

ALLERGYWATCH®

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

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Go to the Mat with the Cat!

PREVIOUS reports have documented the effectiveness of immunotherapy (IT) using high doses of standardized allergen extracts, including pollens, dust mite, and cat. A study of cat allergen IT found that patients receiving the highest dose—ie, 15 µg of Fel d 1—had the best responses after 5 weeks. Questions remain about how well these improvements are maintained during subsequent maintenance therapy.

The longer-term effects of IT were evaluated in 28 adult patients with allergic rhinitis, with or without asthma, related to cat allergy. Patients were randomized to receive one of three doses of cat hair and dander extract—0.6, 3.0, or 15.0 µg of Fel d 1—or placebo IT. Titrated nasal challenge, skin prick testing, and other outcome assessments were made at baseline; after the maintenance dose was reached, about 5 weeks; and 1 year after the start of IT.

All but 2 patients completed the study. Both at the maintenance dose and at long-term follow-up, responses

to IT differed in dose-dependent fashion. Patients receiving the highest dose of Fel d 1 had the greatest improvement in terms of symptom scores on nasal challenge and response to titrated skin prick testing.

Both the medium- and high-dose groups had significant increases in cat-specific IgG4 levels. This dose-response relationship continued to be evident after 1 year. However, follow-up assessments found no between-group differences on flow cytometric evaluation of whole blood or on enzyme-linked immunosorbent assay of nasal cytokine levels.

For patients undergoing IT for cat allergy, clinical response is significantly influenced by the Fel d 1 dose given. Both at the time the maintenance dose is reached and at long-term follow-up, patients receiving the highest dose of allergen extract have the greatest clinical improvement. The dose-dependent differences between groups show little change from 5 weeks to 1 year.

COMMENT: *The efficacy of IT is highly dose-dependent. This study used a cluster regimen of cat IT to achieve maintenance doses at 4 to 5 weeks. By ►►*

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- 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
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- British Medical Journal
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- European Respiratory Journal

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this time, measures of specific immunity and improvement on nasal allergen challenge were already present at levels equivalent to those after 1 year of IT. A dose-response relationship was confirmed. As they say in real estate investing, "Go big or go home."

R. J. M.

Nanda A, O'Connor M, Anand M, et al: Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract.

J Allergy Clin Immunol. 2005;114:1339-1344. ♦♦

RSV Associated with Asthma

INFANTS with respiratory syncytial virus (RSV) bronchiolitis, whether mild or severe, may experience recurrent wheezing for several years afterward. The long-term prognostic implications of this early RSV disease remain unclear. This study assessed the effects of RSV bronchiolitis during infancy on the risk of asthma or allergic disease in adolescence.

The prospective study was based on a cohort of 47 children hospitalized for RSV bronchiolitis in infancy, mean age 17 weeks. They were compared with 93 control infants, matched for sex, age, and area of residence. At age 13, the two groups were compared for rates of recurrent wheezing, defined as three or more physician-verified episodes; and for physician diagnosis of asthma. Skin prick testing and pulmonary function measurements were performed as well.

During the previous year, asthma or recurrent wheezing was present in 43% of adolescents with a history of RSV bronchiolitis in infancy compared with 8% of non-RSV controls. Rates of allergic rhinoconjunctivitis were 39% vs 15%, respectively. Subjects in the RSV group were also more likely to be sensitized to inhaled allergens. They had a higher rate of mild airway obstruction at rest and in response to bronchodilation, along with somewhat increased airway reactivity.

Infants hospitalized for RSV bronchiolitis are more likely to have asthma or allergic disease as they enter adolescence. The mechanism of this relationship is unclear, but may involve high local levels of interleukin-4 at the time of first exposure to inhaled allergens, thus increasing the risk of sensitization. Population-based, randomized trials of measures to prevent RSV bronchiolitis would be needed to determine whether the association is causal in nature.

COMMENT: *Identifying RSV infected infants who progress to develop asthma would increase the probability of successful prophylactic protocols. Yet the risk of developing asthma later in childhood as a result of infantile RSV has never been fully documented. This study showed that 13-year-olds who developed asthma were five times more likely to have had RSV infections. This further adds to the body of knowledge linking RSV infection with asthma pathogenesis.*

G. D. M.

Sigurs N, Gustafsson PM, Bjarnason R, et al: Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13.

Am J Respir Crit Care Med. 2005;171:137-141. ♦♦

Allergic Rhinitis Isn't Likely to Remit

THERE are few data on the likelihood of symptom remission among patients with allergic sensitization and allergic rhinitis (AR). This 8-year follow-up study compared remission rates among adult patients with AR sensitized to different types of allergens.

The Danish population-based study included 734 subjects, aged 15 to 69 years, who underwent screening assessment in 1990 plus follow-up ►►

assessment in 1998. At both times, the respondents provided data on respiratory symptoms and serum samples for measurement of specific IgE. Subjects who had AR symptoms and specific IgE levels of class 2 or higher at baseline but not at follow-up were considered in remission. Remission rates were compared for patients sensitized to pollen, pets (cat or dog), and house dust mite.

At follow-up, AR had gone into remission in 17% of patients. This rate varied from 38% for patients allergic to house dust mite, to 19% for those allergic to pets, to 12% for those allergic to pollen. Patients with lower specific IgE levels were more likely to achieve remission. The greatest reduction in specific IgE level was one class—this occurred in 22% of patients who went into remission, compared with 7% of those who did not. Eighty-eight percent of patients with remission still had detectable specific IgE. Remission rates were unrelated to patient age or sex, presence of asthma, atopic predisposition, age at AR onset, or duration of AR.

Patients with AR have low rates of symptomatic remission over 8 years' follow-up. Remission rates are higher for patients sensitized to house dust mite than for those sensitized to pets or pollen. The chances of AR remission are predicted by specific IgE level.

COMMENT: *These Danish researchers used prospective, population-based data analyzed from 734 adult patients to determine the rate of remission of AR. The overall rate of remission was 16.7%, which is similar to other studies. However, whereas dust mite-allergic patients had a 38% remission rate, the rate for animal-allergic patients was 19% while that for pollen-allergic patients was only 12%. Interestingly, the key predicting factor was the level of allergy sensitization. Patients who had lower specific IgE levels at the beginning of the study were generally more likely to experience remission of their AR over the 8-year period. Although the authors point out that these data reconfirm the chronic nature of AR, they also show that very sensitive patients are less likely to "outgrow" their rhinitis.*

S. M. F.

Bodtger U, Linneberg A: Remission of allergic rhinitis: an 8-year observational study.

J Allergy Clin Immunol. 2004;114:1384-1388. ♦♦

Th1/Th2 Paradigm: The First Chink in the Armor?

THE Th1/Th2 paradigm occupies an important place in current thinking about the mechanisms of asthma. However, a growing body of evidence suggests that T-cell responses to inhaled allergens vary significantly among patients. Subtle differences in patterns of T-cell immunity might help to account for clinical variability in asthma.

Allergen-specific T-cell immunity was assessed among children participating in a longitudinal birth cohort study of asthma and atopy. The children were recruited antenatally; examinations for the current study were performed at age 9 to 14 years. Parental interviews suggested asthma in 15% of children, wheez-

ing in 17%, and bronchial hyperreactivity (BHR) in 36%. Skin prick testing identified atopy in 55% of children. In vitro T-cell responses to allergens and mitogens were assessed and blood eosinophils and IgE/IgG antibodies were measured. The findings were compared with the children's asthmatic/atopic phenotypes.

Atopic children tended to have allergen-specific Th2 responses, particularly in terms of interleukin (IL)-4, IL-5, IL-9, and IL-13. Whether or not atopy was present, IL-10, tumor necrosis factor- α , and interferon- γ responses were observed. Atopic asthma in particular was related to an eosinophilic/IL-5 response, whereas BHR was associated with eosinophilia and polyclonal interferon- γ production. Nonatopic children with BHR showed high production of allergen-specific and polyclonal IL-10 production.

Children with different asthmatic/atopic phenotypes show differing patterns of in vitro T cell responses to allergens. The presence of BHR is linked to immunologic hyperresponsiveness, including a Th1 cytokine response. Even among children with atopic asthma, immunologic responses are variable. The findings may have important treatment implications and may help to explain the inconclusive results of trials of Th2-antagonists for asthma.

COMMENT: *Just as we have begun to feel extremely comfortable with the Th1/Th2 paradigm as the immunologic foundation of allergic disease, Heaton et al. report that cytokine production in T cells from atopic individuals is not always what this theory predicts. In general, allergic disease and asthma are associated with Th2 production and in particular, with IL-5, eosinophilia, and IgE production. However, there are important exceptions, including an association between interferon- γ and airway hyperreactivity. These observations show that Th1 responses could enhance the severity of allergic diseases and asthma. Heaton et al. studied peripheral blood mononuclear cells, which may not represent immunologic cells found in the lung and nasal mucosa. Stand by, for I am certain we will hear more on this story.*

E. J. B.

Heaton T, Rowe J, Turner S, et al: An immunological approach to asthma: identification of in-vitro T-cell response patterns associated with different wheezing phenotypes in children.

Lancet. 2005;365:142-149. ♦♦

FPIES--Important Insights!

INFANTS with food protein-induced enterocolitis syndrome (FPIES) have diarrhea, vomiting, and other symptoms in reaction to foods, often cow's milk and soy protein. Initial failure to thrive may lead to acidemia and shock. An increasing number of foods have been implicated, along with symptoms starting after infancy. Several cases of FPIES are presented, and their implications for clinical management are discussed.

Differing patterns of reaction can occur—chronic vomiting, diarrhea, and poor growth may be fol- ►►

lowed by more severe, acute symptoms when the offending food is reintroduced. Infants may temporarily improve when switching from cow's milk to soy formula, only to have symptoms recur after a week. Skin prick testing and food-specific IgE levels are usually negative. In severe cases, children may present with acidemia and methemoglobinemia.

The diagnosis is usually clinical and can be difficult to make. Histologic findings vary. If skin prick tests are positive, the chances of a typical anaphylactic reaction are higher. Oral challenges play an important role in confirming the diagnosis and assessing food tolerance. It may be prudent to place an intravenous line before performing challenges. There are insufficient data to recommend any course of treatment as best. Any food the child has tolerated in the past should be allowed—other foods should be introduced with appropriate precautions. Parents must understand the importance of dietary avoidance and be prepared for accidental ingestions, which can induce severe responses.

Some observations on the clinical features, diagnosis, and management of FPIES are presented. More research of this clinical entity is needed. Efforts to improve the clinical management of FPIES rely on intensive studies to determine its immunopathologic basis.

COMMENT: *The science of food allergology is advancing rapidly. However, the mechanism of the pediatric condition called "food protein-induced enterocolitis syndrome" (FPIES) is not known, despite the well-characterized clinical events. This article uses case examples to teach clinical pearls—which will have to suffice, and will serve clinicians well—until our understanding of basic mechanisms improves.*

R. J. M.

Sicherer SH: *Food protein-induced enterocolitis syndrome: case presentations and management lessons.*

J Allergy Clin Immunol. 2005;115:149-156. ♦♦

Negative SPT: Why Do I React to My Dog?

MOST studies of the effects of allergens on the airways have focused on sensitized subjects. However, the elevated response to allergen may be related to factors other than an allergic response per se. Patients with atopic asthma were studied to examine the effects of exposure to an allergen other than the one to which they were sensitized.

The study included 248 patients with atopic asthma who were sensitized to dust mite and/or dog or cat. Asthma severity was assessed by spirometry and measurement of exhaled nitric oxide. Nonspecific bronchial reactivity was measured as well. Home dust samples were collected for measurement of dust mite, dog, and cat allergens. Associations between exposure to these allergens and bronchial reactivity were analyzed.

Among patients not sensitized to dust mite, bronchial reactivity was significantly greater for those exposed to high levels of dust mite at home: mean ratio difference 4.1, compared to patients not exposed to high

levels of dust mite. A similar pattern was observed for patients who were not sensitized to dog but were exposed to high dog allergen levels: mean ratio difference 3.3. Pulmonary function and exhaled nitric oxide were not significantly affected by exposure to non-sensitizing allergens, after adjustment for potential confounders. No increase in bronchial reactivity was noted for non-cat-sensitized asthmatics with high exposure to cat allergen.

For atopic asthmatic patients who are not sensitized to dust mite or dog, high levels of exposure to these allergens is associated with significantly increased airway reactivity. High home exposure to allergens may adversely affect the course of atopic asthma, even for patients not sensitized to that particular allergen.

COMMENT: *These authors explore an interesting area relating to how the lung responds to allergens to which an atopic subject is not sensitized. Interestingly, they show that airway reactivity was significantly greater in atopic asthmatic subjects who were not sensitized to dust mite or dog when exposed to high levels of these antigens. The cause of this phenomenon is unclear, but it has broad implications in a variety of occupational settings if it can be confirmed and clarified with regard to the mechanism operative.*

E. J. B.

Langley SJ, Goldthorpe S, Craven M, et al: *Relationships between exposure to domestic allergens and bronchial hyperresponsiveness in non-sensitized, atopic asthmatic subjects.*

Thorax. 2005;60:17-21. ♦♦

RSV Is Bad; RSV Plus ETS Is Worse!

INFANTS with severe bronchiolitis have elevated rates of childhood asthma. Data from a prospective cohort study were used to analyze the effects of home exposures and family history of atopy on the severity of respiratory syncytial virus (RSV) infection in infants.

The RSV Bronchiolitis in Early Life cohort included 206 infants admitted to one children's hospital with a first episode of wheezing and a positive nasopharyngeal swab for RSV. Mean age was 4 months—59% were boys. The babies were admitted between 1998 and 2001; exclusion criteria included regular bronchodilator or anti-inflammatory treatment and asthma or other lung diseases. Various environmental and host factors were assessed, including clinical variables, family history of atopy, and measurement of allergens in home dust samples. The infants' lowest levels of oxygen saturation and hospital length of stay served as indicators of RSV severity.

Assessment of environmental exposures showed that 25% of infants were exposed to maternal cigarette smoking during pregnancy, 28% to maternal smoking after birth, and 40% to secondhand smoke at home. In the overall cohort, mean lowest oxygen saturation was 91.6% and mean length of stay was 2.5 days. Bronchiolitis severity was lower for black than for white infants.

Oxygen saturation levels were lower for younger infants and for those exposed to maternal smoking after birth. Prenatal smoking was a less important fac- ►►

tor, with no significant difference in bronchiolitis severity compared to infants never exposed to smoke. Maternal history of atopy seemed to have a protective effect on RSV severity. Even though one-fourth of homes had high allergen levels, allergen exposure appeared unrelated to severity.

Among infants hospitalized for RSV bronchiolitis, disease severity is significantly worse for those exposed to maternal smoking after birth. Younger infants also have more severe bronchiolitis. In this cohort, African-American race and maternal history of atopy are associated with less severe bronchiolitis. Parents should be strongly cautioned about the hazards of secondhand smoke exposure, especially to young infants.

COMMENT: *The link between RSV infection and asthma has been clearly demonstrated. Family history of atopy, exposure to household allergens, and prenatal and postnatal tobacco exposure have been identified as risk factors for recurrent lower airway symptoms. In this study there was no association between increased severity of RSV bronchiolitis and allergen exposure. Interestingly, maternal history of atopy seemed to have a protective effect. Is there a difference in the child's immunologic response to RSV in light of the mother's atopic Th2 status? If so, has this dampened the effect of allergen exposure on the lower airways of infants with RSV?*

T. L. H.

Bradley JP, Bacharier LB, Bonfiglio J, et al: Severity of respiratory syncytial virus bronchiolitis is affected by cigarette smoke exposure and atopy.

Pediatrics. 2005;115:e7-e14. ♦♦

More about Skeeter Syndrome!

VARIOUS types of allergic reactions to mosquito saliva can occur, including atypical local reactions, large local reactions known as "skeeter syndrome," and uncommon systemic reactions. Despite the high frequency of local reactions, few epidemiologic studies have looked at the prevalence of mosquito allergy. Mosquito saliva-specific IgE and IgG antibodies were used to investigate the prevalence of mosquito allergy in children.

The study used serum samples from 402 pediatric patients, aged 1 month to 18 years, from a clinical laboratory. Enzyme-linked immunosorbent assays were used to measure serum levels of mosquito saliva-specific IgE and IgG, which were correlated with subject age and sex. Serum samples from 23 infants born in wintertime--and thus not likely ever exposed to mosquitoes--were used as negative controls.

Serum levels of mosquito saliva-specific IgE and IgG were significantly correlated with each other. Mean saliva specific IgE levels were higher for boys than girls: mean optical absorbency at 405 nm was 0.90 vs 0.70, respectively. Age was inversely correlated with both IgE and IgG levels. Levels peaked in infancy, earliest for IgG; then decreased gradually after age 5.

Infants and young children have the highest levels of mosquito saliva-specific IgE and IgG antibodies. The

results are consistent with reports that the rates of large local inflammatory reactions to mosquito bites are highest in this age group. Natural desensitization does occur but may take a long time, particularly if allergic subjects take care to avoid mosquito bites.

COMMENT: *When a subject, usually a child, presents with a history of reaction to mosquito bites, I usually reassure the child and family without testing. This is based on the lack of a reliable reagent for testing of mosquito allergy and the observations that most reactions are non-life-threatening and sensitivity is transient. These investigators use salivary protein testing material and demonstrate the natural decline in sensitivity over 5 years--more rapid with greater exposure. Nevertheless, specific immunologic responses do occur, and young children or older subjects without past exposure to mosquitoes are at increased risk of more serious reactions.*

D. K. L.

Peng Z, Ho MK, Li C, Simons FER: Evidence for natural desensitization to mosquito salivary allergen: mosquito saliva specific IgE and IgG levels in children.

Ann Asthma Allergy Immunol. 2004;93:553-556. ♦♦

Is Asthma Risk Independent of Atopy?

STUDIES of the relationship between bronchiolitis in infancy and the risk of asthma in adulthood have yielded conflicting results. The sole prospective study found no association, but was underpowered; a retrospective study suggested higher rates of asthma among subjects with a history of bronchiolitis in infancy. Children with severe bronchiolitis or pneumonia were followed up to young adulthood to assess asthma and other pulmonary outcomes.

The study included 127 infants hospitalized for bronchiolitis or pneumonia in 1981-82, at a median age of 10 months. Seventy-two newborns with no family history of atopy were followed up as controls. The presence of wheezing and asthma was assessed in 2000, when the subjects were 18 to 21 years old. Bronchial reactivity testing, peak flow monitoring, and skin prick testing were also performed at follow-up.

The rate of current physician-diagnosed asthma at follow-up was 30% among the subjects with bronchiolitis in infancy, compared to 15% for those with pneumonia in infancy and 11% for controls. Associated odds ratio was 3.37. When asthma was defined as a previous physician diagnosis plus current wheezing or cough, the odds ratio in the bronchiolitis group increased to 5.50. On logistic regression analysis, history of bronchiolitis remained a significant risk factor, independent of atopy or smoking. Although lung function parameters were generally normal, patients with a history of bronchiolitis were more likely to have abnormal values. Dog and cat dander were the only allergens associated with a history of wheezing in infancy.

This long-term prospective study documents an increased risk of asthma in young adulthood for ►►

infants hospitalized with bronchiolitis. The impact on asthma risk, and on pulmonary function values, is independent of the development of atopy. Infants with early wheezing have good outcomes in childhood, but are at risk of becoming symptomatic again in adulthood.

COMMENT: *It has always seemed logical to me that infant bronchiolitis severe enough to cause hospitalization would increase the chances the child would have asthma when he or she grew up. This prospective controlled study of 18- to 21-year-old Finnish adults appears to confirm my belief. Few long-term studies of this kind have been published, therefore the new information is very important. It is interesting that the authors report that the increased asthma risk was independent of the development of "atopy" (defined as one positive allergy skin test as an adult). However, there is a correlation between animal sensitivity as an adult and previous infantile wheezing.*

J. A. A.

Püppo-Savolainen E, Remes S, Kannisto S, et al: Asthma and lung function 20 years after wheezing in infancy: results from a prospective follow-up study. *Arch Pediatr Adolesc Med.* 2004;158:1070-1076. ♦♦

Eosinophilic Pneumonia: Rare but Important

PATIENTS with acute eosinophilic pneumonia (AEP) have a febrile illness accompanied by pulmonary eosinophilia and diffuse infiltrates on the chest x-ray. Peripheral eosinophilia may or may not be present, which can contribute to a difficult diagnosis. The cause of this rare disease is unknown. A series of cases of AEP among U.S. military personnel serving in or near Iraq is reported.

The authors investigated 18 cases of AEP among military personnel deployed in support of Operation Iraqi Freedom. Median age was 22 years; time from deployment to initial symptoms ranged from 1 day to 11 months. The most common presenting symptoms were shortness of breath, fever and chills, fatigue, and cough. Of 12 patients requiring mechanical ventilation, 9 were ventilated for 4 days or longer. Two patients died. Treatment for severe cases consisted of at least 1 week of intravenous broad-spectrum antibiotics. Most patients received corticosteroids, which led to respiratory improvement within a few days but prolonged clearance of infiltrates.

Epidemiologic investigation suggested an incidence of about 9 per 100,000 person-years. There was no evidence of any common source or temporal clustering. Fifty-five percent of cases occurred in the summer. All patients smoked, and 78% had recently started smoking—a much higher percentage than in a control group. Nearly all were exposed to airborne sand or dust. Most were involved with convoy operations and came into close contact with the local population. Two-thirds of patients received smallpox and anthrax vaccine before deployment.

In this case series of AEP among soldiers deployed to Iraq, the only apparent contributing exposure was tobacco smoke, especially new-onset smoking. Some

patients with this diagnosis have fulminant respiratory failure, although others have less severe involvement. The possibility of AEP should be considered in military personnel with respiratory illness, during or soon after deployment or training.

COMMENT: *Acute eosinophilic pneumonia is a rare, serious, acute condition with or without peripheral eosinophilia. Allergists/immunologists may be asked to see these patients during hospitalization or after recovery to offer an opinion as to cause. This paper provides information as to diagnoses that should be considered in such patients. The association of AEP with recent onset of tobacco use—and perhaps with the dry, dusty conditions of a desert environment—is also of interest. We may only see one or two cases of AEP in our careers, but knowledge is power, even with rare disorders.*

D. K. L.

Shorr AF, Scoville SL, Cersovsky SB, et al: Acute eosinophilic pneumonia among US military personnel deployed in or near Iraq.

JAMA. 2004;292:2997-3005. ♦♦

Chronic Rhinosinusitis: It's Not Over Till the Fat Lady Stops Singing!

CHRONIC rhinosinusitis (CRS) is a common condition that is of unknown cause and has few effective treatments. It has been suggested that the eosinophilic inflammation of CRS is related to a unique immune response to fungi in the sinuses. Studies of intranasal administration of antifungal drugs have yielded promising results. This study examined the effects of intranasal amphotericin B on CT evidence of mucosal inflammatory thickening in CRS.

Thirty patients with CRS were randomized to receive 6 months of treatment with intranasal amphotericin B 250 µg/mL—20 mL instilled in each nostril twice daily—or placebo. Digitized CT scans of a standardized coronal cut were used for objective measurement of inflammatory mucosal thickening. Other outcome measures included endoscopic and symptom scores and measurement of nasal inflammatory markers.

Of 6 patients who did not complete the trial, 5 were from the amphotericin B group. Ninety percent of patients in the active treatment group had improved symptom scores, as did 64% in the placebo group. Endoscopic scores improved to a significantly greater extent with amphotericin B. The CT measurements showed a mean relative reduction of 8.8% in the percentage of mucosal thickening for patients taking amphotericin B, compared with a 2.5% increase in the placebo group. Levels of eosinophil-derived neurotoxins in the intranasal mucosa decreased with amphotericin B group but increased with placebo.

In patients with CRS, treatment with intranasal amphotericin B leads to reduced CT evidence of sinonasal mucosal inflammation. Improvement in endoscopic disease score is apparent as well. Further study is needed to establish the mechanism and clinical relevance of these effects.

COMMENT: *Is there a benefit to using a topi- ➤➤*

cal antifungal in patients with CRS? Previous studies report that molds such as *Alternaria* play an important role in the pathology of CRS. It is difficult to compare CT scans from before and after therapy, but these researchers used digitized CT scans to measure the number of pixels, in an effort to quantify sinus mucosal inflammation in 30 patients with CRS. They found a significant reduction of mucosal inflammation as well as reductions of various intranasal markers of eosinophilic inflammation in patients using topical amphotericin B twice daily for 6 months. Dr Bush, in his accompanying editorial, points out that other reports have not confirmed the impressive results from these researchers. This should be considered a pilot trial. We await the results of larger studies before using topical antifungal therapy for all our patients with CRS.

S. M. F.

Ponikau J, Sherris DA, Weaver A, Kita H: Treatment of chronic rhinosinusitis with intranasal amphotericin B: a randomized, placebo-controlled, double-blind pilot trial. *J Allergy Clin Immunol.* 2005;115:125-131; and Bush RK: Is topical antifungal therapy effective in the treatment of chronic rhinosinusitis? (editorial).

J Allergy Clin Immunol. 2005;115:123-124. ♦♦

Lactobacillus: Do No Harm!

PROBIOTIC strains of *Lactobacillus* and other lactic acid bacteria are useful in the treatment of acute diarrhea and other infectious diseases. Serious infections caused by probiotic therapy are very rare, with only two cases reported in adults. Two cases of *Lactobacillus* sepsis caused by probiotic therapy in children are reported.

The patients were a 6-week-old boy and a 6-year-old girl being treated for complex medical conditions. Both developed diarrhea thought to be related to the use of broad-spectrum antibiotics and were treated with probiotic *Lactobacillus* GG. Weeks later, the patients developed sepsis with positive cultures for *Lactobacillus* spp. Both responded well to antibiotic therapy. On DNA fingerprinting analysis, the cultured strains of *Lactobacillus* were identical to the probiotic strain.

Two children with *Lactobacillus* sepsis related to the use of probiotic *Lactobacillus* GG are reported. Although such invasive infections are rare, they may occur in certain populations of patients. The pathogenesis of these infections is unclear--the bacteremia seems to have resulted from bacterial translocation from the gut.

COMMENT: "Do no harm!" No medication can be considered completely safe for all individuals, under all circumstances. On the other hand, certain medications are felt to be very safe, including for use in children with diarrhea, presumed to be due to broad-spectrum antibiotic use. Probiotic strains of *Lactobacillus* fall into this category. This report from North Carolina involves the first two pediatric cases of invasive disease (sepsis) proven by DNA fingerprinting analysis to be caused by

GI administration of *Lactobacillus*. These exceptional cases are worth remembering.

J. A. A.

Land MH, Rouster-Stevens K, Woods CR, et al: *Lactobacillus* sepsis associated with probiotic therapy. *Pediatrics.* 2005;115:178-181.

Probiotics: Food for Thought!

PATIENTS with atopic dermatitis (AD) have decreased intestinal barrier function. This may represent either a local inflammatory effect on the mucosa or a distinct abnormality. In a previous study, the authors found that treatment with *Lactobacillus* probiotic reduced the severity of eczema in children with AD. This study examines the effects of probiotic supplementation on intestinal permeability and GI symptoms in pediatric AD.

The study included 41 children with moderate or severe AD, median age 4 years. Serum IgE levels were measured before treatment. The children were then randomized to 6 weeks of treatment with a probiotic *Lactobacillus* preparation or a placebo skim milk preparation. After a 6-week washout period, patients were crossed over to the other group. The lactulose-mannitol test was performed to assess permeability of the small intestine. Treatment effects on GI symptoms were assessed as well.

At baseline, 27% of children experienced diarrhea, vomiting, or abdominal pain at least occasionally. Symptoms were more frequent in children with high serum IgE levels. During the last two weeks of the treatment periods, the percentage of children reporting GI symptoms at least twice weekly was 39% with placebo vs 10% with *Lactobacillus*.

During both treatment periods, the lactulose:mannitol ratio was significantly and positively correlated with eczema severity. *Lactobacillus* treatment was associated with a significant reduction in lactulose:mannitol ratio: 0.073, compared to 0.110 with placebo.

Probiotic treatment with *Lactobacillus* reduces intestinal permeability and GI symptoms in children with AD. The findings strengthen the theory that reduced intestinal barrier function may play a pathogenetic role in AD. More study of the timing and long-term effects of probiotic supplementation for AD is needed.

COMMENT: The use of oral *Lactobacillus* (a probiotic) has been shown to restore a more-normal GI flora with in children with infectious diarrhea. In this Danish study of 41 children with severe atopic dermatitis, 22% reported symptoms of noninfectious diarrhea (with or without abdominal pain), when treated with a placebo skim milk for a week. At the end of 6 weeks treatment with an oral *Lactobacillus*, the percentage reporting GI symptoms was reduced to 5%. In a smaller number of patients, GI permeability was found to normalize with probiotic use.

J. A. A.

Rosenfeldt V, Benfeldt E, Valerius NH, et al: Effect of probiotics on gastrointestinal symptoms and ►►

small intestinal permeability in children with atopic dermatitis. *J Pediatr.* 2004;145:612-616. ♦♦

S. aureus **Enterotoxins: Role in Sinusitis**

ALTHOUGH allergy has long been suspected of playing a role in nasal polyposis, this has not been proven. Recent studies have suggested that many polyps show specific IgE to *Staphylococcus aureus* enterotoxins (SAEs), together with local IgE antibodies and a high rate of asthma. This study examined possible associations between nasal carriage of *S. aureus*, systemic and local formation of IgE to SAEs, and nasal polyposis.

The study included samples of nasal tissue and serum from 24 patients with bilateral nasal polyposis and 12 controls. Twelve of the patients were atopic, as indicated by skin-prick testing. Serum and tissue specimens were tested for total IgE and IgE antibodies.

Nasal cultures showed colonization with *S. aureus* in 71% of patients with nasal polyposis vs 25% of controls. Fifty percent of the patients showed IgE antibodies to SAEs in nasal tissue specimens, compared with none of the controls. The presence of IgE antibodies in nasal polyps was only partially related to the serum IgE and skin prick results. On staining studies, the polyp specimens showed follicular structures with B and T cells and diffuse lymphoid accumulations with plasma cell infiltration.

Samples of nasal polyps show organized secondary lymphoid tissues. Affected patients have elevated serum IgE levels, which are only partly associated with local IgE antibodies specific to SAEs. An increased rate of *S. aureus* colonization is present along with tissue eosinophilia.

COMMENT: These investigators studied the relationship between the presence of *S. aureus* in the nasal vestibule, IgE formation to SAEs, and nasal polyposis. Their observations provide insight into an area fraught with some controversial linkages by others between fungal allergens, eosinophils, and chronic rhinosinusitis. These authors demonstrate locally formed IgE antibodies to staphylococcal enterotoxins with associated increased eosinophilic inflammation in a group of nasal polyp patients. It would be interesting to see similar studies in patients with nonatopic chronic rhinosinusitis.

E. J. B.

Gevaert P, Holtappels G, Johansson SGO, et al: Organization of secondary lymphoid tissue and local IgE formation to *Staphylococcus aureus* enterotoxins in nasal polyp tissue.

Allergy. 2005;60:71-79. ♦♦

SIT: An Added Twist on Mechanism

SPECIFIC immunotherapy (SIT) is recognized as an effective treatment for allergic rhinitis, yet its cellular mechanisms remain unclear. Costimulatory mole-

cules acting in the process of antigen recognition--such as CD80 and CD86 on antigen-presenting cells and CD28 on T cells--may be affected. The model of late phase reaction of the skin was used to study SIT's effects on costimulatory molecule expression.

Forty-one patients with birch pollen allergy were studied after a year of active or placebo SIT. The late phase reaction was induced by injection of birch pollen antigen extracts and biopsy specimens were obtained. Staining studies were performed using antibodies against CD68 (macrophages), EG2 (eosinophils), CD4 (T cells), CD68 (macrophages), CD1a (Langerhans cells), and CD28 (T cells), as well as against the CD80 and CD86 costimulatory molecules.

Active SIT was associated with significantly reduced symptom scores during pollen season and a much smaller late phase reaction in response to allergen injection, compared with placebo SIT. The CD4+ and CD68+ response was greater in the placebo group than in the SIT group, with no significant change in CD1a+ cell numbers. Patients in the placebo group had significant increases in CD80+ and CD28+ cells, which those in the SIT group did not. Patients in the SIT group had a lesser increase in CD86+ cells. Both groups had significant increases in EG2+ cells.

Allergy patients undergoing SIT show reduced numbers of cells expressing costimulatory molecules in response to allergen provocation, compared with those undergoing placebo treatment. The reduced costimulatory response may be a key factor in the reduced immune response, and thus in clinical improvement, after SIT.

COMMENT: Debate has raged over the years regarding the mechanism of allergen immunotherapy. The leading arguments have supported its effects on either humoral responses (eg, IgG "blocking antibody") or T cell cytokine profile effects (eg, shift from Th2 to Th1 inflammatory response). This study demonstrates that immunotherapy specifically attenuates the so-called costimulatory "second signal" that is necessary for activation when antigen presenting cells interact with T helper cells. Add yet another immunologic mechanism to the long list of ways in which this timeless treatment achieves its remarkable effect.

S. A. T.

Plewako H, Arvidsson M, Oancea I, et al: The effect of specific immunotherapy on the expression of costimulatory molecules in late phase reaction of the skin in allergic patients.

Clin Exp Allergy 2004; 34:1862-1867. ♦♦

More on Obesity and Asthma

NORTHERN Sweden has a relatively high rate of adult asthma, with an annual incidence of 2.3 per 1,000 population. Previous studies have suggested that obesity may increase the risk of asthma, although this link remains uncertain. Population-based data were used to assess obesity as a risk factor for adult incident asthma in northern Sweden. >>>

The study included data on all adult residents, aged 20 to 60 years, living in three northern Swedish towns. Case-referent analysis included 309 subjects with new-onset asthma within the last 12 months, confirmed by the presence of bronchial variability. The same number of referents was selected, with matching for age, sex, and area. Body mass index and other potential risk factors for asthma were evaluated.

On multivariate analysis, the strongest risk factor for incident asthma was presence of hay fever, odds ratio (OR) 4.8. Previous smoking was also a significant risk factor, OR 1.6. On analysis of body weight, risk was increased for subjects with a body mass index of 25 to less than 30, OR 2.0; and for those with a body mass index of 30 or higher, OR 2.7. The risk associated with elevated body mass index was similar for men and women, as well as for subjects with vs without allergic sensitization.

Elevated body mass index—25 kg/m² or greater—is among the significant risk factor for adult-onset asthma in this Swedish population. This relationship is independent of other characteristics, including sex and allergic status. The pathophysiology of the relationship between obesity and asthma remains unclear; a metabolic mechanism is possible.

COMMENT: *This report shows again that obesity is an independent risk factor for asthma in adults. This is independent of allergic status and gender. The study population was from Sweden and thus predominantly Caucasian. In patients with a family history of asthma, counseling for obese individuals could be useful in reducing risk for developing asthma. Caution is needed in extending these data to non-Caucasian populations.*

G. D. M.

Rönmark E, Andersson C, Nyström L, et al: Obesity increases the risk of incident asthma among adults. *Eur Respir J.* 2005;25:282-288. ♦♦

Latex Allergy in Infants

RISK factors for latex allergy in children include atopy and previous surgical procedures. There have been few reports of latex allergy in infants.

Nine Japanese infants who became allergic to latex during the first year of life are reported. All were full-term at birth; none had any birth defects or previous surgeries. Six of the infants had atopic eczema/dermatitis while one had asthma. Symptoms included swelling of the face or lips in 4 infants, wheezing in 3, facial rash in 1, and anaphylaxis in 1. In each case, symptoms occurred at home. The most common sources of exposure were natural rubber nipples and pacifiers.

All patients had a positive skin-prick response to latex, while all but 1 tested positive for latex-specific IgE. For 7 of the 9 infants, at least one parent had latex allergy.

Latex allergy can develop in the first year of life in infants without a history of multiple operations. Family history of latex allergy appears to be an important risk factor. Latex-allergic parents should avoid exposing their infant to latex products.

COMMENT: *The commonly accepted risk factors for latex allergy include known atopy, multiple surgical procedures, and occupational exposure to powdered latex gloves. This Japanese report details 9 cases of latex allergy in infants younger than 12 months. None of these patients had spina bifida or prior surgical procedures, although 7 had at least one parent with latex allergy. Perhaps we should be counseling our latex-allergic patients about the risks of exposing their newborn children to latex-containing products.*

S. A. T.

Kimata H: Latex allergy in infants younger than 1 year. *Clin Exp Allergy.* 2004;34:1910-1915. ♦♦

Step-Up or Step-Down? That Is the Question

CURRENT guidelines call for a "step-down" approach to inhaled corticosteroid (ICS) therapy for asthma—ie, once disease control is achieved, ICS treatment is reduced to the lowest effective dose. The current study assessed the effects of a step-down vs fixed-dose approach on two measures of asthma control: sputum eosinophils and bronchial hyperresponsiveness.

The randomized, controlled trial included 35 patients with mild to moderate asthma. One group received a step-down approach, with inhaled fluticasone propionate starting at 1,000 µg/d for 8 weeks then decreasing to 200 µg/d for 6 weeks. The other group received a fixed dose of 200 µg/d for 14 weeks. The two treatments were compared for their effects on BHR to methacholine and on sputum eosinophils.

The two approaches yielded similar and significant increases in methacholine PD₂₀. Sputum eosinophil responses were comparable as well. Sputum eosinophils dropped to 3% or lower after 8 weeks in 69% of patients in the step-down group and 50% in the fixed-dose group. After 14 weeks, the figures were 60% and 57%, respectively. After 8 weeks of subsequent placebo treatment, sputum eosinophilia remained at this level in one-third of patients.

In mild to moderate asthma, step-down and fixed-dose ICS treatment yield similar improvements in BHR and sputum eosinophils. The latter effect is the longer-lasting of the two. The findings question the need for high initial doses of ICS to control eosinophilia.

COMMENT: *To use a step-up or step-down approach in the treatment of persistent asthma—that is the question. In our approach to the individual patient we are guided by several parameters, including symptoms and pulmonary function. This study compares two other parameters: BHR and sputum eosinophilia. There was no statistically significant difference in improvement in these parameters between the patients treated with a fixed dose of fluticasone propionate at 200 µg/d and those in whom 1,000 µg/d for 6 weeks was the dose at which therapy was initiated. One may conclude that in many patients asthma control may be obtained with lower doses of inhaled corticosteroids. This serves as evidence in support of a step-up therapeutic approach.* ►►

A larger sample may be more beneficial in clearly defining the optimal approach.

T. L. H.

Foresi A, Mastropasqua B, Chetta A: Step-down compared to fixed-dose treatment with inhaled fluticasone propionate in asthma.

Chest. 2005;127:117-124. ♦♦

Prognosis of Childhood Asthma

ALTHOUGH some children eventually "outgrow" their asthma, others have asthma that persists or relapses in adulthood. A group of patients treated for moderate to severe allergic asthma in childhood were followed up to determine their asthma status in young adulthood.

The analysis included 85 of 121 patients from the Childhood Asthma Study, a randomized, controlled trial of adjunct immunotherapy. All had moderate to severe asthma, based on symptoms and medication use, with at least 1 year of medical treatment before enrollment at age 5 to 12 years. Follow-up examinations—including skin testing, spirometry, and assessment of symptoms and medication use—were performed when the subjects were 17 to 30 years old. Modified National Heart Lung, and Blood Institute (NHLBI) criteria were used to classify the severity of adulthood asthma.

The patients were 74% male, mean age 24 years at follow-up—55% were white and 44% African-American. Asthma was classified as in remission in 15% of patients, while another 22% had mild intermittent asthma. Mild persistent asthma was present in 14%, moderate persistent asthma in 29%, and severe persistent asthma in 19%. Patients whose asthma was currently in remission had less severe atopy in childhood, evidenced by lower total serum IgE; fewer positive skin prick tests; and lesser use of medications, including inhaled corticosteroids.

Half of the sample received immunotherapy in childhood, but their adult asthma outcomes were no different from those of untreated children. Childhood methacholine responsiveness and FEV₁ were also unrelated to adult asthma status. Adult variables associated with current asthma severity included a higher number of positive skin tests. Subjects with milder adult asthma tended to be taller in adulthood.

Nearly two-thirds of children with moderate to severe asthma continue to have mild, moderate, or severe persistent asthma when re-evaluated as young adults. The long-term prognosis of asthma seems to be largely determined by childhood factors, especially the degree of atopy.

COMMENT: Have you ever wondered how those children with allergic asthma you treated are doing now that they are adults? Johns Hopkins investigators were able to answer this question in 85 of 121 patients they had previously studied over 10 years before. Using the cohort that had participated in a placebo-controlled trial of immunotherapy for allergic asthma, these researchers characterized the patients' current condition based on NHLBI guidelines. Interestingly, predictors of persistent adult asthma included childhood asthma

severity and degree of atopy, measured by positive skin tests and total serum IgE. Airway methacholine responsiveness, FEV₁, BMI, and use of allergen immunotherapy were not predictive of later asthma severity. The authors suggest that the degree of atopy in childhood may be a major determinant of prognosis in adult asthma.

S. M. F.

Limb SL, Brown KC, Wood RA, et al: Adult asthma severity in individuals with a history of childhood asthma.

J Allergy Clin Immunol. 2005;115:61-66. ♦♦

More on the Hygiene Hypothesis

CHILDREN who grow up on farms appear to have reduced rates of allergic disease, particularly wheezing and asthma. Few studies have looked at rates of asthma among non-urban children or children of farming families in the United States, where farming practices may differ from those in Europe. Asthma and other allergic diseases were compared for rural U.S. children who did and did not live on farms.

A questionnaire was sent to a population of 36,500 children attending schools in rural areas of Wisconsin. The prevalence of asthma was compared between for children who had or had not ever lived on a farm. The survey included questions on farm-related and other environmental characteristics.

Responses were received for 4,152 children, 18% of whom had lived or were currently living on a farm. Children in the farm group had more siblings, a higher rate of breast-feeding, more pets, and a lower rate of daycare attendance than rural children who had not lived on farms. A history of wheezing was reported for 28% of children who had lived on farms, compared with 34% of the nonfarm group. Rates of asthma diagnosis were 22% vs 26%, respectively.

With adjustment for age and sex, the reduction in asthma associated with farming was greater for younger children than for adolescents. Asthma prevalence was reduced for children who lived on farms during the first 5 years of life, but not thereafter: 24% vs 34%, respectively.

Children living on farms in the United States have a lower rate of asthma than children living in rural areas but not on farms. Other allergic outcomes appear unaffected. Exposures during early childhood appear to have a greater impact than those occurring later on.

COMMENT: Numerous studies have reported a reduced incidence of asthma and allergies in children growing up on farms. Most of these studies have been from Europe and areas in which the farms are smaller and the animals are usually in close proximity to the family living quarters. Using mailed questionnaires to families with children in rural schools in Wisconsin, these researchers found that asthma was less commonly reported among children living in farms than those in rural nonfarm homes. Unfortunately, there was only a 12.8% return rate from the 36,500 questionnaires, but the researchers were able to analyze data on 4,152 children. Although the authors found a reduction in ►►

asthma reporting in the farming children, there was no consistent association with other markers of atopy. Other confounding factors may include the fact that the farming families tended to have more children and more outdoor pets and were less likely to use daycare. Overall, this study adds to the literature supporting the hygiene hypothesis.

S. M. F.

Adler A, Trager I, Quintero DR: Decreased prevalence of asthma among farm-reared children compared with those who are rural but not farm-reared.

J Allergy Clin Immunol. 2005;115:67-73.

First North American Study on SLIT

SUBLINGUAL swallow immunotherapy (SLIT) has emerged as an effective alternative to parenteral immunotherapy. Most studies of SLIT have started therapy well before the onset of pollen season. A SLIT protocol for ragweed allergy, initiated shortly before pollen season, is reported.

The randomized, controlled trial included 83 adults and children with seasonal allergic rhinoconjunctivitis and confirmed reaction to ragweed pollen. They were assigned to active or placebo SLIT. Treatment started 2 weeks before ragweed season with a 17-day progression phase. This consisted of increasing daily doses of 0.5 to 300 index of reactivity (IR)—a 100 IR dose contained 116 µg of Amb a 1 major antigen. Maintenance doses continued through pollen season. Doses were given as drops, which patients were to hold under the tongue for 2 minutes before swallowing.

Fifty-seven patients completed the study. Of 10 patients who dropped out because of inefficacy, 9 were from the placebo group. Nine patients in the active SLIT group dropped out because of adverse events, none of which were serious. Researcher ratings suggested that clinical improvement was more likely and deterioration less likely for patients receiving active SLIT. Treatment brought significant improvements in ragweed IgE and IgG4 levels, with near-significant improvements in sneezing and nasal itching. The latter improvement was significant after exclusion of patients from an urban area where the pollen season was unusually mild.

This Canadian trial demonstrates the safety and efficacy of SLIT for patients with ragweed rhinoconjunctivitis. An effect is demonstrated even when commencing treatment near the start of pollen season.

COMMENT: Data supporting the efficacy of SLIT continue to increase. The interesting wrinkle (no pun intended) in this study was that treatment was initiated just 2 weeks before ragweed season. Efficacy, albeit minimal, was demonstrated. One factor contributing to limited efficacy may have been a relatively mild pollen season, along with starting treatment so close to the season. Sublingual/oral immunotherapy is a potential treatment strategy in the United States.

D. K. L.

Bowen T, Greenbaum J, Charbonneau Y, et al: Canadian trial of sublingual swallow immunotherapy

for ragweed rhinoconjunctivitis.

Ann Allergy Asthma Immunol. 2004;93:425-430. ♦♦

Comparison of Antihistamines: Fexofenadine vs Cetirizine

SUPPRESSION of the histamine-induced wheal-and-flare effect provides an objective measure of the peripheral H₁-receptor blocking activity of antihistamines. This method was used to compare the actions of fexofenadine and cetirizine in healthy subjects.

The double-blind, crossover study included 52 volunteers treated with 180 mg of fexofenadine hydrochloride or 10 mg of cetirizine. Mean time to 95% wheal inhibition was somewhat less than 3 hours, with a non-significant 7-minute difference in favor of fexofenadine. Rates of 95% inhibition of wheal and flare were also similar for the two antihistamines.

Studies in healthy volunteers suggest that fexofenadine and cetirizine have a similar onsets of action and frequency of inhibition of histamine-induced wheal-and-flare reactions.

COMMENT: When patients ask us, "What is the best antihistamine?" the answer is frequently, "That depends." This study lends further insight on the characteristics of the two most commonly used antihistamines in practice. It challenges the notion that cetirizine has greater efficacy in the skin.

A. M.

Purohit A, N'Gom AS, Deslandes B, et al: Similar rapid onset of action and magnitude of effect of fexofenadine and cetirizine as assessed by inhibition of histamine-induced wheal-and-flare reaction.

Ann Allergy Asthma Immunol. 2004;93:562-567.

ALLERGY AND IMMUNOLOGY REVIEWS OF NOTE

COMMENT: Chemokines play a central role in autoimmune, inflammatory, viral and allergic diseases due to their potential to attract and activate leukocytes. This review provides an overview of the role of chemokines. It also introduces the concept of treating allergic diseases using chemokine receptor antagonists. E. J. B.

Elsner J, Escher SE, Forssmann U: Chemokine receptor antagonists: a novel therapeutic approach in allergic diseases. *Allergy*. 2004;59:1243-1258. ♦♦

COMMENT: Inhaled corticosteroids are absorbed, and there is a risk (albeit low) of systemic side effects, determined by dose, molecule and duration of treatment. This review of the literature includes the authors' opinion, supported by data, as to the critical question: the magnitude of the risk. As we use inhaled steroids earlier in the treatment of respiratory disease--with longer duration and greater total dose exposures--we should be knowledgeable about potential risks and any measures that may minimize risk.

D. K. L.

Mortimer KJ, Harrison TW, Tattersfield AE: Effects of inhaled corticosteroid on bone.

Ann Allergy Asthma Immunol. 2005;94:15-22. ♦♦

COMMENT: This is a very interesting approach to potentially cost effective evaluation of chronic cough. The authors describe an algorithm that approaches identifying the cause of the cough with history, examination, and, when clinically indicated, chest radiograph and/or spirometry. The success rate of treatment of underlying causes of chronic cough was 74%, making this algorithm a highly cost-effective approach to diagnosis and management.

G. D. M.

Kastelik JA, Aziz I, Ojoo RH, et al: Investigation and management of chronic cough using a probability-based algorithm. *Eur Respir J*. 2005;25:235-243. ♦♦

COMMENT: The authors present a comprehensive review of a poorly understood area of immunology. Complement biology and its relevance to human disease models are presented.

A. M.

Glovsky MM, Ward PA, Johnson KJ: Complement determinations in human disease.

Ann Allergy Asthma Immunol. 2004;93:513-522. ♦♦

COMMENT: Twenty-two trials involving 979 patients were included in this analysis. The authors conclude that SLIT is a safer treatment that significantly reduces symptoms and medication requirements in allergic rhinitis. However, we still have much to learn about the effects of this therapy including the optimal dose to be used; whether it can be effective in the format of rush therapy; and, most important, its cost compared with other therapeutic modalities.

E. J. B.

Wilson DR, Torres Lima M, Durham SR: Sublingual immunotherapy (SLIT) for allergic rhinitis: systematic review and meta-analysis. *Allergy*. 2005;60:4-12. ♦♦

COMMENT: The hazards of outdoor air pollution to the health of children is an important area of science that is not often reviewed. This excellent policy statement of the AAP focuses on that subject. It should be of interest to all allergists treating asthmatic children.

J. A. A.

American Academy of Pediatrics Committee on Environmental Health: Ambient air pollution: health hazards to children.

Pediatrics. 2004;114:1699-1707. ♦♦

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