AllergyWatch®

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

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Severe Asthma: What Does It Look Like?

PATIENTS with severe asthma have continued symptoms despite intensive treatment, leading to high morbidity and health care utilization. The Severe Asthma Research Program (SARP) of the National Heart, Lung, and Blood Institute was developed to gain insights into the characteristics of patients who continue to experience severe asthma symptoms despite appropriate treatment. A new report presents detailed findings of a large cohort of patients with severe asthma.

The SARP cohort was drawn from nine U.S. and one U.K. sites. Severe asthma was defined according to criteria developed by the American Thoracic Society, including poor disease control despite high-dose corticosteroid treatment. Detailed information on asthma phenotype was collected, including questionnaires, pulmonary function testing, skin prick testing, and exhaled nitric oxide measurement. The findings in 204 patients with severe asthma were compared with those of 70 with moderate and 164 with mild asthma.

Patients with severe asthma were older and had a longer duration of disease than the two lower-severity groups. Severe asthma was associated with an increased frequency of symptoms; more frequent urgent health care utilization, including emergency visits and hospitalization; and increased rates of sinusitis and pneumonia. The severe asthma group had decreased lung function accompanied by marked improvement on bronchodilator testing. Patients with severe asthma had decreased atopy on skin testing, but were similar to the less-severe groups in terms of blood eosinophil levels, IgE, and exhaled nitric oxide.

Multivariate analysis identified five independent predictors of severe asthma: prebronchodilator FEV_1% predicted, history of pneumonia, decreased blood basophils, symptoms during routine physical activities, and fewer positive skin test reactions. Patients with disease onset before age 12 had a longer duration of disease and increased use of urgent care, especially intensive care. Patients with onset after age 12 had decreased lower lung function and increased rates of sinus infections and pneumonia. ➤➤

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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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The findings help to clarify the phenotype of severe asthma. Patients with continued symptoms despite appropriate treatment exhibit pulmonary function abnormalities with marked reversibility to bronchodilators, a history of sinus and lung infections, and high rates of health care utilization. The data suggest some differences between early- and late-onset severe asthma; future studies will likely identify other clinical subgroups.

COMMENT: *One of the challenges of understanding asthma is identifying which phenotypic characteristics are associated with the various degrees of severity. Since 2000, the NHLBI has been studying in detail a cohort of 438 asthmatic subjects. This project has analyzed the clinical and laboratory features, the better to "paint a picture" of the severe group. Some interesting tidbits: severity was not correlated with eosinophilia, IgE levels, or exhaled nitric oxide, but the severe group had less atopy.*
R. J. M.

Moore WC, Bleecker ER, Curran-Everett D, et al: Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program.
J Allergy Clin Immunol. 2007;119:405-413. ♦♦

HFA versus CFC... What's the Difference?

ENVIRONMENTAL concerns have led to the transition from chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) propellants in albuterol inhalers. The authors review some differences between CFC and HFA inhalers, along with data on the safety and effectiveness of HFA inhalers.

The Montreal Protocol, signed by the United States and other countries in 1987, calls for reductions in the use of CFCs and other ozone-depleting substances. As a result, stratospheric ozone levels have begun to recover. Hydrofluoroalkane inhalers have been introduced as a substitute, and are designed to work in the same way as CFC inhalers. However, reports have described some important differences. The HFA inhalers may deposit smaller amounts of albuterol in the spacer--this could lead to increased drug inhalation, although interactions between inhalers and spacers can be complex. Clogging has been reported with HFA inhalers; once-weekly cleaning can enhance performance. With most products, it is difficult to tell when the HFA inhaler is near empty, so patients should be encouraged to keep an extra canister handy. The modified valves of HFA inhalers may need to be primed less often.

Although HFA inhalers have been compared with CFC inhalers in children and adults with asthma, few studies have evaluated their use in patients with chronic obstructive pulmonary disease. Cumulative-dose studies show little clinical effect of differences in spray characteristics, but few studies have included bronchodilation as an endpoint. At higher doses, HFA-albuterol may have more systemic β_2-agonist effects. Overall, however, adverse effects appear no more frequent with HFA than with CFC inhalers. Because of patent issues, the withdrawal of CFC inhalers will eliminate the widely used, less-expensive generic CFC-albuterol inhalers.

In general, HFA-albuterol inhalers have efficacy and safety performance similar to that of the CFC inhalers they were designed to replace. However, physicians should be aware of the differences resulting from the use of the new propellants and discuss the transition with patients. The impact of the increased costs of HFA inhalers, particularly on patients paying out-of-pocket, remains to be determined.

COMMENT: *Things are never as simple as they seem. You probably thought that the transition from CFC-albuterol to HFA-albuterol was simply a change of initials. NOT! There are three new HFA-albuterol products, and a fourth for levalbuterol. There are differences in priming intervals, taste, ethanol content (important for certain patient groups), cost, presence of a dose counter, shelf life, and affinity for ambient moisture. We really do have to make an informed decision for our patients, and this article helps.*
R. J. M. ➤➤

Hendeles L, Colice GL, Meyer RJ: Withdrawal of albuterol inhalers containing chlorofluorocarbon propellants.
N Engl J Med. 2007;356:1344-1351. ♦♦

Avoiding Milk and Mites Reduces Allergies for High-Risk Infants

EFFECTIVE methods of preventing allergic diseases in infants at high genetic risk are needed. Studies have evaluated various approaches to reducing allergen exposure during infancy, with conflicting results. A program of food and dust mite allergen avoidance for high-risk infants was evaluated in a randomized, controlled trial.

The Isle of Wight prevention study included 120 infants genetically predisposed to allergic diseases, recruited before birth. For infants in the intervention group, exposure to milk was avoided by breast-feeding (with the mother on a low-allergen diet), with supplemental use of extensively hydrolyzed formula. An acaricide and mattress covers were used to reduce exposure to house dust mite. Control infants received standard medical advice. The children were followed up at 1, 2, 4, and 8 years for the development of allergic diseases and sensitization to common allergens.

Asthma risk was reduced by three-fourths for children assigned to allergen avoidance: odds ratio (OR) 0.24, with adjustment for potential confounders. There were also large reductions in atopic dermatitis, OR 0.23, and allergic sensitization, OR 0.13. For allergic rhinitis, the OR was 0.33. Allergen avoidance seemed especially effective in preventing persistent disease--the percentage of children with asthma symptoms at all follow-up visits was 1.7% in the intervention group, compared with 11.3% for controls. The protective effect also appeared particularly strong among children with allergic sensitization.

Avoiding exposure to food and dust mite allergens during the first year of life reduces the risk of asthma and allergies for children at high genetic risk. This benefit persists at least through age 8. Although further follow-up is needed, the authors recommend strict allergen avoidance measures for "high-risk children and highly motivated parents."

COMMENT: *Many studies have been done to assess the effects of dietary and environmental interventions in early life on the later development of atopic diseases. The collective results have been more confusing than enlightening. This study combined stringent dietary measures in the infants and lactating mothers, along with dust mite avoidance, up to the age of 12 months. The children were then followed up to 8 years of age. There was a beneficial effect on the development of asthma, rhinitis, and atopic dermatitis. I wish the "avoidance" people would get together with the "tolerization" people and tell us what works.*
R. J. M.
Arshad SH, Bateman B, Sadeghnejad A, et al. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight Prevention Study.
J Allergy Clin Immunol 2007; 119:307-313. ♦♦

Long-Term Effects of ICS on Lung Function Vary with IgE Level

THE short-term benefits of inhaled corticosteroids (ICS) for asthma are well known. However, there are few data on the long-term benefits of ICS in terms of slowing decline in lung function or preventing or reversing airway remodeling. Data from a population-based study with 9-year follow-up were used to assess the effects of long-term ICS use on lung function in asthmatic patients.

The analysis included data on an international cohort of 667 young adult patients with asthma. Patients enrolled in the study in 1991-93 and were followed up to 1999-2002. The effects of regular ICS treatment on the rate of decline in FEV_1 were analyzed. Other independent variables included age, sex, height, body mass index, total IgE level, and smoking, with adjustment for potential confounders.

Longer durations of ICS use were associated with lesser declines in FEV_1. About half of the patients did not use ICS--their rate of decline in FEV_1 was 34 mL/y. For the 18% of the sample who used ICS for at least 4 years, the rate of decline was 12 mL/y. Adjusted analysis found a significant interaction between ICS use and total IgE. Among patients with an IgE level greater than 100 kU/L, those using ICS for 4 years or longer had a 23 mL/y decline in FEV_1. For patients with lower total IgE levels, there was no significant association.

Long-term ICS use is associated with greater preservation of lung function in patients with asthma. The protective effect appears greatest for patients with high total IgE levels. Measurement of total IgE may contribute to decisions about long-term anti-inflammatory therapy; the authors suggest further study to assess the possibility of calibrating ICS dose to IgE level.

COMMENT: *Presenting data from the European Community Respiratory Health Survey, these researchers found that adults with asthma tended to have less loss of lung function when treated with a prolonged course of ICS. Those with higher IgE levels had a more dramatic protective effect of regular ICS use. The main weakness of this study is the use of patient questionnaires to collect data about medication use. The data suggest that asthmatic patients with allergic inflammation are more responsive to continual treatment with ICS.*
S. M. F.
de Marco R, Marcon A, Jarvis D, et al: Inhaled steroids are associated with reduced lung function decline in subjects with asthma with elevated total IgE.
J Allergy Clin Immunol. 2007;119:611-617. ♦♦

Prednisolone Prevents Recurrent Wheezing in Kids with Rhinovirus

RECENT studies suggest that early rhinovirus-induced wheezing may be a risk factor for recurrent wheezing later in childhood. Effective intervention for children at high risk of recurrent wheezing is an ➤➤

important priority. Young children with wheezing were followed up to assess risk factors for recurrent wheezing and the possible benefits of prednisolone therapy.

The prospective study included 118 children, aged 3 to 35 months, with a first episode of wheezing requiring hospitalization. In an efficacy trial, the children were randomized to treatment with oral prednisolone or placebo. One-year follow-up data were used to assess factors associated with recurrent wheezing, defined as three physician-confirmed episodes of wheezing within 12 months.

Thirty-seven percent of the children had recurrent wheezing. This outcome was more likely for children less than 1 year old, those with atopy, and those whose mothers had asthma. In the placebo group, children whose initial episode of wheezing was associated with rhinovirus had a higher rate of recurrent wheezing than those with respiratory syncytial virus (RSV): hazard ratio (HR) 5.05

Prednisolone significantly reduced the rate of recurrent wheezing for children with eczema, HR 0.15, but not for those without eczema. Among children with rhinovirus, prednisolone was also associated with a reduction in recurrent wheezing, HR 0.19. Prednisolone had no protective effect in children with RSV, or in those negative for both rhinovirus and RSV.

The findings confirm that early childhood wheezing associated with rhinovirus infection is a significant risk factor for recurrent wheezing 1 year after the index episode. For children with rhinovirus-induced wheezing and those with eczema, treatment with prednisolone may reduce the risk of recurrent wheezing. The authors call for a clinical trial to evaluate this possibility.

COMMENT: *Rhinovirus infection in infancy is a major risk factor for recurrent wheezing and may be an even more important predictor of asthma than RSV. This report is a post hoc analysis of hospitalized children treated with either 3 days of prednisolone or placebo during their first episode of wheezing. In those with rhinovirus infection the initial steroid treatment did not influence the time to discharge in either group. However, after 1 year only 22% of the group receiving prednisolone had recurrent wheezing, compared to 50% of those receiving placebo. Infants with eczema also had a dramatic disease-altering effect with the short initial steroid treatment. A prospective trial would be helpful to confirm these findings.*
S. M. F.

Lehtinen P, Ruohola A, Vanto T, et al: Prednisolone reduces recurrent wheezing after a first wheezing episode associated with rhinovirus infection or eczema.
J Allergy Clin Immunol. 2007;119:570-575. ♦♦

Once Again, Fluticasone Beats Montelukast for Childhood Asthma

INHALED corticosteroids are the treatment of choice for children with mild persistent asthma. Almost all studies of the issue have found fluticasone propionate superior to montelukast for this purpose. Administrative claims data were used to compare the outcomes and costs of fluticasone versus montelukast for asthmatic children.

A large medical and pharmaceutical database was used to identify asthmatic children, aged 4 to 17 years, with documented asthma who were previously treated with inhaled corticosteroids and were now receiving fluticasone or montelukast. Two groups of 1,837 patients were identified--one treated with fluticasone and the other with montelukast--with propensity matching based on health care utilization. Outcomes analysis focused on treatment failure rate, asthma-related hospitalizations, and asthma-related costs.

The treatment failure rate was 26% in the fluticasone group versus 49% in the montelukast group. During treatment, the rate of asthma-related hospitalization was 1.5% with fluticasone versus 2.4% with montelukast. The increases in adverse outcomes with montelukast remained significant on adjusted analysis: odds ratio 2.55 for treatment failure and 1.99 for asthma hospitalization. Mean asthma-related costs were also lower with fluticasone: $861 per year, compared to $1,316 with montelukast. With controlling for confounders, costs were 52% higher in the montelukast group.

This observational study supports randomized trials showing the superiority of fluticasone propionate over montelukast for children with asthma. Fluticasone is associated with a lower treatment failure rate, fewer asthma-related hospitalizations, and lower costs for asthma related medical care.

COMMENT: *This study reaffirms the concept that monotherapy for asthma favors inhaled corticosteroids over montelukast, both from an outcomes standpoint and in terms of cost reduction. The choice of inhaled corticosteroid in this study was limited to fluticasone--not surprisingly, given pharmaceutical sponsorship. Weaknesses of the study include its retrospective design and inability to identify asthma severity in study cohorts.*
K. R. M.

Stempel DA, Kruzikas DT, et al: Comparative efficacy and cost of asthma care in children with asthma treated with fluticasone propionate and montelukast.
J Pediatr. 2007;150:162-167. ♦♦

No Pain, No Gain

RECENT reports have raised the possibility that vaccinations could contribute to the development of atopic eczema in infants. Studies of this topic have had important limitations and yielded inconsistent results. Data from a Dutch birth cohort study were used to analyze the effects of vaccinations during the first 6 months of life on rates of eczema and recurrent wheezing by age 1.

The analysis included 2,764 families enrolled in the KOALA Birth Cohort Study. Infants who had not received all vaccines in the standard vaccination schedule--ie, three diphtheria, pertussis, poliomyelitis, tetanus, and *Haemophilus influenzae* type b vaccinations by age 6 months--were classified as unvaccinated. Infants with prematurity and any congenital abnor-➤➤

mality affecting immunity were excluded. Rates of eczema and recurrent wheezing during the first year of life were compared for vaccinated and unvaccinated children, in multiple logistic regression models adjusted for confounders.

Twenty-three percent of infants developed eczema during the first year of life and 8.5% developed recurrent wheezing. Seventy-seven percent of infants received all vaccinations in the standard schedule by age 6 months, while 15% did not receive the complete schedule; the remaining 7% were never vaccinated. There was no difference in the incidence of eczema or recurrent wheezing among infants receiving all standard vaccinations within the first 6 months versus those vaccinated according to an incomplete schedule. Allergic disease outcomes were also similar for infants who were never vaccinated. Few infants received less than complete vaccinations because of illness during the first 6 months of life; the most common reason was to allow "natural development" of the immune system.

Vaccinations during the first 6 months of life do not appear to affect the risk of eczema or recurrent wheezing during the first year. Rates of these outcomes are similar for infants receiving all recommended vaccinations, less than the standard schedule, or no vaccinations at all.

COMMENT: *Reassuringly, these data do not indicate increased risk of infantile eczema or wheeze by age 1, in children receiving the usual series of early immunizations. This is another of report from the ongoing Dutch KOALA birth cohort study.*
K. R. M.

Kummeling I, Thijs C, Stelma F, et al: Diphtheria, pertussis, poliomyelitis, tetanus, and Haemophilus influenza *type b vaccinations and risk of eczema and recurrent wheeze in the first year of life: the KOALA Birth Cohort Study.*
Pediatrics. 2007;119:367-373. ♦♦

Perinatal Factors Affect Infants' AD Risk

ATOPIC dermatitis (AD), one of the earliest manifestations of allergic disease in children, is a risk factor for later sensitization and asthma. Identifying early risk factors for AD might lead to new approaches to asthma prevention. Cytokines play important roles in the maturation of the fetal immune system, but little is known about factors affecting immune competence at birth and during the first few months of life. Perinatal factors affecting the risk of AD during the first year of life were evaluated, including cytokine levels and indicators of skin barrier disruption.

Two hundred seventy-nine pregnant women were recruited at a Japanese obstetric clinic at 35 to 37 weeks' gestation. Potential predictors of AD were analyzed, including family history, infection during pregnancy, and cytokine concentrations in umbilical cord blood. Skin physiologic measures included assessment of stratum corneum hydration using an impedance meter, performed once daily for the first 5 days after delivery and again at 1 month.

Of 213 infants with complete data, 26 were diagnosed with infantile eczema during the first month and 27 received a physician diagnosis of AD during the first year. Maternal AD was a significant risk factor for AD in the child, as was a decreased level of macrophage inflammatory protein-1β in the cord blood sample. Of the skin physiologic measures, increased skin moisture in the surface and stratum corneum of the forehead and cheek at age 1 month were associated with an increased risk of AD.

Infections during pregnancy or breast-feeding were not risk factors for AD, while a paternal history of hay fever was associated with a decreased risk. Several factors were associated with an increased rate of infantile eczema during the first month: high cord blood concentrations of interleukin-2, interleukin-17, and macrophage chemotactic protein-1 and surface moisture in the cheek.

In addition to maternal history, certain perinatal factors affect the risk of AD in infants. The association with a reduced cord blood level of macrophage inflammatory protein-1β suggests a possible role of immune system immaturity at birth. Indicators of stratum corneum barrier disruption suggest impaired skin adaptation to the extrauterine environment. The differing risk factors suggest that the causes of eczema and AD in infants may differ as well.

COMMENT: *Maternal AD is a risk factor for development of the disease in children. Additionally, this Japanese study prospectively evaluated a range of cord blood cytokines, finding significantly lower levels of macrophage inhibitory factor-1β in those who ultimately developed AD. That these same infants had higher levels of facial moisture at 1 month of age seems paradoxical, as does the apparent protective effect of paternal allergic rhinitis. Interleukin-4 levels were undetectable in nearly all of the cord blood samples. However, the study was small, evaluating only 27 affected infants.*
K. R. M.

Sugiyama M, Arakawa H, Ozawa K, et al: Early-life risk factors for occurrence of atopic dermatitis during the first year.
Pediatrics. 2007;119:E716-E723. ♦♦

Large Study Finds Modified Allergen Vaccines Safe

ALTHOUGH rare, severe reactions to allergen immunotherapy are an important complication. Previous studies have shown the safety and effectiveness of depigmented and polymerized allergen extracts, which permit administration of high allergen doses in a short period of time. The safety of depigmented, glutaraldehyde-modified extracts was evaluated in a large, multicenter study.

The prospective, open study included 766 patients undergoing immunotherapy for rhinoconjunctivitis and/or asthma at 35 Spanish allergy centers. All patients were sensitized to dust mite, pollen, or both. ➤➤

Immunotherapy was performed using individualized therapeutic vaccine consisting of depigmented and polymerized allergen extracts adsorbed onto aluminum hydroxide. After a buildup phase of 4- to 6-weekly injections, patients received 12-monthly maintenance injections. All adverse reactions were recorded.

The study completion rate was 100%. There were 54 local reactions--43 immediate and 11 delayed--involving 7% of patients and 0.4% of injections. Thirty-four systemic reactions occurred in 12 patients, including 6 immediate reactions, all grade 2; and 18 delayed reactions, almost all grade 1 or 2. Grade 2 or 3 systemic reactions occurred in 0.12% of injections. None of the systemic reactions required rescue medication.

The modified allergen vaccines evaluated in this trial are safe and well-tolerated for use in immunotherapy. Adverse reactions appear less common than with unmodified allergen extracts. Together with previous data, the results suggest that modified allergen extracts may offer a better safety profile than sublingual allergen immunotherapy.

COMMENT: *Modifying allergenic extracts before use in immunotherapy has been pursued as a strategy to avoid clinical reactions. Depigmented polymerized extracts were used in this phase IV, multicenter, open-label subcutaneous immunotherapy trial involving 766 patients with dust mite and/or pollen allergy. Each subject's extract was individualized by mixing together relevant allergen polymers. Although the systemic reaction rate was not trivial (0.12% of injections), all of the reactions were mild and none required treatment with epinephrine. This method appears to have a safety advantage over subcutaneous immunotherapy using unmodified extracts. It remains to be seen whether treating with depigmented polymerized extracts achieves comparable efficacy.*
S. A. T.
Casanovas M, Martin R, Jiménez, et al: Safety of immunotherapy with therapeutic vaccines containing depigmented and polymerized allergen extracts.
Clin Exp Allergy. 37:434-440. ♦♦

Specific IgE Levels Predict Bronchial Response to Cat Allergen

ESPECIALLY when the recommendation to remove a pet from the home is involved, it is important to make an accurate diagnosis of pet allergy. In diagnosing cat allergy, it can be difficult to interpret the results of skin tests and serum specific IgE measurements. This study assessed the diagnostic efficiency of skin testing and specific IgE measurement in predicting airway reactivity to cat allergen.

The study included 64 patients with asthma, 49 exposed to cats. Each patient had a positive screening test for cat allergy but an uncertain clinical history. All underwent skin prick and intradermal skin testing and measurement of serum-specific IgE using the CAP system. This was followed by bronchoprovocation testing with cat epithelium. Skin test results and specific IgE levels were evaluated as predictors of airway reactivity.

The bronchoprovocation results were positive in 42.2% of patients. Median decline in FEV_1 was 28.3%, with a median PD20 value of 19 BAU. Serum specific IgE was a good predictor of airway reactivity, with an area under the receiver operating characteristic (ROC) curve of 0.85. In predicting the results of bronchoprovocation testing, intradermal skin testing performed better than skin prick testing--area under the ROC curve was 0.74 versus 0.54, respectively.

On logistic regression analysis, patients with CAP values of 17 kU_A/L were more than 93% likely to have a positive bronchoprovocation test. With CAP values below this cutoff, the probability of a bronchial response was 16%. When the intradermal skin test was negative, the probability of a positive bronchoprovocation test was just 9%.

Serum specific IgE measurement can help to clarify the contribution of cat allergy to asthma when the clinical history is unclear. Patients with higher CAP values are more likely to have a positive airway reaction to cat epithelium. When the intradermal skin test is negative, a positive bronchoprovocation result is unlikely.

COMMENT: *Many symptomatic skin test positive pet-owners vehemently believe that the beloved animal is not contributing to their asthma symptoms. This study used cat allergen bronchial challenge to define likelihood ratios for the use of intradermal and in vitro testing to cat. All patients had positive screening tests (prick skin testing or ImmunoCAP) to cat and none of the patients reported cat exposure as a trigger of symptoms. Not surprisingly, the predictive value of clinical history was low. Somewhat surprisingly, skin prick testing was not particularly specific unless the wheal diameter was at least 8 mm. ImmunoCAP testing was more sensitive than skin prick tests but had poor specificity at levels below 13 kU/L. A negative intradermal skin test was the best predictor of a negative bronchial challenge. The authors describe ImmunoCAP as the "optimal" test to aid in the diagnosis of cat allergy. However, a critical analysis of the data might argue for screening with either skin prick skin testing or ImmunoCAP, followed by careful intradermal testing if the wheal diameter is small or ImmunoCAP level is low.*
S. A. T.
Fernández C, Cárdenas R, Martin D, et al: Analysis of skin testing and serum-specific immunoglobulin E to predict airway reactivity to cat allergens.
Clin Exp Allergy. 2007;37:391-399. ♦♦

Omalizumab Reduces Specific and Nonspecific Airway Responsiveness

ANTI-IgE therapy with omalizumab can improve asthma control, but there is continued debate over its effects on airway hyperresponsiveness. Passive sensitization of human airway specimens with serum from allergic asthma patients leads to in vitro hyperresponsiveness with an increase in IgE-positive cells and mast cell degranulation. Further in vitro experiments were performed to evaluate omalizumab's effects on hyperresponsiveness and other effects of passive sensitiza- ➤➤

tion. Specimens of proximal and distal human bronchi were incubated with serum from asthmatic patients or normal controls, in the presence of varying concentrations of omalizumab. An organ bath system was used to assess contractile responses to histamine or *Dermatophagoides pteronyssinus*. Immunohistochemistry was performed using anti-IgE or anti-tryptase monoclonal antibodies, and mast cell degranulation was assessed.

In both proximal and distal airway samples, omalizumab reduced airway hyperresponsiveness--both specific hyperresponsiveness induced by allergen and nonspecific sensitization induced by histamine. The increase in IgE-positive cells following passive sensitization was also lessened by omalizumab, in concentration-dependent fashion. Omalizumab-related inhibition of mast cell degranulation was significantly and positively correlated with the contractile response to *D. pteronyssinus*.

These in vitro studies demonstrate inhibition of specific and nonspecific bronchial hyperresponsiveness by omalizumab. The study model also shows reductions in IgE-positive cells and mast cell degranulation. In vivo studies of omalizumab's effects on bronchial responsiveness are needed, including assessment of mast cell degranulation.

COMMENT: *These in vitro studies of human lung tissue further highlight the therapeutic potential of omalizumab. In addition to binding IgE, this molecule appears to abolish the post-sensitization increase in IgE-positive cells. The demonstration of diminished nonspecific BHR in upper and lower airway samples is also reassuring. Now if we could only get insurers to pay for it!*
A. M.

Berger P, Scotto-Gomez E, Molimard M, et al: Omalizumab decreases nonspecific airway hyperresponsiveness in vitro.
Allergy. 2007;62:154-161. ♦♦

Does Single-Allergen SLIT Benefit Polysensitized Patients?

ADULTS with respiratory allergens are typically sensitized to multiple allergens. The role of allergen-specific immunotherapy in such polysensitized patients is open to debate; it is unclear whether they should receive multiple allergen extracts, or if the effects of single-allergen immunotherapy can extend to other allergens. The clinical and functional effects of single-allergen and multi-allergen sublingual immunotherapy (SLIT) were compared in polysensitized adult patients.

The randomized, open trial included 58 adults sensitized to both birch and grasses. All had symptoms of rhinitis and bronchial hyperreactivity during both, nonoverlapping pollen seasons. Patients were assigned to receive SLIT for birch allergy, SLIT for grass allergy, SLIT for both allergens, or medications only. Assessments included symptom and medication scores, pulmonary function testing, and nasal eosinophil counts.

Forty-eight patients completed the study. Patients treated with medications only had no change in clinical or functional outcomes. In contrast, those receiving SLIT for either birch or grass had clinical improvement along with reduction in nasal eosinophil counts. The improvements were significant compared to baseline and compared to patients who did not receive SLIT--either during the target season or in the unrelated pollen season. Patients receiving SLIT for both birch and grass pollen had greater improvement in clinical outcomes and inflammatory markers. Across groups, only small changes in FEV_1 were observed.

For adults sensitized to birch and grass, giving SLIT for either allergen alone yields significant clinical and functional improvements during the relevant pollen season. Greater improvements are noted when patients receive SLIT for both allergens. Additional, rigorous trials are needed to confirm that the benefits of single-allergen SLIT extend to other allergens in polysensitized patients.

COMMENT: *Allergists most frequently care for polysensitized individuals. Previous data have indicated that the clinical and immunologic improvement in subcutaneous immunotherapy is both dose dependent and allergen specific. From these limited data, it would appear that SLIT is similar to injection immunotherapy in this regard, although selecting one potent antigen such as grass is better than nothing!*
A. M.

Marogna M, Spadolini I, Massolo A, et al: Effects of sublingual immunotherapy for multiple or single allergens in polysensitized patients.
Ann Allergy Asthma Immunol. 2007;98:274-280. ♦♦

Eosinophilic Esophagitis: an Update for Allergists

PATIENTS with eosinophilic esophagitis (EE) have severe eosinophilic infiltration of the esophagus, causing symptoms such as dysphagia, food impaction, abdominal pain, vomiting, and failure to thrive. Since this condition is frequently associated with atopy, many patients are seen by allergists. The diagnosis, clinical findings, pathogenesis, epidemiology, and treatment of EE are reviewed.

A long list of conditions besides EE can cause esophageal eosinophilia, the most frequent being gastroesophageal reflux disease (GERD). Acid-blocking therapy is ineffective in EE. Patients with EE have eosinophilic infiltration in both the proximal and distal esophagus, compared to the mainly distal pattern of GERD. Once other causes have been excluded, the diagnosis of EE is made by the detection of 20 to 24 eosinophils per high-power field in an esophageal biopsy specimen. Endoscopic findings include diffuse white plaques and linear furrowing.

There are many questions regarding the pathogenesis of EE, particularly why the eosinophils migrate to the esophagus. Genetic factors may be involved. The ➤➤

role of IgE-mediated allergy is also unclear, including sensitization to aeroallergens as well as foods. The incidence of EE appears to be increasing, although this may reflect increased awareness and recognition. Earlier diagnosis may decrease long-term complications.

There is a lack of evidence regarding the therapeutic options for EE. Treatment must be individualized and the results confirmed by follow-up endoscopy and biopsy. Approaches to dietary manipulation have ranged from an elemental diet to elimination of specific food allergies. Consultation with a nutritionist is recommended. There is no specific drug therapy--approaches that have been tried include corticosteroids, leukotriene antagonists, and cytokine-based therapies.

The review provides an important update on EE from the allergist's point of view. Priorities for future study include optimal evaluation of allergic sensitivity, dietary manipulation and other treatment approaches, and the duration of treatment and follow-up.

COMMENT: *This is an extremely valuable review of a condition increasingly recognized in both children and adults.*
A. M.
Norvell JM, Venarske D, Hummell DS: Eosinophilic esophagitis: an allergist's approach.
Ann Allergy Asthma Immunol. 2007;98:207-214. ♦♦

HFA-BDP Inhaler with Spacer Improves Lung Deposition

NEW beclomethasone dipropionate (BDP) inhalers using hydrofluoroalkane (HFA) propellant produce an extrafine aerosol, leading to improved lung deposition and penetration into the peripheral airways. However, studies of a breath-actuated HFA-BDP metered-dose inhaler (Autohaler) found gastrointestinal drug deposition of up to 60%. An HFA-BDP pressurized metered-dose inhaler with attached spacer device (Aerochamber Plus), used with tidal breathing or breath-holding technique, was assessed in terms of airway, oropharyngeal, and gastrointestinal drug deposition.

Twenty-four children with mild asthma were studied after inhaling ^{99m}Tc-labeled HFA-BDP. One group was instructed to take five tidal breaths after each actuation, while the other group was taught to perform a slow maximal inhalation followed by a 5- to 10-scond breathhold. Deposition of the ultrafine HFA-BDP aerosol was assessed using anterior posterior planar γ-scintigraphic scans. Deposition values were expressed as the percentage ex-acuator dose, corrected for attenuation.

With tidal breathing, mean HFA-BDP lung deposition was 35.4% for children aged 5 to 7 years, 47.5% for 8- to 10-year-olds, and 54.9% for 11- to 17-year-olds. Oral and gastrointestinal deposition in these age groups was 24.0%, 10.3%, and 10.1%, respectively. The breath-holding technique achieved higher lung deposition in all three age groups: 58.1% for 5- to 7-year-olds, 56.6% for 8- to 10-year-olds, and 58.4% for 11- to 17-year-olds. Oropharyngeal and gastrointestinal deposition values were 12.9%, 20.1%, and 20.8%, respectively.

With the Aerochamber Plus HFA-BDP inhaler, the breath-holding technique achieves better lung drug deposition in children with asthma, compared to the tidal breathing technique. With either technique, gastrointestinal deposition is lower than reported with the Autohaler device. Spacer inhalation technique can improve the lung deposition achieved by new extrafine aerosol inhalers.

COMMENT: *Spacer inhalation technique and deposition of extra fine aerosol become more important with the advent of HFA preparations and newer nonstatic spacers. This article is extremely important. (See also* J Pediatr. 2006;149:793-797.)
B. E. C.
Roller CM, Zhang G, Troedson RG, et al: Spacer inhalation technique and deposition of extrafine aerosol in asthmatic children.
Eur Respir J. 2007;29:299-305. ♦♦

Steroid/LABA Beats LTRA/LABA for Moderate Asthma

FOR patients with asthma, the main effect of long-acting β-agonists (LABAs) is to improve lung function, while leukotriene receptor antagonists (LTRAs) work to reduce exacerbation rates. The effects of these two drugs in combination--particularly compared with the standard combination of a LABA plus an inhaled corticosteroid--are unknown. A montelukast-salmeterol combination was evaluated for efficacy in moderate asthma.

The randomized, crossover trial included 192 patients with moderate asthma, aged 12 to 65 years. Each completed 14 weeks of treatment with montelukast-salmeterol and 14 weeks with beclomethasone-salmeterol, with a 4-week washout period. The main outcome was time to treatment failure, defined by clinical, home, and other measures.

The study was halted after 3 months after the data and safety monitoring board concluded that the main study question had been answered. The treatment failure rate was 26% for patients taking montelukast-salmeterol, compared with 9% with beclomethasone-salmeterol. Time to treatment failure also tended to be shorter with the LTRA/LABA combination. Secondary outcomes also favored the standard corticosteroid/LABA arm, including a 26 L/min difference in morning peak expiratory flow, a 0.22-point difference in Asthma Control Questionnaire score, and reductions in markers of inflammation and airway reactivity.

For patients with moderate asthma, standard treatment with a corticosteroid and LABA provides better clinical outcomes than an LTRA/LABA combination. The synergistic effect of montelukast and salmeterol is inferior to that of beclomethasone plus salmeterol.

COMMENT: *This again reinforces the guideline-based directive that long-acting beta agonist is superior to LTRA as add on therapy with ICS. Also see the editorial in same issue by Neal Barnes (*Am J Respir ➤➤

Crit Care Med. *2007;175:208-209).*
B. E. C.
Deykin A, Wechsler ME, Boushey HA, et al: Combination therapy with a long-acting β-agonist and a leukotriene antagonist in moderate asthma.
Am J Respir Crit Care Med. 2007;175:228-234. ♦♦

Ambulatory Approach to OSA Diagnosis and Treatment

CURRENT guidelines for the diagnosis of obstructive sleep apnea (OSA) and initiation of continuous positive airway pressure (CPAP) call for overnight polysomnography in the sleep laboratory. However, this is a costly technique with limited availability, especially considering the high prevalence of OSA. A diagnostic and treatment algorithm for initial management of OSA was evaluated.

The randomized, open trial included 68 patients with high pretest suspicion or moderate to severe OSA, based on the Epworth Sleepiness Scale, Sleep Apnea Clinical Score, and overnight oximetry. Patients were randomly assigned to standard polysomnography or an ambulatory algorithm, which included a combination of auto-CPAP with overnight pulse oximetry. After 3 months, both groups underwent overnight polysomnography to measure apnea-hypopnea index.

The two groups were comparable at baseline: median body mass index of 38 kg/m^2, age of 55 years, Epworth Sleepiness Scale score of 14, and respiratory disturbance index of 31 episodes per hour. At 3 months, apnea-hypopnea index on effective CPAP was similar between groups: median 3.2 in the polysomnography group and 2.5 in the ambulatory group. Other outcomes were comparable as well, including daytime sleepiness and disease-related quality of life. Patients in the ambulatory group had better compliance with CPAP: median 5.4 versus 6.0 hours per night.

The ambulatory algorithm appears feasible and effective for initial management of patients with a high probability of moderate to severe OSA. Diagnosis and CPAP treatment are similar to those of patients treated with standard polysomnography, while adherence to CPAP may be better with the ambulatory approach. The study algorithm may facilitate prompt initiation of therapy for OSA, particularly where access to overnight polysomnography is limited.

COMMENT: *Obstructive sleep apnea is a common problem with significant comorbidities. Currently, diagnosis requires overnight stays in a sleep lab. This article offers a diagnostic and treatment approach in an ambulatory setting without the expense and inconvenience of a formal sleep study. The study was performed on a select subpopulation, thus the results may not be applicable to your clinic.*
D. K. L.
Mulgrew AT, Fox N, Ayas NT, Ryan CF: Diagnosis and initial management of obstructive sleep apnea without polysomnography.
Ann Intern Med. 2007;146:157-166. ♦♦

Study Looks at Characteristics of Fatal Anaphylaxis

ANAPHYLAXIS is potentially life-threatening, with death resulting from circulatory collapse and/or respiratory arrest. Previous studies have reported elevated tryptase levels during anaphylaxis, which may provide a valuable clue when the diagnosis is uncertain. This and other characteristics of fatal anaphylaxis were evaluated in a review of 25 deaths.

The study included 25 unselected cases of documented fatal anaphylaxis. The analysis included review of medical records, interviews with witnesses, and laboratory and autopsy findings. Serum tryptase levels were measured in 7 cases.

Mean age at death was 59 years. Anaphylaxis resulted from reactions to medications in 7 cases, radiocontrast material in 6, Hymenoptera stings in 6, and foods in 4. In 84% of cases, the reaction occurred within 30 minutes after exposure; 52% of deaths occurred within 1 hour. Of 5 subjects with previous anaphylaxis, just 1 had and used self-injectable epinephrine.

Postmortem urticaria was present in only 1 case. Autopsy findings were consistent with anaphylaxis in 18 of 23 cases, including nonspecific pulmonary congestion and pulmonary edema. Eighty-eight percent of subjects had significant comorbidity, including 11 with ischemic heart disease and 5 with chronic obstructive pulmonary disease. Four of seven patients had markedly elevated serum tryptase levels.

In most cases of fatal anaphylaxis, the reaction develops within 30 minutes of exposure and autopsy shows specific anatomic findings. At least some cases are associated with very high serum total tryptase concentrations. Fatal anaphylaxis in elderly patients is associated with a high rate of cardiovascular disease and other comorbid conditions.

COMMENT: *Anaphylaxis will seldom be investigated in a controlled study so clinicians must rely on series of cases carefully described. This relatively small series provides interesting insights: the lack of urticaria or skin manifestations, the occurrence of comorbid disease, and rapid onset of symptoms leading to fatality. Allergists/immunologists should be the most informed specialists concerning anaphylaxis, and this article will help add to this information.*
D. K. L.
Greenberger PA, Rotskoff BD, Lifschultz B: Fatal anaphylaxis: postmortem findings and associated comorbid diseases.
Ann AllergyAsthma Immunol. 2007;98:253-257. ♦♦

Kids Living Near Freeways Have Reduced Lung Function

EXPOSURE to air pollution has known adverse effects on lung function in children. This long-term follow-up study evaluated the effects of exposure to local traffic patterns on lung development through puberty and adolescence. ➤➤

The analysis included 3,677 children enrolled in the Children's Health Study, recruited from southern California communities with varying regional air quality. Follow-up included annual lung function studies from age 10 to 18 years. Growth in lung function during this time was compared with multiple indicators of exposure to residential traffic from large roads.

Growth in FEV_1 was significantly reduced for children living within 500 m of a freeway: -81 mL lower than for children who lived at least 1,500 m from a freeway. Living near a freeway was also associated with a decrement in maximum midexpiratory flow rate, with a difference of -127 mL/s. Joint models showed that the harmful effects of living near a freeway were independent of the effects of regional air pollution. At age 18, mean FEV_1 was 97.0% of predicted for subjects who grew up living near a freeway. Maximum midexpiratory flow was 93.4% of predicted.

Living near freeway traffic is associated with reduced lung function growth in children. The effect of residential proximity to heavy traffic is independent of the effects of regional air pollution, and is observed in nonasthmatic and nonsmoking subgroups. Since lung development is nearly complete by age 18, reduced pulmonary function is likely to be a lifelong condition for these subjects.

COMMENT: *Urbanization has a variety of societal effects. Inner-city asthma has been well characterized. Children, whether asthmatic or normal, had decreased lung growth during the 8-year study if they lived with 500 meters of a Southern California freeway. The authors corrected for socioeconomic status as well as other confounders. The findings were still evident even after correcting for regional air quality. There was no correction for allergen (eg, cockroach or mite) exposure. There is significant societal implication of decreased lung growth in adults who were raised in close proximity to freeways.*
S. F. W.
Gauderman WJ, Vora H, McConnell R, et al: Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study.
Lancet. 2007;369:571-577. ♦♦

Portable FENO Analyzer Compares Well with "Gold Standard"

FRACTIONAL exhaled nitric oxide (FENO) measurement appears to be useful for asthma diagnosis and monitoring. Until recently, use of this technique has been largely limited to research and secondary-care settings. A new portable nitric oxide analyzer was evaluated, including comparison with laboratory FENO measurements.

The MINO hand-held nitric oxide sampling device was used to measure FENO in 101 patients with asthma, 64 receiving regular inhaled corticosteroid therapy. The same patients were also tested using a NIOX laboratory chemiluminescence analyzer, followed by spirometry. Fifty healthy volunteers were studied as well.

In asthma patients and controls, the two FENO measurements showed good correlation, with a significant linear association between the two. A high level of agreement was also demonstrated by Altman-Bland plots. On receiver operating characteristic curve analysis, both approaches to FENO measurement performed well in distinguishing asthma patients from healthy controls; cutoff levels were 13.0 ppb with the NIOX unit and 12.5 ppb with the MINO device.

Exhaled nitric oxide measurements obtained with the portable MINO analyzer show high correlation with measurements made using a standard laboratory analyzer. With further study, the use of portable nitric oxide analyzers may allow FENO measurement to be incorporated into primary care for asthma patients.

COMMENT: *Exhaled nitric oxide is associated with airway inflammation and asthma control. Measurement of FENO may help us identify ongoing inflammation and improve disease control for our asthmatic patients. This portable (and presumably less expensive) device demonstrated good correlation with a larger, more expensive device measuring FENO. The authors imply that this device, in the hands of primary care practitioners, could be used to monitor asthmatic patients better than symptom scores or spirometry. This of course remains to be proven, since measurement of only one domain does not correlate with multiple other measures including exacerbations. Furthermore, the device cannot be calibrated and its useful life is unknown.*
S. F. W.
Menzies D, Nair A, Lipworth BJ: Portable exhaled nitric oxide measurement: comparison with the "gold standard" technique.
Chest. 2007;131:410-414. ♦♦

Inflammation Doesn't Explain Delayed Recovery from Viral Exacerbations

WHEN asthma exacerbations are triggered by viral infections, recovery is sometimes prolonged. Persistent inflammatory responses may be noted as well. This study evaluated the contribution of airway inflammation to prolonged airway obstruction after viral asthma exacerbations.

The study included 40 patients hospitalized for acute asthma exacerbation, with respiratory virus infection confirmed by viral nucleic acid detection or cell culture. Lung function measures, cold and asthma symptoms, and induced sputum profiles were assessed during the episode. Patients were followed up at 4 to 6 weeks to compare the findings of those with and without persistent airway obstruction. Twenty-six patients with stable asthma were studied for comparison.

Twenty-five percent of patients had persistent airway obstruction, defined as less than a 15% change in FEV_1 percent predicted. For the remaining 75% of patients who had airway recovery, the sputum sample obtained in the hospital showed a higher total cell count, increased neutrophil count, and increased neutrophil percentage, than in patients with stable asthma. ➤➤

At follow-up, their neutrophil number had decreased while the percentage of eosinophils had increased.

In contrast, for patients with persistent airway obstruction, airway inflammatory markers were no different than in the stable asthma group. The delayed recovery group also had no change in cell counts after the exacerbation. Although symptoms improved in both exacerbation groups, the patients with persistent airway obstruction continued to have uncontrolled asthma.

Persistent airway obstruction may occur in about one-fourth of asthma patients hospitalized for viral exacerbations. This pattern of delayed recovery is not associated with the cellular profiles in induced sputum specimens--rather, noncellular elements may be involved. More study is needed to define the mechanisms of incomplete recovery and persistence of uncontrolled asthma in this group of patients.

COMMENT: *Many of our patients demonstrate prolonged symptoms and airway obstruction after an exacerbation as a result of viral infections. The authors characterize the frequency of this finding (25%) and note that it is more likely in patients who are taking high-dose ICS. In addition, patients who recovered quickly demonstrated increased inflammatory cells and neutrophils in induced sputum during their exacerbation, compared to asthmatics who had persistent obstruction. Future studies in this population measuring other biomarkers will be interesting.*
S. F. W.
Wood LG, Powell H, Grissell T, et al: Persistent airway obstruction after virus infection is not associated with airway inflammation.
Chest. 2007;131:415-423. ♦♦

CLINICAL TIDBITS

Asian Ladybugs: A New Indoor Allergen

THE Asian ladybug (ALB) is a recently introduced species that is now found across a large part of the United States, and has been reported to cause allergic symptoms. The authors report the development of an ALB extract for skin testing and an assay for measurement of specific IgE antibody. Proteins were purified from ALB extracts, and purified fractions were screened for IgE antibody using the streptavidin CAP technique. Specific IgE antibody to ALB was measured in sera from 15 of 20 allergic patients living in ALB-infested homes, including 7 patients with high titers (over 10 IU/mL).

Two proteins were fully purified: a 10 kd protein Har a 1 and a 55 kd protein Har a 2. Sera from 18 of 68 adult asthma patients were positive to IgE antibody for ALB all were also positive to the German cockroach, *Blatella germanica*. Binding to the ALB IgE antibody was largely blocked in inhibition studies using cockroach extract. Asian ladybug appears to be significant new indoor allergen. The ALB proteins identified show cross-reactivity with *B. germanica*. The Har a 1 protein appears specific to ladybugs.

COMMENT: *As if dust mites and cockroaches weren't enough, people in the Midwest and on the East coast now have to contend with Asian ladybugs as a possible source of indoor allergy. The bugs seek the indoors when weather gets cold. This study documents two purified allergens and the in vitro assay for them, showing cross-reactivity with certain cockroach antigens.*
R. J. M.
*Nakazawa T, Satinover SM, Naccara L, et al: Asian ladybugs (*Harmonia axyridis*): a new seasonal indoor allergen.*
J Allergy Clin Immunol. 2007;119:421-427. ♦♦

Clarithromycin Has Benefits in RSV Bronchiolitis

NEW treatments for respiratory syncytial virus (RSV) bronchiolitis are needed, in the hope of modifying the increased risk of wheezing after RSV infection in infants and young children. Twenty-one infants with RSV bronchiolitis were randomly assigned to 3 weeks of treatment with the macrolide antibiotic clarithromycin or placebo. Children receiving clarithromycin had a significantly shorter length of hospital stay: 51 versus 88 hours. Clarithromycin was also associated with less need for supplemental oxygen, 31 versus 72 hours; and intravenous fluids, 26 versus 56 hours.

At the end of treatment, children in the clarithromycin group had decreased plasma levels of interleukin-4, interleukin-8, and eotaxin. Six-month readmission rate was 1% in the clarithromycin group versus 4% with placebo. Clarithromycin has significant clinical benefits in the treatment of RSV bronchiolitis. Further studies are needed, including the effects of macrolide treatment on morbidity after RSV infection.

COMMENT: *Although this study is not applicable to patients with persistent asthma, it again reinforces the potential value of macrolide antibiotics for their anti-inflammatory properties.*
B. E. C.
Tahan F, Ozcan A, Koc N: Clarithromycin in the treatment of RSV bronchiolitis: a double-blind, randomised, placebo-controlled trial.
Eur Respir J. 2007;29:91-97. ♦♦

Little Benefit of Theophylline or Montelukast for Poorly Controlled Asthma

QUESTIONS remain concerning the clinical benefits of low-dose theophylline and montelukast for patients with poorly controlled asthma. In a three-way trial, 489 patients with poorly controlled asthma were randomly assigned to treatment with theophylline 300 mg/d, montelukast 10 mg/d, or placebo. The yearly rate of episodes of poor asthma control was similar between groups: 4.9 with theophylline, 4.0 with montelukast, and 4.9 with placebo. ➤➤

Both active treatments produced modest improvements in prebronchodilator FEV_1, but neither yielded significant improvement in symptoms or quality of life. For patients not taking inhaled corticosteroids, low-dose theophylline did improve symptoms, asthma control, and pulmonary function. Add-on treatment with low-dose theophylline or montelukast is not helpful for patients with poorly controlled asthma. However, theophylline may be a useful alternative controller therapy for patients not taking inhaled corticosteroids.

COMMENT: *This study continues to reinforce guideline-based treatment, only showing benefit for theophylline when not used with inhaled corticosteroid.*
B. E. C.
The American Lung Association Asthma Clinical Research Centers: Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma.
Am J Respir Crit Care Med. 2007;175:253-242. ♦♦

REVIEWS OF NOTE

COMMENT: *The critical role of the Th2 lymphocytes in controlling allergic responses has become more apparent as our knowledge about these immunologic pathways expands. This review explains the state of the art for T cells and suggests that allergen-derived epitope vaccines and the control of T-cell responses may be helpful in the future management of allergic patients.*
S. M. F.
Woodfolk J: T-cell responses to allergens.
J Allergy Clin Immunol. 2007;119:280-294. ♦♦

COMMENT: *This review looks at the causation of smaller-airway disease in asthma.*
B. E. C.
Singh AM, Moore PE, Gern JE, et al: Bronchiolitis to asthma: a review and call for studies of gene-virus interactions in asthma causation.
Am J Respir Crit Care Med. 2007;175:108-119. ♦♦

COMMENT: *An excellent evidence-based review of the application of exercise testing in a clinical respiratory practice.*
B. E. C.
Palange P, Ward SA, Carlsen K-H, et al: Recommendations on the use of exercise testing in clinical practice.
Eur Respir J. 2007;29:185-209. ♦♦

COMMENT: *This is an excellent summary of a tertiary care center's experience with angioedema due to ACE inhibitors and angiotensin receptor blockers.Since allergists/immunologists are often consulted for drug reactions, we should be knowledgeable of publications related to these commonly prescribed medications.*
D. K. L.
Malde M, Regaldo J, Greenberger PA: Investigation of angioedema associated with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.
Ann Allergy Asthma Immunol. 2007;98:57-63. ♦♦

COMMENT: *A comprehensive review of the issues surrounding use of self-injectable epinephrine in children, from the American Academy of Pediatrics Section on Allergy and Immunology.*
K. R. M.
Sicherer SE, Simons FER, et al: Self-injectable epinephrine for first-aid management of anaphylaxis.
Pediatrics. 2007;119:638-646. ♦♦

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