AllergyWatch®

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

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Potential New Treatment Modality for Allergy

A central step in the allergic response is activation of IgE-loaded FcεRI receptors on the cell surface of mast cells. An agent capable of antagonizing IgE- FcεRI signaling might offer a valuable new approach to the treatment of allergic disease. A new small-molecule inhibitor of IgE-dependent mast cell activation, designated R112, is reported and described.

The investigators used a high-throughput screening technique to identify molecules that blocked IgE signaling in cultured human mast cells. These experiments led to the discovery of R112 as a potent, reversible, selective inhibitor of the spleen tyrosine kinase (Syk) pathway. R112 was further studied using biochemical and cell-based assays, including comparison of its effects in mast cells and basophils with those of other mast cell inhibitors.

R112 produced significant inhibition of IgE-mediated mast cell activation pathways, including dose-dependent inhibition of degranulation induced by anti-IgE cross-linking in mast cells and basophils. R112 also inhibited histamine release by basophils in response to dust mite allergen and blocked production of leukotriene C4, as well as proinflammatory cytokines. It had an immediate onset of action and its activity in cells was completely and rapidly reversible. R112 also inhibited IgE-induced mast cell degranulation, lipid mediator production, and cytokine production--none of the other mast cell inhibitors tested affected all three functions.

R112 is a fast, potent, reversible inhibitor of Syk that antagonizes IgE-FcεRI signaling leading to mast cell activation cascades. This and related Syk inhibitors might offer a promising new approach to the treatment of allergic inflammation.

COMMENT: *Using in vitro human mast cells, these researchers from the company that produces R112 described the effects of this Syk kinase inhibitor on mast cell degranulation. This molecule inhibits the activity of Syk kinase which plays an essential role in the IgE-loaded FcεRI receptors on mast cells. R112 was* ➤➤

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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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unique in that it inhibited all three IgE-induced mast cell functions including degranulation, lipid mediator production, and inflammatory cytokine production. It appears that Syk inhibition could become a new potential modality for treatment of allergic disorders.
S. M. F.
Rossi A, Herlaar E, Braselmann S, et al: Identification of the Syk kinase inhibitor R112 by a human mast cell screen.
J Allergy Clin Immunol. 2006;118:749-755. ♦♦

More May Not Be Better!

CURRENT World Health Organization recommendations call for exclusive breast-feeding through the first 6 months of life to help prevent allergy. It is unclear whether longer periods of breast-feeding could have greater protective effects. This question was addressed in an analysis of very long-term prospective follow-up data.

The study included 200 unselected healthy newborns, enrolled in a study of the nutritional benefits of breast-feeding in 1981. The mothers were asked to breast-feed exclusively for as long as possible: exclusive breast-feeding continued for 2 months in 167 infants, 6 months in 116, 9 months in 36, and 12 months in 7. A family history of allergy was noted for 42% of infants. The children participated in regular follow-up examinations, including skin-prick testing--the analysis included 20-year follow-up examinations in 164 subjects.

Seven percent of children had atopy during the first year of life. The prevalence of allergic symptoms increased from 25% during the first 5 years, to 46% at age 11 years, to 52% at age 20 years. On logistic regression analysis, children who were breast-fed exclusively for 9 months or longer were at increased risk of atopic dermatitis at age 5, odds ratio (OR) 3.9. They also had a higher rate of food hypersensitivity symptoms, OR 3.3. The increase in atopic dermatitis was no longer present at age 11, but food hypersensitivity was still more prevalent in children with prolonged breast-feeding: OR 3.6. By age 20, there were no significant differences in the prevalence of allergic symptoms by duration of breast-feeding.

Among children with a family history of allergy, the prevalence of allergic symptoms at age 5 was highest (56%) for those breast-fed exclusively for 9 months or longer: OR 3.3. Prolonged breast-feeding was also associated with an increased rate of food hypersensitivity symptoms at age 11, OR 6.9.

Prolonged periods of exclusive breast-feeding--9 months or longer--do not reduce the risk of atopy or allergic disease. Rather, prolonged breast-feeding may lead to increased rates of atopic dermatitis and food hypersensitivity, particularly in children with a family history of allergy.

COMMENT: *Current WHO guidelines recommend breastfeeding for 6 months, and some parents and providers advocate prolonging exclusive breastfeeding until age 12 months or more. The results of this prospective study from Finland suggest that exclusive breastfeeding for 9 months increases the child's chance of having food allergy and/or eczema at age 5. In fact, among children with a family history of atopy, exclusive breast-feeding for the first 9 months was associated with an almost seven-times-greater risk of having food hypersensitivity at age 11. Probably best to stick to the guidelines.*
S. A. T.
Pesonen M, Kallio MJT, Ranki A, Siimes MA: Prolonged exclusive breast-feeding is associated with increased atopic dermatitis: a prospective follow-up study of unselected healthy newborns from birth to age 20 years.
Clin Exp Allergy. 2006;36:1011-1018. ♦♦

Race and Severity of Acute Asthma

ASTHMA carries a disproportionately higher burden for African-American patients, including increased rates of urgent care visits, hospitalization, and death. The reasons for these differences are unclear--African-Americans may have greater attack severity or may be less responsive to β_2-adrenergic agents. The clinical characteristics and response to albuterol therapy were compared for African-American versus white patients making ED visits for asthma.

The study included 295 adult patients seen for acute exacerbations of asthma at eight EDs in a university health system. One hundred fifty-five patients were African-American and 140 were white. Across EDs, patient assessments and admission and discharge decisions were made according to standardized criteria. Outcomes of interest included presenting signs and symptoms, degree of airway obstruction measured by peak expiratory flow, and immediate response to standardized albuterol therapy.

Most clinical characteristics were similar for African-American and white patients. However, African-American patients tended to have greater airway obstruction at presentation: mean peak expiratory flow rate was 175 L/min, compared with 203 L/min in whites. African-Americans were also more likely to have severe or life-threatening attacks: only about 17% of African-American patients presented with mild attacks, compared with 33% of whites. The two racial groups had similarly good responses to albuterol--post-treatment flow rates were similar, regardless of the presenting intensity of the attacks. Hospitalization rates were comparable between groups.

Among adult patients seen in the ED for asthma exacerbations, African-Americans appear to have more severe obstruction and a higher frequency of severe or life-threatening attacks than whites. However, there is no racial difference in response to standardized albuterol therapy, which rapidly eliminates the differences in attack severity. It remains unclear why African-Americans present with more severe attacks.

COMMENT: *African-Americans with asthma present more frequently to the emergency room and have more severe attacks. However, when appropriate treatment is given, we can expect response to occur, and as a result, no significant increase in hospitalizations in this group.*
B. E. C.
El-Ekiaby A, Brianas L, Skowronski ME, et al: Impact of race on the severity of acute episodes of asthma and adrenergic responsiveness.
Am J Respir Crit Care Med. 2006;174:508-513. ♦♦

LTRA and Childhood Asthma

EXHALED breath condensates (EBCs) collected from children with asthma show increased levels of leukotriene $_4$ (LTE_4) and 8-isoprostane. The effects of treatment with the leukotriene receptor antagonist (LTRA) montelukast on exhaled leukotrienes and prostanoids in asthmatic children are unknown. This study examined the effects of montelukast on concentrations of LTE_4 and prostanoids in EBCs from atopic children with and without asthma, including measurement of exhaled nitric oxide (eNO).

The open-label trial included two groups of atopic children: 17 with and 16 without asthma. All children received 4 weeks of treatment with oral montelukast, 5 mg once daily. In addition to measurement of exhaled LTE_4 and prostanoids in EBCs, assessments included eNO measurement and pulmonary function tests.

At baseline, LTE_4 and 8-isoprostane levels in EBCs were significantly higher in the asthmatic children. With montelukast treatment, LTE_4 concentration decreased by 35%, in correlation with the initial LTE_4 level. However, even after treatment, the asthmatic children still had higher LTE_4 concentrations than atopic children without asthma. In the nonasthmatic group, montelukast treatment had no effect on LTE_4. Exhaled 8-isoprostane and prostaglandin E_2 levels were unaffected in both groups. Montelukast was associated with a 27% decrease in eNO levels in the asthmatic children.

Treatment with an LTRA significantly reduces LTE_4 concentration in EBCs from atopic children with asthma. The extent of reduction is correlated with the baseline exhaled LTE_4 value. Exhaled LTE_4 levels might provide a useful approach to targeting asthmatic children who are likely to benefit from LTRA therapy.

COMMENT: *We are continuing to learn more about the potential usefulness of EBCs for monitoring our patients with asthma. This carefully controlled open-label pilot study in children with asthma used exhaled breath condensates to measure LTE_4 and the prostanoids 8-isoprostane and prostaglandin E_2, as well as nitric oxide (eNO). Exhaled LTE_4 and eNO were significantly reduced by montelukast (an LTRA) in atopic children with asthma, whereas the prostanoid markers of oxidative stress were not. Measurement of EBCs, particularly LTE_4, may be useful in helping identify children with atopic asthma who are most likely to benefit from LTRA therapy.*
S. M. F.
Montuschi P, Mondino C, Koch P, et al: Effects of a leukotriene receptor antagonist on exhaled leukotriene E_4 and prostanoids in children with asthma.
J Allergy Clin Immunol. 2006;118:347-353. ♦♦

SLIT with GRAZAX in SAR

ALLERGEN immunotherapy is effective treatment for seasonal allergic rhinitis (SAR), and may lead to long-term remission. The sublingual route is an attractive alternative to injection immunotherapy, potentially enabling treatment at home. However, large controlled trials are needed to prove its efficacy. A multicenter study of sublingual immunotherapy (SLIT) for grass-allergic patients with SAR is reported.

The trial included 634 patients from 51 European centers. All had at least a 2-year history of grass ➤➤

pollen-related rhinoconjunctivitis, with grass allergy confirmed by a positive skin-prick test and serum-specific IgE measurement. Patients were randomly assigned to receive a rapidly dissolving grass allergen tablet (GRAZAX), in a daily dose of 75,000 SQ-T, or placebo. Treatment began at least 16 weeks before pollen season, and continued throughout the season.

Patients receiving active SLIT had a 30% reduction in rhinoconjunctivitis symptom score, compared with placebo. There was also a significant 38% reduction in rhinoconjunctivitis medication score with SLIT, along with a 31% decrease in mean daily visual analog scale score. Eighty-two percent of patients receiving active SLIT thought that their symptoms had improved compared with previous pollen seasons, compared with 52% of the placebo group.

The rate of study withdrawals for adverse events was 4%. The main side effects were mild oral itching and swelling; there were no serious local side effects or severe systemic adverse events.

Sublingual immunotherapy is a safe, well-tolerated, and effective treatment for patients with SAR related to grass pollen allergy, this large randomized trial concludes. The results support grass pollen SLIT as an alternative to injection immunotherapy that is appropriate for home use. Starting treatment long in advance of pollen season means that the effects of treatment are already present when grass pollen appears.

COMMENT: *Previous studies have demonstrated modest efficacy with SLIT when started 8 weeks before pollen season. These European researchers report impressive results in a large, multicenter parallel group double-blind, placebo-controlled study using a single-dose, single-antigen (grass), rapidly dissolving tablet. The fact that SLIT was started at least 16 weeks before the grass pollen season probably resulted in the remarkable reduction for both symptom and medication scores compared to the placebo group. It is difficult to evaluate the adverse events, which may have varied by site. However, there the fact that there were no serious adverse events suggests that this may be beneficial in-home therapy for patients with SAR who plan ahead and start their treatment 4 months before the pollen starts.*

S. M. F.

Dahl R, Kapp A, Colombo G, et al: Efficacy and safety of sublingual immunotherapy (SLIT) with grass allergen tablets for seasonal allergic rhinoconjunctivitis (SARC).

J Allergy Clin Immunol. 2006;188:434-440. ♦♦

Prognosis of Asymptomatic BHR

BRONCHIAL hyperresponsiveness (BHR) is commonly present in patients with asthma and chronic obstructive pulmonary disease (COPD). It is also found in many asymptomatic patients, in whom its clinical relevance is uncertain. Long-term follow-up data were used to assess the outcomes of asymptomatic subjects with BHR.

The analysis included 7,126 subjects from the population-based Swiss Study on Air Pollution and Lung Diseases in Adults who underwent evaluation of respiratory symptoms and BHR to methacholine in 1991. In 2002, 5,825 subjects were re-evaluated, including pulmonary function testing in 4,852. The presence or absence of BHR at baseline was evaluated as a predictor of new symptoms and changes in pulmonary function at follow-up. The study definition of COPD was an FEV_1/FVC ratio of less than 0.70.

Seventeen percent of patients had BHR at baseline, of whom 51% were asymptomatic. At follow-up, asthma was present in 5.7% of previously asymptomatic subjects with BHR, compared with 2.0% of those without BHR. Asymptomatic BHR was also associated with an increased prevalence of wheezing, 8.3% vs 3.4%; and shortness of breath, 19.1% vs 11.9%. Chronic cough developed in 5.9% of subjects with BHR, compared to 2.3% of those without. Rates of COPD were 37.9% and 14.3%, respectively.

On multivariate analysis, asymptomatic BHR was associated with adjusted odds ratios of 2.9 for wheezing and 4.5 for COPD. Subjects with asymptomatic BHR also had a faster rate of decline in FEV_1, related to smoking history. Rates of decline were 12 mL/y in current smokers and 11 mL/y in former smokers, compared with 4 mL/y in never smokers.

Asymptomatic adults with BHR are at increased risk of respiratory problems at long-term follow-up. They have increased prevalences of asthma, wheezing, and COPD, regardless of atopic status. Rates of decline in FEV_1 are higher in subjects with asymptomatic BHR, especially smokers.

COMMENT: *This large prospective population based study confirms that BHR is associated with the development of respiratory symptoms, asthma and COPD. There are some significant weaknesses in this study, but impressive effects were observed in a population defined as asymptomatic at baseline. The elusive key is the mechanism that triggers the interaction between BHR and either allergic inflammation resulting in asthma or tobacco smoke-induced inflammation leading to COPD. Hence, stay tuned for further studies addressing the pathogenesis of these observations.*

E. J. B.

Brutsche MH, Downs SH, Schindler C et al, for the SAPALDIA Team: Bronchial hyperresponsiveness (BHR) and the development of asthma and COPD in asymptomatic individuals: SAPALDIA cohort study.

Thorax. 2006;61:671-677. ♦♦

Pet Avoidance and Subsequent Asthma and Allergy

EPIDEMIOLOGIC data suggest that childhood exposure to pets may have a protective effect against asthma and allergy. Although this is possible, an alternative explanation is selective avoidance: at-risk individuals might avoid having pets, in response to symptoms, medical advice, or other factors. Population-based data from the European Community Respiratory Health Survey (ECRHS) were used to assess ➤➤

whether having asthma or allergies affects subsequent keeping of pets.

The analysis included 9,812 ECRHS subjects from 22 countries who provided information on asthma and pet keeping at various periods of life, from early childhood through middle-age. The effects of asthma and allergies on continuation or acquisition of pet-keeping were analyzed.

Subjects who had onset of childhood asthma before age 5 were less likely to keep a cat from age 5 to 15, odds ratio 0.60. However, this effect was significant only for subjects with no parental history of asthma or allergy. Otherwise, childhood asthma did not affect pet ownership--a significant effect was noted only if symptoms were present in adulthood. Adults were less likely to acquire a cat if they had three or more asthma symptoms, were taking asthma medications, had hay fever, had atopy, or had cat-specific IgE at baseline. Adults who had pets were more likely to continue keeping the same kind of pet, with the exception that subjects with three or more asthma symptoms were less likely to keep a dog. Less than 5% of subjects reported removing pets to reduce allergen exposure.

Asthma or allergy is associated with subsequent avoidance of pets in some situations, particularly for cats. In childhood, such selective avoidance behavior might produce a substantial protective effect against asthma. There is little evidence of selective avoidance of dogs and birds. For children as well as adults, keeping pets previously is a much stronger predictor of continuing to keep pets.

COMMENT: *The hygiene hypothesis has become a popular topic in recent years. Some question the impact of selective avoidance in the analysis of data suggesting that pet exposure may reduce allergies. The ECRHS collected retrospective information about pet exposure during several periods of life from over 9,000 subjects. Although there was some effect of selective avoidance for cats, it was not observed for either birds or dogs in the homes of allergic patients. This should be considered when reviewing studies relating to the hygiene hypothesis.*
S. M. F.

Svanes C, Zock JP, Antó, et al: Do asthma and allergy influence subsequent pet keeping? An analysis of childhood and adulthood.
J Allergy Clin Immunol. 2006;118:691-698. ♦♦

Montelukast Affects Airway Remodeling

AIRWAY remodeling is thought to play an important role in the pathophysiology of asthma, but it is uncertain whether current asthma treatments significantly affect the remodeling process. The effects of leukotriene receptors on indicators of airway remodeling are unknown. An allergen-challenge study was performed to evaluate the effects of montelukast on airway structural cells thought to be involved in remodeling.

The randomized trial included 20 patients with mild, stable atopic asthma. After a 2-week run-in period, the patients underwent low-dose allergen challenge and endobronchial biopsy. This was followed by 8 weeks of treatment with montelukast or placebo, after which low-dose allergen challenge and bronchial biopsy were repeated. Electron microscopy was performed to evaluate the effects of allergen challenge and montelukast treatment on airway myofibroblasts, fibroblasts, and inflammatory cells.

Montelukast treatment was associated with a significantly higher FEV_1 after low-dose allergen challenge. Patients receiving montelukast also showed a significant reduction in airway myofibroblast number after allergen challenge. Lamina reticularis thickness was not significantly different between treatment groups. Montelukast treatment was also followed by a reduction in lymphomononulear cells and an increase in neutrophils.

In response to low-dose allergen challenge in asthmatic patients, treatment with montelukast appears to inhibit the response of airway structural cells involved in remodeling. Myofibroblast numbers are reduced, along with significant effects on inflammatory cells. The results of this small study suggest that leukotriene modifiers may help to prevent airway remodeling in asthma.

COMMENT: *Our best predictions regarding how to prevent airway remodeling have so far turned out to be wrong. It certainly is not enough to merely aggressively control asthma with inhaled corticosteroids. In this study montelukast treatment was associated with a decrease in allergen-stimulated changes in a variety of cell types that are relevant to remodeling. Additional studies are necessary to confirm that this effect is both real and clinically significant over the long term.*
S. A. T.

Kelly MM, Chakir J, Vethanayagam D, et al: Montelukast treatment attenuates the increase in myofibroblasts following low-dose allergen challenge.
Chest. 2006;130:741-753. ♦♦

Wait-and-See Rx for Acute Otitis Media

ACUTE otitis media (AOM) is the most common reason for antibiotic prescriptions in children. Previous studies have evaluated approaches in which antibiotic treatment for AOM is optional--a prescription is written, but parents are instructed not to fill it unless the child's condition has not improved or has worsened in 48 hours. This "wait-and-see" approach was evaluated in a 1-year study of children seen in the emergency department (ED) for AOM.

The randomized trial included 283 eligible patients, aged 6 months to 12 years, seen for AOM in an urban pediatric ED. Children were randomly assigned to receive a "wait-and-see" antibiotic prescription or a standard prescription. All were sent home with ibuprofen and otic analgesic eardrops. The main outcome of interest was the proportion of both groups filling their prescription within 3 days.

The two groups had comparable baseline characteristics--AOM was unilateral in more than 80% of➤➤

cases. Sixty-two percent of the "wait-and-see" prescriptions went unfilled, compared with just 13% of the standard prescriptions. At 4 to 6 days' follow-up, filling of prescriptions was significantly related to the presence of fever and otalgia, but not to insurance status or race/ethnicity. There were no serious adverse events, and only a 0.4-day increase in duration of ear pain in the "wait-and-see" group. The two groups of parents were similar in their willingness to delay antibiotic treatment for future episodes of AOM.

A "wait-and-see" approach to prescribing in children with AOM reduces antibiotic use by 56%. The main factors associated with filling of "wait-and-see" prescriptions are fever and ear pain--consistent with previous studies, immediate antibiotic treatment shortens the duration of otalgia somewhat. "Wait-and-see" prescribing might help to reduce costs, adverse events, and antimicrobial resistance.

COMMENT: *My experience is that patients generally fill prescriptions for antibiotics immediately if given an optional treatment that is to be started in several days if no improvement. This study demonstrates that, in an emergency room setting, over 50% of patients with a potential antibiotic prescription did not choose to fill it. This is a powerful finding that could be applied to acute upper respiratory infections with unconfirmed acute sinusitis. A point to be emphasized is that the investigators provided analgesic treatment for the children not receiving immediate antibiotic, a strategy that could also be applied to sinusitis.*
D. K. L.
Spiro DM, Tay K-Y, Arnold DH, et al: Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial.
JAMA. 2006;296:1235-1241. ♦♦

Stress and Immunity

PREVIOUS studies have suggested that psychosocial stress can affect atopic disease indicators, including a shift toward Th2 in the balance between Th1/Th2 cytokines. Interdisciplinary approaches are needed to investigate how anxiety and stress might affect complex diseases like asthma and allergy. A variety of techniques were used to investigate the effects of stress on immune function in allergic vs nonallergic volunteers.

The subjects were 41 medical students, 19 of whom had a history of allergic symptoms and atopy confirmed by radioallergosorbent testing. Students were evaluated on a battery of psychologic, physiologic, and immunologic tests on two occasions: a low-stress period in the middle of the semester and a high-stress period during exam week. Immunologic measures of interest included the Th1/Th2 balance; regulators of allergic inflammation, such as natural killer (NK) cells and regulatory T cells; and markers of allergic aggravation, such as exhaled nitric oxide.

Levels of stress and anxiety were significantly higher during exam week, particularly in atopic subjects. There were few changes in health behaviors, except for a decrease in subjective sleep quality. Urine cortisol level was increased only in the atopic students. Both groups had a general reduction in cytokine production during the high-stress period, with an increased percentage of regulatory T cells. Only in the atopic group, high stress was associated with a reduction in the Th1/Th2 ratio and a decrease in NK cell numbers. In contrast, a reduction in exhaled NO and an increase in FEV_1 were noted only in the control group. Bronchial responsiveness to methacholine did not change in either group.

Atopic subjects show a shift toward Th2 cytokine activity during periods of high stress, along with a sharp drop in NK cells. The results suggest a number of significant associations between stress and various processes involved in atopic disease. The between-group differences in cytokine responses to stress may reflect differences in immune regulation among atopic individuals.

COMMENT: *The effects of emotional stress on the immune system have been previously shown to include a skew of inflammatory markers toward the Th2 phenotype. This study used psychologic, physiologic, and immunologic techniques to study the effects of examination stress in a group of 41 Swedish medical students, 19 of whom were atopic. Stress effects unique to atopic students included a fall in the Thl/Th2 ratio and in NK cell number. Interestingly, stress was not associated with a change in exhaled NO in asthmatic subjects.*
S. A. T.
Höglund CO, Axén J, Kemi C, et al: Changes in immune regulation in response to examination stress in atopic and healthy individuals.
Clin Exp Allergy. 2006;130:982-992. ♦♦

Atopy Has Lasting Imprint on Childhood Asthma

BEGINNING around school age, children with chronic asthma show a drop in pre-bronchodilator pulmonary function. The factors affecting this progressive loss of lung function between birth and school age are unknown. Early-life allergic sensitization and allergen exposure were investigated as risk factors for persistent asthma and declining lung function in children.

In the German Multicentre Allergy Study, 1,314 healthy children were followed up from birth to age 13. Four hundred ninety-nine children had risk factors for atopy, ie, elevated cord blood IgE or two or more atopic family members. Follow-up included parental interviews regarding asthma symptoms and measurement of IgE levels. Dust samples were collected for assessment of allergen exposure at frequent intervals, especially during the first 5 years. Other tests included pulmonary function studies at age 7, 10, and 13.

When wheezing was present without atopy, 90% of children were no longer symptomatic by the time they reached school age. These children also retained normal lung function at puberty. However, children exposed to house dust mite or dog or cat hair from birth to age 3 had significant loss of lung function at age 5. The reductions were more pronounced for children with high exposure to perennial allergens during early life. The FEV_1/FVC ratio was 87.4 for sensitized children with high early-life allergen exposure, compared to 92.6 ➤➤

for nonsensitized children. Values for maximal expiratory flow at 50% were 86.4 vs 101.5, respectively.

Early-life allergen exposure also promoted the emergence of airway hyperresponsiveness in sensitized children with wheezing, as well as a chronic course of asthma with more severe symptoms. The occurrence of sensitization and perennial allergen exposure later in childhood had a much lower impact on pulmonary function; sensitization to seasonal allergens had no effect at all.

Among young children with wheezing, those who are not sensitized to perennial allergens during early life become asymptomatic by school age and have normal lung function at puberty. In contrast, early-life atopic sensitization is linked to chronic asthma with airway hyperresponsiveness and decreased lung function. Studies are needed to evaluate the use of inhaled corticosteroid therapy for infants and toddlers with wheezing and atopy.

COMMENT: *Reduced lung function is a feature of chronic asthma in children. Unknown factors between birth and school age determine the progressive loss of lung function. This study addresses many details about childhood asthma including IgE levels, allergy exposure, lung function post-bronchodilator response, and histamine challenge. The authors show most children with wheeze without atopy lost asthma symptoms by school age, but those with atopy by age 3 were likely to lose lung function at school age. This has implications for how we treat atopic and nonatopic wheezing children.*
E. J. B.
Illi S, von Mutius E, Lau S, et al: Perennial allergen sensitization early in life and chronic asthma in children: a birth cohort study.
Lancet. 2006;368:763-770. ♦♦

Steroid Insensitivity in Severe Asthma

SEVERE asthma is associated with a poor response to treatment with corticosteroids, suggesting a possible role of relative resistance to corticosteroid effects. One potential measure of such drug insensitivity is the ability of corticosteroids to block cytokine release from activated peripheral blood mononuclear cells (PBMCs). This indicator was compared for patients with severe vs nonsevere asthma.

The study included 16 patients meeting American Thoracic Society criteria for severe asthma and 19 patients with nonsevere asthma, along with 10 normal controls. Cultures of PBMCs were prepared and stimulated with lipopolysaccharide (LPS). The ability of dexamethasone to inhibit release of cytokines from activated PBMCs was compared between groups.

At baseline, PBMCs the two asthma groups showed no differences in cytokine release under spontaneous or LPS-stimulated conditions. At a concentration of 10^{-6}, dexamethasone was less effective in suppressing cytokine release from PBMCs from patients with severe asthma, compared with the nonsevere asthma group. The between-group difference was less pronounced at a dexamethasone concentration of 10^{-8}. Severe asthma was associated with lower levels of nuclear histone deacetylase (HDAC) activity, which was directly related to the degree of steroid insensitivity.

In patients with severe asthma, dexamethasone is less effective in suppressing the release of cytokines from activated PBMCs, compared to patients with less severe asthma. The degree of corticosteroid insensitivity is correlated with a reduction in HDAC activity. Previous steroid treatment does not appear to affect these PBMC responses.

COMMENTS: *Severe asthmatics showed diminished sensitivity of their peripheral mononuclear cells to corticosteroid. The insensitivity may be linked to the presence of more severe asthma. This may be a mechanism determining impaired steroid responsiveness and may yield new therapeutic targets for patients with asthma.*
B. E. C.
Hew M, Bhavsar P, Torrego A, et al: Relative corticosteroid insensitivity of peripheral blood mononuclear cells in severe asthma.
Am J Respir Crit Care Med. 2006;174:134-141. ♦♦

Adverse Drug Reactions in Children

ADVERSE drug reactions (ADRs) are an important cause of morbidity and mortality in children. The precise incidence of ADRs among hospitalized children in the United States remains is unclear. A 10-year review was performed to evaluate the incidence of ADRs among inpatients at a children's hospital.

The retrospective analysis included all ADRs reported at a 197-bed California children's hospital over a 10-year period. Information was obtained by reviewed of standardized ADR reporting forms. For each event, severity was rated from 1 to 6.

The analysis included 1,087 ADRs, with an overall incidence of 1.6%. Annual incidence ranged from 0.4% to 2.3%--reporting of ADRs increased significantly from 1998 to 1999. Eighty-nine percent of ADRs were classified as low severity: severity rating 1 to 3. Two thirds of events led to drug discontinuation or a change in dosing or frequency. Antibiotics were involved in 33% of cases, most commonly vancomycin. Other drug classes implicated were narcotic analgesics in 12% of ADRs, anticonvulsants in 11%, and anxiolytics in 10%.

Most events were rated as probable or possible ADRs--only 8% were definite. The skin was involved in 37% of incidents, the cardiovascular system in 23%, and the neurologic system in 16%. Fifty-one percent of ADRs were considered "allergic/idiosyncratic," the rest as pharmacologic in nature. Pharmacists reported 89% of ADRs, physicians less than 1%.

This study reports an average 1.6% incidence of ADRs among hospitalized children. Although most events are mild, about 11% are classified as severe. Severe ADRs may be more frequent in children who had an ADR before hospital admission or who received drugs during surgery. Further studies are needed to improve management and especially prevention of pediatric ADRs. ➤➤

COMMENT: *This 10-year (1995 to 2005) study of ADRs in hospitalized children is the largest and most current of its kind. The overall ADR incidence was reported to be 1.6%, and most reactions were of low severity. Thirty-one percent of all cases were due to antibiotics. I was interested in the fact that, when the types of ADR were classified by major symptoms, those which were allergy-like--rash, flushing, pruritus, and urticaria--accounted for 61% of the cases!*
J. A. A.
Le J, Nguyen T, Law AV, Hodding J: Adverse drug reactions among children over a 10-year period.
Pediatrics. 2006;118: 555-562. ♦♦

Allergen Exposure and eNO

As a marker of airway inflammation, fraction of nitric oxide in exhaled air (FENO) could be a useful aid to the management of childhood asthma. However, many questions remain about the factors affecting FENO levels in asthmatic children. Environmental factors affecting FENO in children with asthma were assessed, focusing on sensitization and indoor allergen exposure.

The analysis included data on FENO levels, allergen-specific sensitization, and home dust allergen levels in 170 children with physician-diagnosed asthma. Mean age was 8.6 years--63% of the children were boys and 51% were African-American.

On bivariate analysis, FENO level was not significantly related to most housing characteristics, such as housing volume or density. However, FENO was significantly higher for children exposed to higher levels of house dust mite. Sensitization to all four indoor allergens studied--dust mite, dog, cat, and cockroach--was also associated with higher FENO level. Environmental tobacco smoke and corticosteroid use were not significantly related to FENO level. Surprisingly, the presence of carpeting, owning a cat, and higher exposure to cat allergen were all associated with lower FENO levels.

Sensitization to indoor allergens is associated with higher FENO levels in asthmatic children. Exposure to allergens, especially dust mite and cat, also seems to contribute to higher FENO levels. In contrast, passive smoking and corticosteroid treatment are not significantly related to FENO.

COMMENT: *The fraction of nitric oxide in exhaled air is felt to be a marker of asthma inflammation. Elevated FENO levels have been proposed as indicating the need for additional asthma controller medications. Allergen sensitization now can be shown to double the FENO values. In some cases, allergen exposure also influences FENO levels. This new information complicates the interpretation of an elevated FENO determination. Only time will tell if further studies can clarify the clinical value of this test.*
J. A. A.
Spanier AJ, Hornung R, Lierl M, Lanphear BP: Environmental exposures and exhaled nitric oxide in children with asthma.
J Pediatr. 2006;149:220-226. ♦♦

Budesonide/Formoterol as Reliever Therapy in Acute Asthma

MAINTENANCE therapy for persistent asthma now includes inhaled corticosteroids combined with long-acting β2 agonists (LABAs). However, questions remain as to the best strategy for reliever therapy--recent studies have suggested good outcomes with a budesonide/formoterol combination as both maintenance and as-needed therapy. This combination was compared with a short-acting β2 agonist and a rapid-acting LABA as reliever therapy for persistent asthma were compared in a randomized trial.

The multicenter, international study included 3,394 patients, aged 12 years or older, with moderate to severe persistent asthma. All were receiving inhaled corticosteroids at baseline. During a 2-week run-in period, they remained symptomatic while taking maintenance therapy with budesonide/formoterol, 160/4.5 µg, one inhalation twice daily. Patients were randomly assigned to receive one of three as-needed treatments: terbutaline 0.4 mg, formoterol 4.5 µg, or the budesonide/formoterol 160/4.5 µg combination. All groups remained on budesonide/formoterol maintenance therapy. Severe exacerbations were defined as those requiring hospitalization and/or emergency department treatment, or 3 or more days of oral steroids.

Time to first severe exacerbation was longer with as-needed budesonide/formoterol than with formoterol only, and longer with formoterol than with terbutaline. Expressed as number of exacerbations per 100 patients per year, the rate of severe exacerbations was 19 with budesonide/formoterol, 29 with formoterol only, and 37 with terbutaline. Based on associated rate ratios, budesonide/formoterol reduced the risk of severe exacerbations by 33% vs formoterol and by 48% vs terbutaline, while formoterol reduced the risk by 22% compared with terbutaline. All groups had similar improvement in days with asthma control days; formoterol did not improve symptoms compared with terbutaline. All three strategies were well-tolerated.

For patients with moderate to severe asthma receiving budesonide/formoterol maintenance therapy, as-needed therapy with budesonide/formoterol provides better protection against severe exacerbations than formoterol alone or terbutaline. Formoterol provides better protection than terbutaline. The findings add important information on the use of inhaled steroids plus LABAs to prevent asthma exacerbations.

COMMENT: *Over the past decade, maintenance therapy in patients with persistent asthma has evolved to combination therapy with LABAs and inhaled corticosteroids. Since the ideal approach is not yet known, Rabe et al compared three reliever approaches--a traditional short-acting β2 agonist (terbutaline), a rapid-onset LABA (formoterol), or a combination of budesonide and formoterol--in symptomatic patients receiving combination therapy. The time to first severe exacerbation was longer when budesonide/formoterol was used for both maintenance and relief. In a separate comment, Soren Pedersen warns that more studies are needed before these findings are generalized to the*➤➤

entire asthma population.
E. J. B.
Rabe KF, Atienza T, Magyar P, et al: Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study.
Lancet. 2006;368:744-53. ♦♦

Proinflammatory Cytokine Profiles in Sputum of Severe Asthmatics

THE classification of "severe asthma" includes a heterogeneous group of patients with differing clinical phenotypes. The airway inflammatory markers associated with severe asthma are unclear. Inflammatory markers were analyzed in sputum samples from patients with severe asthma, including comparisons with clinical phenotype.

The study included 45 patients with severe asthma; all were taking long-acting inhaled β2-agonists plus inhaled corticosteroids, at a dosage of 1,000 μg/d of beclomethasone dipropionate or its equivalent. The patients were divided into clinical groups characterized by frequent exacerbations, 24 patients; persistent bronchoconstriction, 11 patients; or both characteristics, 10 patients. Nine untreated patients with mild persistent asthma and 10 healthy controls were studied for comparison. Sputum samples were obtained for measurement of inflammatory cells, especially eosinophils and neutrophils; eosinophil cationic protein concentration, and specific proinflammatory cytokines. Findings were compared among the three clinical/functional subgroups of patients with severe asthma.

Inflammatory cell percentages were not significantly different among the severe asthma phenotypes. There was also no difference in sputum eosinophil cationic protein; interleukin-8 tended to be higher in patients with persistent bronchoconstriction. The patients with frequent exacerbations had significantly higher sputum concentrations of granulocyte-macrophage colony-stimulating factor and interleukin-5. The sputum eosinophil levels of patients with severe asthma were between those of patients with mild persistent asthma and healthy controls.

Among patients with severe asthma, those with a clinical pattern of frequent exacerbations show increased levels of proesinophilic cytokines in sputum, compared to those with persistent bronchoconstriction. The latter group may have higher levels of sputum interleukin-8. Assessment of cytokine profiles may provide useful insights into the clinical phenotypes of patients with severe asthma.

COMMENT: *Phenotyping asthma is an unmet clinical need, as it would facilitate the rational choice of a specific therapy for a specific patient. Our current approach is to try one therapy after another or combine treatments until some measure of success is achieved. A method of separating asthma populations would be ideal. One such method is suggested in this study using induced sputum. I fear induced sputum is not ready for clinical "prime time" because of the difficulty in obtaining a sample, complexity of preparation, and significant overlap of results despite differences in means. We are still searching.*
D. K. L.
Dente FL, Carnevali S, Bartoli ML, et al: Profiles of proinflammatory cytokines in sputum from different groups of severe asthmatic patients.
Ann Allergy Asthma Immunol. 2006;97:312-320. ♦♦

Effects of Smoking Cessation in Asthma

ASTHMA patients who smoke have worse symptoms, a faster decline in pulmonary function, and a reduced response to corticosteroids. This prospective study evaluated the short-term benefits of smoking cessation in asthma patients.

The study included 32 smokers with asthma, with a baseline FEV_1 of 85% predicted or less. All patients were given the option to attempt to quit smoking--of 21 patients who tried, 10 successfully quit smoking for 6 weeks. The remaining 10 patients opted to continue smoking. These two groups underwent examination at 1, 3, and 6 weeks, including spirometry and induced sputum analysis. Further assessments were performed at 6 weeks, including cutaneous vasoconstrictor response to topical betamethasone and airway response to oral prednisolone.

At 6 weeks, FEV_1 was higher by a mean of 407 mL in asthmatic patients who quit smoking, compared with those who continued to smoke. Smoking cessation was also associated with a mean 29% decrease in percentage of sputum neutrophils. Patients who quit smoking furthermore had a significant improvement in skin vasoconstrictor response to topical steroid, compared with those who continued to smoke. Airway responsiveness to corticosteroid treatment was not significantly changed.

Asthma patients who quit smoking can expect numerous, clinically significant short-term benefits. By 6 weeks, smoking cessation brings significant improvement in lung function and a reduction in sputum neutrophils. The benefits of smoking cessation in asthma are far greater than those achieved even by high-dose prednisolone treatment.

COMMENT: *Smoking cessation has significant positive effects in asthmatics, including a decrease in neutrophil infiltration in the airway. The response to inhaled corticosteroid is in fact improved as early as 1 week after the patient quits smoking. This reinforces the need for aggressive smoking cessation efforts in patients with asthma.*
B. E. C.
Chaudhuri R, Livingston E, McMahon AD, et al: Effects of smoking cessation on lung function and airway inflammation in smokers with asthma.
Am J Respir Crit Care Med. 2006;174:127-133. ♦♦

CLINICAL TIDBITS

Testing in Patients with Drug Reactions

CURRENT *European guidelines call for testing to verify the cause of suspected drug reactions. The authors report their experience with structured investigation of 325 drug reactions in 291 consecutive patients over an 18-month period. The approach included history, skin testing or measurement of β-lactam-specific IgE, and drug provocation testing (DPT), if necessary. The drug was confirmed as the cause of the reaction in 100 cases, and excluded in 157. Results to DPT were positive in 14 of 104 cases, including 4 reactions to placebo. No firm conclusion was reached in 68 cases. Evaluation led to clear recommendations in 82% of patients. The authors' standard approach to evaluation of suspected drug reactions yields a high rate of practical recommendations, with a low risk of side effects.*

COMMENT: *Wöhrl and colleagues retrospectively analyzed the records of 291 consecutive patients with histories of reactions to a variety of drugs including antibiotics, NSAIDs, anesthetics, and many others. They were able to confirm an association between the drug and a reaction in 100 cases. Importantly, their approach to evaluation resulted in a definitive recommendation in 82% of the patients. Much can be learned from this analysis.*
E. J. B.
Wöhrl S, Vigl K, Stingl G: Patients with drug reactions--is it worth testing?
Allergy. 2006;61:928-934. ♦♦

Screening for Adrenal Suppression

SUPPRESSION of the hypothalamic-pituitary-adrenal (HPA) axis is a potential concern in children receiving inhaled corticosteroids for asthma. Previous tests of HPA axis function have important disadvantages. Measurement of dehydroepiandrosterone sulfate (DHEA-S) was evaluated as a screening test for HPA axis dysfunction in 22 children with moderate to severe asthma. The cortisol response to cosyntropin testing was abnormal in 59% of children. The mean DHEA-S *z* score was -1.2822 in this group--significantly lower than the 0.2964 value in children with a normal response to cosyntropin. On receiver operating characteristic curve analysis, 100% sensitivity was reached at a DHEA-S *z* score of -1.5966 or less. Specificity was 100% at a DHEA-S *z* score of greater than 0.0225. Measurement of DHEA-S levels may be a useful screening test for HPA axis dysfunction in asthmatic children.

COMMENT: *Clinicians struggle with monitoring the potential, sometimes subtle, risks of inhaled corticosteroid therapy, particularly as we have an increasing number of therapeutic options for management of asthma. A simple, laboratory test that would suggest an individual is at risk of systemic side effects from inhaled corticosteroid would be very useful. This paper suggests that DHEA-S may be such a test. Confirmation is needed, but this observation is of great interest.*
D. K. L.
Dorsey MJ, Cohen LE, Phipatanakul W, et al: Assessment of adrenal suppression in children with asthma treated with inhaled corticosteroids: use of dehydroepiandrosterone sulfate as a screening test.
Ann Allergy Asthma Immunol. 2006;97:182-186. ♦♦

Accidental Peanut Ingestion

FOR peanut-allergic patients, accidental exposure to peanuts is a real hazard. This survey study asked parents of peanut-allergic children about accidental exposure to peanut over the past year. Questionnaires were received from the parents of 252 children, mean age 8 years. Twenty-nine children had a total of 35 accidental exposures, for an annual incidence rate of 14.3%. There were 15 mild and 20 moderate to severe reactions. Just 4 of the moderate to severe reactions were treated with epinephrine. Just 1 accidental exposure occurred at school. Increased awareness of the problem may be reducing the rate of accidental exposure to peanuts in allergic children.

COMMENT: *Several previous studies have analyzed the incidence of accidental peanut exposure in peanut-allergic American or British children, and show that about half have had exposures in the preceding one to five years. But recent attention to this subject in schools and the lay media may be having a beneficial effect, as demonstrated in this Canadian study showing a 14% incidence rate per year. Unfortunately, 80% of kids with moderate-to-severe reactions did not receive epinephrine. More education is needed.*
R. J. M.
Yu JW, Kagan R, Verreault N, et al: Accidental ingestions in children with peanut allergy.
J Allergy Clin Immunol. 2006;118:466-472. ♦♦

Vitamin E and Childhood Asthma

IN previous results from a cohort of children recruited before birth, the authors reported an increased risk of wheezing at age 2 among children whose mothers had low intake of vitamin E during pregnancy. The current study looked at the relationship between maternal nutrition during pregnancy and asthma-related outcomes at age 5 in a cohort of 1,861 children. Higher maternal vitamin E intake during pregnancy was associated with lower rates of wheezing and asthma at age 5. For each 1 μg/mL increase in the mothers' plasma α-tocopherol level during pregnancy, the children's post-bronchodilator FEV_1 increased by 7 mL. Asthma and other respiratory outcomes were unrelated to the children's nutrition. Maternal consumption of vitamin E may reduce the risk of wheezing and asthma in school-age children. The study also suggests a possible protective effect of maternal zinc intake. ➤➤

COMMENT: *Low vitamin E intake during pregnancy along with decreased maternal intake has now been shown to be associated with increased risk for the development of asthma at age 5. This is an important statement regarding how primary prevention may in fact counteract the increased prevalence of asthma.*
B. E. C.
Devereux G, Turner SW, Craig LCA, et al: Low maternal intake during pregnancy is associated with asthma in 5-year-old children.
Am J Respir Crit Care Med. 2006;174:499-507. ♦♦

History vs Skin Testing

WHILE about 10% of the population says they are allergic to penicillin, just over 1% have a positive skin test reaction. Clinical history was evaluated as a predictor of the results of penicillin skin testing. The retrospective study included 91 patients referred for evaluation of possible penicillin allergy. Skin testing was positive in 18% of patients--most had hives as their main symptoms, although one each had respiratory symptoms and angioedema. In most cases, the reaction occurred at least 3 years ago. Positive skin test results were unrelated to any aspect of the clinical history, including type and timing of the reaction or time since last reaction. Oral challenge was negative in 70 of 72 patients with negative skin test results. In patients with suspected penicillin allergy, the clinical history is not a reliable predictor of skin test results. Patients with a negative penicillin skin test are very unlikely to react to oral penicillin challenge.

COMMENT: *While we rely on the clinical history to establish most diagnoses in Medicine, this is one setting in which the history falls short. It is once again clear that when there is a clear indication for β-lactams in history-positive patients, skin testing--with follow up challenge in skin-test-negative patients--is the most useful approach.*
A. M.
Wong BBL, Keith PK, Waserman S: Clinical history as a predictor of penicillin skin test outcome.
Ann Allergy Asthma Immunol. 2006;97:169-174. ♦♦

High-Dose ICS Don't Replace Systemic Steroids

ORAL corticosteroids, rather than inhaled corticosteroids (ICS), are needed in children with severe acute asthma. This randomized trial compared the outcomes of inhaled fluticasone with oral prednisolone in a group of 69 children, aged 5 to 17, with mild to moderate acute asthma: FEV_1 50% to 79% of predicted. Children assigned to inhaled fluticasone received 2 mg in the emergency department (ED), followed by 500 µg twice daily for 10 doses after discharge. In the oral prednisolone group, dosage was 2 mg/kg in the ED plus 1 mg/kg/d for 5 days after discharge. After 4 hours, FEV_1 increased by about 19% in the ICS group, compared to 30% in the oral steroid group. Although pulmonary function was similar at 48 hours, relapse occurred in 12.5% of the fluticasone group, compared with none of the prednisolone group. For children seen in the ED with mild to moderate asthma attacks, oral steroids provide a faster response than ICS.

COMMENT: *I have always been skeptical of ED studies indicating that ICS are as good as or superior to systemic corticosteroids in the management of acute asthma. The majority of patients with asthma that allergists see in the office are already on ICS, if they come in sick. A mild clinical exacerbation or a drop in pulmonary function may stabilize with an ICS adjustment, along with bronchodilators. However, in any more serious episode, both systemic and increased inhaled corticosteroids are usually advised.*
J. A. A.
Schuh S, Dick PT, Stephens D, et al: High-dose inhaled fluticasone does not replace oral prednisolone in children with mild to moderate acute asthma.
Pediatrics. 2006;118:644-650. ♦♦

Classification of Asthma Severity

ACCURATE ratings of asthma severity are essential to proper treatment decision-making. However, questions remain about the roles of symptom frequency and pulmonary function variables in making these ratings. Data from two large studies of asthma in inner-city children were used to determine the impact of pulmonary function data on severity classifications made on the basis of clinical history. When pulmonary function results were added to clinical severity ratings, many children with mild intermittent asthma were upgraded to moderate or severe persistent asthma: 23% in one cohort of children and 28% in the other. About one-third of children who had mild persistent asthma, based on symptoms, were also reclassified as having moderate or severe persistent asthma. Using symptom frequency as the sole criterion underestimates the severity of childhood asthma, the investigators conclude. Although it may be challenging to do so, the authors call for efforts to increase the use of spirometry in primary care for asthma.

COMMENT: *One of the distinguishing features of asthma management by allergists vs general pediatricians is that, in the allergist's office, if the child is old enough, pulmonary function testing is usually done at each visit! As shown by Dr. Stout and colleges, the addition of pulmonary function data to clinical information offers the best chance of correctly assessing the degree of asthma initially, rather than relying upon symptoms alone. Repeated testing over time offers additional help to the doctor in adjusting the asthma severity classification and treatment.*
J. A. A.
Stout JW, Visness CM, Enright P, et al: Classification of asthma severity in children: the contribution of pulmonary function testing.
Arch Pediatr Adolesc Med. 2006;160:844-850. ♦♦

REVIEWS OF NOTE

COMMENT: *Over the past decade we have witnessed the arrival of many new biologic immune modulators. These include cytokines, monoclonal antibodies and fusion proteins. Biologic agents differ from most drugs in that they are not small chemical compounds. They are metabolized differently and pose different challenges in the context of adverse reactions. This excellent review presents a paradigm on how to approach adverse reactions to biologic agents. (Please also see Mutlu GM, Mutlu EA, Bellmeyer A, Rubinstein I: Pulmonary adverse events of anti-tumor necrosis factor-alpha antibody therapy.*
Am J Med. 2006;119:639-646.)
E. J. B.

Pichler WJ: Adverse side-effects to biological agents.
Allergy. 2006;61:912-920.

COMMENT: *This excellent review focuses on the underlying mechanisms, risk factors, diagnosis and natural history of asthma with insights into management where there are mechanistic implications.*
E. J. B.

Holgate ST, Polosa R: The mechanisms, diagnosis, and management of severe asthma in adults.
Lancet.2006;368:780-793.

COMMENT: *Over the many years that I have studied and treated patients with asthma, I have repeatedly heard many astute clinicians indicate that asthma is unlikely to be a single disease entity. Richard S. Farr made this point repeatedly in the late 1960s. Wenzel describes an approach to distinguish different phenotypes and sub-phenotypes. Is it time to abolish the term asthma?*
E. J. B.

Wenzel SE: Asthma: defining of the persistent adult phenotypes. Lancet. 2006;368:804-813.

COMMENT: *These authors from Europe and Latin America present a meta-analysis of SLIT's efficacy. SLIT appears to be gaining steam around the world. It will be interesting to follow its path through the FDA approval process in the United States.*
A. M.

Penagos M, Compalati E, Tarantini F, et al: Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials.
Ann Allergy Asthma Immunol. 2006;97:141-148.

COMMENT: *While inhaled corticosteroids appear to be safe in most patients, this review highlights the potential benefit of ciclesonide in patients requiring long-term, high-dose therapy.*
A. M.

Meltzer EO, Derendorf H: The systemic safety of inhaled corticosteroid therapy: a focus on ciclesonide.
Ann Allergy Asthma Immunol. 2006;97:149-157.

COMMENT: *This is a must-read for anyone interested in current issues involving children's allergy, asthma or immunology! Many thanks for the reviews of our colleagues.*
J. A. A.

Sicherer SH, ed: Synopsis book: best articles relevant to pediatric allergy and immunology.
Pediatrics. 2006;118(suppl):(1).

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