes for patients with persistent asthma despite inhaled corticosteroid therapy. Future studies should evaluate whether mepolizumab can help to control exacerbation rate in patients with persistent airway eosinophilia.

COMMENT: *This study suggests that therapy directed at IL-5 as a single target has no significant benefit. The accompanying editorial by Paul O'Byrne (Am J Respir Crit Care Med. 2007;176:1059-1060) points to other potential uses for anti-IL-5 therapy, including hypereosinophilic syndrome. He also suggests that the use of mepolizumab in a selected population of patients with very elevated sputum eosinophils could provide potential benefit.*
B. E. C.
Flood-Page P, Swenson C, Faiferman I, et al: A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma.
Am J Respir Crit Care Med. 2007;176:1062-1071. ♦♦

Pollutant Exposure Modifies Asthma Risk of TGF-β1 Gene Variants

TRANSFORMING growth factor-β1 (TGF-β1) appears to be involved in both airway inflammation and remodeling, suggesting that variations in the TGF-β1 gene could affect asthma risk. Conflicting results regarding the link between the TGF-β1 C-509T polymorphism and childhood asthma might be explained by differences in environmental exposures. This study assessed the effects of exposure to tobacco smoke and traffic-related air pollution on the relationship between TGF-β1 polymorphisms and childhood asthma.

The analysis included 3,023 Hispanic and non-Hispanic white children from the Children's Health Study. Genotyping data suggested that two TGF-β1 single-nucleotide polymorphisms--C-509T and rs4803457 C>T--accounted for 94% of variability in the haplotype block containing the promoter region in both racial groups. Differences in asthma occurrence by genotype were analyzed with reference to exposure to maternal smoking in utero and exposure to freeway traffic pollution.

The risk of early persistent asthma was significantly increased for children with the -509TT genotype, odds ratio 1.8. In utero exposure to maternal smoking had a marginally significant effect on this relationship: for children with the -509TT genotype and in utero smoking exposure, the odds ratio for early persistent asthma was 3.4, compared to children with the -509CC/CT genotype and no in utero exposure. The -509TT genotype was also associated with increased risk among children who lived within 500 m of a freeway: odds ratio 3.10.

The effects of a functional variant of the TGF-β1 gene on childhood asthma are modified by common exposures related to oxidant stress-mediated airway inflammation. Children with the -509TT genotype have approximately a threefold increase in risk if exposed to maternal smoking in utero or to freeway traffic pollution. More research is needed to clarify the role of TGF-β1 gene variants in childhood asthma and the mechanisms of their interactions with air pollutants.

COMMENT: *This study again supports our emerging body of knowledge regarding the characterization of patients who are at high risk for adverse effects from environmental factors, including in utero tobacco smoke and subsequent exposure to an environment with increased pollution. Although this study will not direct us to changes in daily patient care, it is an important supportive piece of information to previously published data.*
B. E. C.
Salam MT, Gauderman WJ, McConnell R, et al: Transforming growth factor-β1 C-509T polymorphism, oxidant stress, and early-onset childhood asthma.
Am J Respir Crit Care Med. 2007;176:1192-1199. ♦♦

REVIEWS OF NOTE

COMMENT: *From the American Academy of Pediatrics Committee on Nutrition and Section on Allergy and Immunology, this policy statement incorporates the latest data on maternal diet, breast-feeding, and infant feeding with regard to atopy. A lack of evidence for altering the maternal diet during pregnancy or breastfeeding is reinforced, as is lack of effect from altering the infant diet beyond 4 to 6 months. At least 4 months of breast-feeding for at-risk infants is recommended over intact cow's-milk formulas, with beneficial findings cited.*
K. R. M.
Greer FR, Sicherer SG, Burks AW, and the Committee on Nutrition and Section of Allergy and Immunology: Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas.
Pediatrics. 2008;121:183-191 ♦♦

COMMENT: *This report concerns the risk of anaphylaxis from omalizumab (Xolair) and was composed by a joint task force of the AAAAI and ACAAI. If you give omalizumab to your patients, you must read this 5-page review and incorporate the information into your informed consent and postdose monitoring procedures.*
R. J. M.
Cox L, Platts-Mills TA, Finegold I, et al: American ➤➤

Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force report on omalizumab-associated anaphylaxis.
J Allergy Clin Immunol. 2007;120:1373-1377. ♦♦

COMMENT: *This is an up-to-date review that ties together the hygiene hypothesis and oral tolerance studies.*
S. A. T.

Hammelmann E, Beyer K, Lau S, et al: Primary prevention of allergy: avoiding risk or providing protection?
Clin Exp Allergy. 2007;38:233-245. ♦♦

COMMENT: *Although the latest National Heart, Lung, and Blood Institute guidelines do not emphasize the need to use exhaled nitric oxide in clinic, there is increasing evidence of its value, and this technology will very soon become affordable for everyday use by us on the frontlines. This is a nice review of the utility of exhaled NO as an "inflammometer" for managing asthma in children.*
S. A. T.

Pijnenburg MWH, De Jongste JC: Exhaled nitric oxide in childhood asthma: a review.
Clin Exp Allergy. 2008;38:246-259. ♦♦

COMMENT: *In clinical practice, it is common to encounter infants with a frequent "barking" cough that worries parents. There may even be wheezing. Many of these infants get labeled asthmatic, but in truth may have self-limited tracheomalacia or bronchomalacia, and they do not improve with bronchodilators or steroids. This malacia can be primary or secondary, and this short review reminds us of the useful diagnostic considerations.*
R. J. M.

Doshi J, Kraviec ME: Clinical manifestations of airway malacia in young children.
J Allergy Clin Immunol. 2007;120:1276-1278. ♦♦

COMMENT: *Between subcutaneous and sublingual (SLIT) immunotherapy, many issues are being considered, studied, and debated. It's still early. I have seen no better summary of the substantial unresolved issues facing SLIT than this letter to the* Journal of Allergy and Clinical Immunology, *written by five of our specialty's most eminent scientists. Although it is merely a letter, it informs the debate in a thoughtful way. You may want to use this to update your primary care colleagues.*
R. J. M.

Greenberger PA, Ballow M, Casale TB, et al: Sublingual immunotherapy and subcutaneous immunotherapy: issues in the United States.
J Allergy Clin Immunol. 2007;120:1466-1468. ♦♦

COMMENT: *This excellent review of nasal physiology in obstructive sleep apnea helps our understanding of the role of nasal congestion in sleep-disordered breathing. The article supports the notion that increasing nasal airway patency will decrease turbulent airflow (snoring) but will not have a significant effect on apnea.*
B. E. C.

Kohler M, Bloch KE, Stradling JR: The role of the nose in the pathogenesis of obstructive sleep apnoea and snoring.
Eur Respir J. 2007;30:1208-1215. ♦♦

American College of
Allergy, Asthma & Immunology
85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005-4425