AllergyWatch®

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

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The "United Airway" Has Implications

IN children as in adults, bronchial hyperresponsiveness (BHR) may be present in the absence of asthma symptoms. In addition to direct approaches such as methacholine bronchial provocation, BHR can be diagnosed through indirect methods such as exercise or isocapnic hyperventilation of cold air (IHCA). This 2-year follow-up study assessed the rate of asthma development among children with hay fever, along with the predictive value of tests for BHR.

The study included 28 Swedish children with birch pollen allergy, mean age 11 years, enrolled in a trial of immunotherapy in 1992. Twelve of the children had an initial diagnosis of asthma during the baseline pollen season. Assessments included measurement of BHR by methacholine challenge testing and IHCA. Rates of clinical asthma--defined in terms of subjective asthma symptoms, a positive IHCA test, or physician-diagnosed asthma--were assessed in 1994, including evaluation of the prognostic performance of the various tests.

At follow-up, one-half of the children who initially had hay fever only now had a physician's diagnosis of asthma. Fourteen of these patients had a positive response to IHCA and 13 to methacholine provocation. All 12 children who had asthma at baseline were still asthmatic at follow-up. Twenty-three children had a positive methacholine challenge test in 1992. In 1994, 17 of these had physician-diagnosed asthma while 20 had a positive IHCA test.

Overall, 24 of the 28 children had a positive methacholine challenge test at follow-up and the same number had a positive response to IHCA. Both IHCA and methacholine challenge testing had high sensitivity but low specificity for subjective asthma symptoms. Both challenge tests had high sensitivity for physician-diagnosed asthma.

Many children who have hay fever but not asthma at initial assessment will go on to develop asthma within a few years. The presence of BHR, assessed by either methacholine provocation or IHCA, is highly sensitive in predicting the development of physician-diagnosed ➤➤

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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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asthma. The findings should alert clinicians to carefully monitor for the possible emergence of asthma and the need for appropriate therapy.

COMMENT: *This small but extensively evaluated group of children provides many valuable lessons. While it has been appreciated for decades that BHR is found in many adult patients with allergic rhinitis who do not have asthmatic symptoms, very little information has been available in children. This study clearly shows that the great majority of children with asymptomatic BHR will develop clinical asthma. The authors further highlight the safety of methacholine and IHCA in school-aged children. Given the tremendous number of at-risk children, these tests appear safe and effective in confirming the diagnosis of asthma in unclear cases.*
A. M.

Ferdousi HA, Zetterström O, Dreborg S: Bronchial hyper-responsiveness predicts the development of mild clinical asthma within 2 yr in school children with hay-fever.
Pediatr Allergy Immunol. 2005;16:478-486. ♦♦

Food for Thought on Tree Nut Allergy!

PATIENTS with tree nut allergy are generally told that their condition is a lifelong one. Studies suggest that up to one-fifth of children will eventually "outgrow" peanut allergy. This study examined the likelihood of outgrowing tree nut allergy in children.

The study included 278 children, median age 7 years, with tree nut allergy, based on a history of a reaction and/or the presence of tree nut-specific IgE. Of these, 101 children had a history of acute reactions, including 12 with reactions to multiple tree nuts. Seventy-three patients had a history of moderate to severe reactions to tree nuts.

Double-blind placebo-controlled food challenges were offered to patients whose current specific IgE level was less than 10 kU_A/L and who had had no acute reactions to tree nut within the past year.

Food challenges were negative in 9 of 20 patients. Thus 8.9% of patients "outgrew" their tree nut allergy. Another 14 of 19 patients who had no history of tree nut reactions but had detectable levels of specific IgE also had no reaction to tree nut challenge. The remaining patients were either ineligible for challenges or declined to participate. The rate of negative challenge tests was 58% for patients with specific IgE levels less than 5 kU_A/L and 63% for those with levels of less than 3 kU_A/L.

This study shows that some children with reactions to tree nut will outgrow their allergy. The 9% rate documented includes some patients with a history of severe reactions. Food challenges may be indicated for children aged 4 years or older with no recent reactions and a current specific IgE level was less than 10 kU_A/L.

COMMENT: *Severe food allergies profoundly affect the lives of the afflicted patients and their families. The ability to predict who will outgrow this curse is highly desirable but elusive. The current study confirms that tree nut allergy can be outgrown (at least 9%), and identifies a specific IgE level of about 5 kU/L as a threshold for oral challenge--similar to the data for peanut allergy. The severity of the prior clinical reaction was not important.*
R. J. M.

Fleischer DM, Conover-Walker MK, Matsui EC, Wood RA: The natural history of tree nut allergy.
J Allergy Clin Immunol. 2005;116:1087-1093. ♦♦

Guidelines: Still a Work in Progress

PUBLISHED asthma guidelines differ in their approach to assessing asthma severity. The National Asthma Education and Prevention Program (NAEPP) guidelines emphasize patient reports of symptoms along with lung function measurements, while the Global Initiative for Asthma (GINA) guidelines consider clinical features plus asthma medications. The NAEPP and GINA approaches were compared with physician assessments in a cohort of patients with severe or difficult-to-treat asthma.

The study included 2,927 patients, age range 6 to 55 years, drawn from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) cohort. Asthma severity was assessed according to the NAEPP and GINA guidelines, and independently assessed by TENOR physicians. Agreement between the three approaches was assessed, and the severity classifications were compared with asthma-related health care utilization.

Rates of agreement with the TENOR physicians' assessment were 45% for the NAEPP classification and 59% for the GINA guidelines. Sixteen percent of cases were rated more severe by TENOR physicians than by the GINA classification, while 26% were rated more severe by GINA. The NAEPP guidelines classified 29% of cases as mild, compared with about 3% for GINA and the physicians' assessments.

Agreement was low across age groups, particularly children. Asthma-related health care utilization tended to be higher in patients whose asthma was designated moderate to severe by all three approaches. However, many patients with mild asthma according to the NAEPP guidelines had recent unscheduled office visits and other types of resource utilization.

The three approaches to classifying asthma severity yield substantially different results, with poor agreement between systems. A surprisingly large proportion of cases are rated mild by the NAEPP guidelines. Asthma-related health care utilization is significantly and positively correlated with asthma severity. Improved approaches to classifying asthma severity are needed, including information on medications and health care utilization as well as symptoms and pulmonary function.

COMMENT: *A physician's choice of asthma treatment is predicated on the assessment of its clinical severity. But there is no gold standard for assessing severity. This study compared two sets of guidelines (NAEPP and GINA) and a physician's global assessment against the health care utilization of real patients and found no agreement among them. Guidelines are still a work in progress.*
R. J. M.

Miller MK, Johnson C, Miller DP, et al: Severity assessment in asthma: an evolving concept.
J Allergy Clin Immunol. 2005;116:990-995. ♦♦

ASA Sensitivity Reflects Asthma Severity

RATES of airway remodeling in patients with asthma are highly variable. Patients with aspirin-exacerbated airway disease, or aspirin-sensitive asthma, have hyperplastic eosinophilic sinusitis with nasal polyps. A similar mechanism involving the lower airway could lead to more severe asthma with aggressive airway remodeling. Aspirin sensitivity was evaluated as a risk factor for airway remodeling in asthma.

The study included two groups of adult patients from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) cohort: 459 with ASA and 2,848 with non-aspirin-sensitive asthma. Asthma outcomes were compared between groups, including degree of airway obstruction, refractoriness to β-agonist therapy, and asthma severity.

Average postbronchodilator FEV_1 was 75.3% of predicted for patients with ASA, compared to 79.9% for those with non-aspirin-sensitive asthma. The association remained significant after adjustment for potential confounders. Patients with ASA were more likely to be classified by their physician as having severe asthma, 66% vs 49%. Aspirin sensitivity was also associated with higher rates of intubation, recent steroid burst therapy, and high-dose inhaled corticosteroid therapy.

For patients with asthma, aspirin sensitivity is associated with more severe disease, possibly reflecting an increase in upper and lower airway remodeling. Patients with ASA demonstrate reduced lung function, despite evidence of more intensive treatment. Leukotriene modifiers and other treatments should be evaluated for their impact on the development of progressive airflow obstruction in patients with ASA.

COMMENT: *This study confirms that patients with aspirin-sensitive asthma (ASA--get it?) often have a relatively severe phenotype compared to aspirin-insensitive asthmatics. Based on pulmonary function testing and response to bronchodilators and steroids (fixed obstruction), it seems they also have more airway remodeling.*
R. J. M.

Mascia K, Haselkorn T, Deniz YM, et al: Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma.
J Allergy Clin Immunol. 2005; 116:970-975. ♦♦

More Good Stuff on Aspirin

LEUKOTRIENES make a substantial contribution to the reactions to aspirin and other nonsteroidal anti-inflammatory drugs observed in patients with aspirin-exacerbated respiratory disease (AERD). This suggests that leukotriene modifier drugs (LTMDs) might affect the results of aspirin challenge tests, although discontinuation of controller medications for challenge is not practical for most patients. This study examined the effects of asthma controller medications, with or ➤➤

without LTMDs, on the outcomes of aspirin challenges in patients with AERD.

The study included 678 patients with suspected AERD who were admitted for oral aspirin challenges and desensitization between 1981 and 2004. All patients had asthma with a history of reaction to nonsteroidal anti-inflammatory drugs, along with chronic sinusitis and nasal polyposis. The prescribed controller medications being taken by the patients at the time of aspirin challenge were noted, and their effects on four potential outcomes--naso-ocular reaction, lower airway reaction, and classic upper and lower airway reaction--were analyzed.

The outcomes of aspirin challenge were significantly affected in patients using LTMDs in combination with inhaled corticosteroids and long-acting β_2-agonists, compared to patients using no controller medications. The main effect was a shift toward naso-ocular reactions only, compared with the typical upper and lower respiratory tract reaction. Use of LTMDs appeared to have the greatest impact, particularly in terms of inhibiting lower respiratory tract reactions. Systemic corticosteroids had little effect on the outcomes of aspirin challenge. Rather than completely blocking aspirin-induced reactions, LTMDs seemed to be associated with an increased rate of positive challenges.

Combinations of asthma controller medications--particularly LTMDs plus inhaled corticosteroids and long-acting β_2-agonists--can block respiratory tract reactions to aspirin in at least some patients with AERD. The higher overall rate of positive challenges in patients using LTMDs may reflect the increased use of these medications in patients with AERD. Use of LTMDs does not appear to result in false-positive challenge results.

COMMENT: *This retrospective analysis provides further insight into the problematic condition of AERD. While the authors conclude that essential controller medications do not result in false-negative challenges, the standard of comparison is historical and not absolute. The only way to prove that false-negative challenges do not occur would be to challenge the patients off of their controller drugs. Since this is not practical in most situations, we must continue to practice with the best objective data available, which the Scripps group has consistently provided over the years.*
A. M.

White AA, Stevenson DD, Simon RA: The blocking effect of essential controller medications during aspirin challenges in patients with aspirin-exacerbated respiratory disease.
Ann Allergy Asthma Immunol. 2005;95:330-335. ♦♦

SLIT: Getting Ready for Prime Time!

HAZELNUT is a common cause of systemic allergic reactions. Because it is widely used in packaged foods, complete avoidance of hazelnut is difficult. Specific immunotherapy has been suggested but carries a high risk of systemic reactions. A randomized trial of sublingual immunotherapy for hazelnut allergy is reported.

The study included 23 patients with a history of hazelnut allergy, confirmed by skin prick testing and double-blind placebo-controlled food challenge. Patients were randomly assigned to active SLIT using standardized hazelnut allergen, including a 4-day in-hospital rush buildup phase; or placebo SLIT. Both groups underwent a standardized home maintenance phase as well. Double-blind, placebo-controlled food challenges were repeated after 8 to 12 weeks of treatment.

Mean hazelnut-specific IgE level at baseline was 5.34 kU/L in the SLIT group and 6.41 kU/L in the placebo group; most patients had pollen allergies as well. On efficacy assessment, the mean quantity of hazelnut necessary to cause an objective reaction increased from 2.29 to 11.56 g in the SLIT group, compared to no significant change (3.49 vs 4.14 g) in the placebo group. Nearly half of patients in the SLIT group were able to tolerate 20 mg of hazelnut, the highest planned dose; compared with 9% of the placebo group. All patients reached the planned maximal dose of hazelnut allergen during the buildup phase--just three systemic reactions occurred in a total of 1,466 doses. Both groups had reductions in specific IgE, but IgG_4 and interleukin-10 levels increased only in the active SLIT group.

This trial demonstrates the efficacy of SLIT in increasing the allergen dose necessary to induce reactions in patients with hazelnut allergy, based on double-blind placebo-controlled food challenge. The standardized SLIT regimen described is well tolerated and effective in patients with histories of both local and systemic reactions. Further studies are needed to establish the long-term efficacy of SLIT for food allergies.

COMMENT: *These Spanish researchers report the first well-done double-blind, placebo-controlled study of SLIT for the treatment of nut allergy. After a rapid buildup schedule that took only 4 days, patients continued the maintenance dose until re-challenge with hazelnut after 8 to 12 weeks. The group receiving active hazelnut SLIT was able to tolerate over five times the amount of hazelnut, compared with pretreatment challenges. Impressive changes in immunologic parameters were also seen in the active treatment group. This study provides hope for our patients with severe nut allergy.*
S. M. F.

Enrique E, Pineda F, Malek T, et al: Sublingual immunotherapy for hazelnut food allergy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract.
J Allergy Clin Immunol. 2005;116:1073-1079. ♦♦

When Viral Infections Wane, Allergy May Not

INFECTION with respiratory syncytial virus in infancy is associated with excessive production of Th2 cytokines. This may lead to an increased risk of asthma, and possibly of allergic sensitization as well. Levels of cytokines, chemokines, and eosinophil cationic protein (ECP) were measured in nasopharyngeal secretions ➤➤

from infants with RSV or other respiratory viral infections.

The study included infants aged 7 months or younger, seen in the emergency department for respiratory infection with RSV, influenza virus, or parainfluenza virus during two consecutive RSV seasons. Samples of nasopharyngeal secretions were obtained for assessment of interleukin (IL)-4, IL-5, and interferon-γ; macrophage inflammatory protein 1β (MIP-1β), a T-cell chemoattractant; and ECP. The findings were compared with those of a group of healthy infants with no history of infection.

The analysis included 39 infants with RSV infection, 9 with influenza or parainfluenza virus infection, and 50 healthy controls. The presence of RSV was associated with significantly increased levels of IL-4, MIP-1β, and ECP, compared with controls. Within the RSV group, the increase in IL-4 was significantly greater in infants aged 3 months or younger, compared with those older than 3 months. Younger infants with influenza virus or parainfluenza virus infection had a Th2-like response similar to that observed in the RSV group.

Infants with RSV infection show evidence of a local Th2 response, accompanied by eosinophil infiltration and activation. This pattern is most pronounced in infants aged 3 months or younger--in that age group, a similar response also occurs in infants with influenza or parainfluenza infection. The findings suggest an age-dependent immune response to viral respiratory infections, which is strongest in very young infants and not specific to RSV.

COMMENT: *Respiratory syncytial virus infections in infancy have been associated with a predilection for asthma and allergic sensitization. These researchers studied the immune responses of children seen in the emergency room with viral respiratory illnesses. Although it was not surprising that Th2 cytokines IL-4, IL-5, and MIP-1β were higher in the younger infants with RSV infections, there was also a comparable response in younger infants after influenza and parainfluenza virus infections. In very young infants, respiratory infections with a variety of viruses can trigger the Th2 immune response.*
S. M. F.

Kristjansson S, Bjarnarson SP, Wennergren G, et al: Respiratory syncytial virus and other respiratory viruses during the first 3 months of life promote a local Th2-like response.
J Allergy Clin Immunol 2005;116:805-811. ♦♦

FeNO Predicts EIB

EXERCISE-induced bronchoconstriction (EIB) is a central feature of asthma in children and an important indicator of uncontrolled disease. A more practical alternative to exercise testing would be diagnostically useful. Measurement of fractional concentration of exhaled nitric oxide (FeNO) was evaluated as a predictor of EIB in children with asthma.

The study included 111 children, aged 6 to 15 years, with stable, mild to moderate asthma: 72 boys and 39 girls, mean age 12 years. Each patient underwent FeNO measurement, followed by a standardized exercise challenge test. Twenty-seven percent of the children had a 15% or greater decrease in FEV_1 on exercise challenge testing, the criterion for EIB.

Median FeNO value was 15.0 ppb overall: 29.5 ppb in patients with EIB vs 10.2 ppb in those with no reaction to exercise testing. The most accurate FeNO cutoff values for EIB were 21 ppb in children not receiving inhaled steroids and 12 ppb in those receiving steroids. Areas under the curve were 0.77 and 0.744, respectively. At a steroid dose equivalent to 800 µg of budesonide or higher, a FeNO value of 10 ppb or higher was 100% sensitive and specific for EIB.

Measuring FeNO provides useful information on the likelihood of EIB in children with asthma. The defined cutoff values provide a predictive value of nearly 90%, depending on whether or not the patient is receiving steroids. Using FeNO as a screening test could help to avoid a large number of negative exercise tests.

COMMENT: *Measurement of FeNO has become a well-accepted marker of asthma control, providing information independent of symptoms and spirometry. In this study, a FeNO level of less than 20 ppb in steroid-naive children accurately excluded EIB 90% of the time. Add suspected pediatric EIB to the list of situations in which FeNO measurement could provide useful information to guide therapy.*
S. A. T.

Buchvald F, Hermansen MN, Nielsen KG. Bisgaard H: Exhaled nitric oxide predicts exercise-induced bronchoconstriction in asthmatic school children.
Chest. 2005;128:1964-1967. ♦♦

FeNO: An Important Monitoring Strategy

GUIDELINES for corticosteroid treatment for asthma generally rely on symptoms, which are not necessarily a good indicator of the patient's level of airway inflammation. Fraction of exhaled nitric oxide is emerging as a useful, noninvasive indicator of airway inflammation. This study compared symptom-based and FeNO-based approaches to guiding inhaled steroid treatment for children with asthma.

The randomized trial included 85 pediatric patients with atopic asthma, stratified for baseline FeNO (30 ppb or higher vs less than 30 ppb) and for inhaled corticosteroid dose (equivalent to 400 µg budesonide or higher vs less than 400 µg). Steroid treatment was guided by FeNO and symptoms in one group, and by FeNO only in the other group. Patients were evaluated every 3 months for 1 year--the cutoff points for dose adjustment were a cumulative symptom score of 14 over the past 2 weeks or a FeNO level of 30 ppb. Assessments included airway hyperresponsiveness and FEV_1, measured at the beginning and end of the study; and cumulative steroid dose.

There was no significant difference in mean cumulative inhaled steroid dose between the two groups--both had a mean dose increase of approximately 170 µg/d. There was a small increase in FEV_1 for patients ➤➤

whose treatment was guided by FeNO plus symptoms, but the difference was not significant compared to patients whose treatment was guided by symptoms only. The two groups were also similar in terms of change in symptom scores.

Airway hyperresponsiveness improved to a significantly greater extent in the FeNO group: their mean increase in PD_{20} was 2.5 doubling doses, compared with 1.1 doubling doses in the symptom group. The total number of severe exacerbations was 8 in the FeNO group, compared with 18 in the symptom group. Geometric mean FeNO increased by 32% in children whose treatment was guided by symptoms only, compared with no significant change in the FeNO group.

Exhaled nitric oxide measurement is a valuable guide to monitoring inhaled corticosteroid treatment in children with asthma. Compared with a symptom-based approach, an algorithm incorporating FeNO improves airway hyperresponsiveness without increasing steroid dose. Further study will help to clarify the optimal frequency of follow-up visits and FeNO measurements and the FeNO cutoffs for dose titration.

COMMENT: *This yearlong study in children allowed for another adjunctive way to assess airway inflammation in asthma. The group in which FeNO was used to guide steroid dose showed a significant decrease in bronchial hyperresponsiveness by 1.4 doubling doses of methacholine, along with a decrease in FeNO. There were also fewer severe exacerbations in the FeNO-directed group. This was achieved with comparable doses of inhaled corticosteroid. These data--along with studies published in adults (see Smith AD, et al: N Engl J Med. 2005;352:2163-2173)--continue to lead us to incorporate exhaled nitric oxide as an important monitoring strategy.*
B. E. C.

Pijnenberg MW, Bakker EM, Hop WC, De Jongste JC: Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial.
Am J Respir Crit Care Med. 2005:172:831-836. ♦♦

Premature Birth's Imprint on the Airway

PREMATURE infants with bronchopulmonary dysplasia (BPD) are at risk of developing asthma-like symptoms with airway hyperresponsiveness (AHR). The mechanisms underlying these associations are unclear. This study examined the factors associated with pediatric asthma and AHR among children with a history of preterm birth and BPD.

The study included two Norwegian population-based cohorts of children born at 28 weeks' gestation or less or with birth weights of 1,000 g or less. A total of 81 preterm infants were included--mean age at follow-up evaluation was 17.7 years in one cohort and 10.6 years in the other. In the neonatal period, BPD was absent in 19 subjects, mild in 38, and moderate to severe in 24. Rates of asthma and AHR were assessed, along with contributing factors such as inheritance, allergy, eosinophilic airway inflammation, and exposure to cigarette smoke. The findings were compared with those of 81 term-born controls.

Preterm birth was significantly associated with maternal smoking during pregnancy and maternal history of asthma. Current asthma was present in 27% of children in the preterm group, compared with 12% of controls. For term-born children, asthma was associated with a higher rate of allergy, increased eosinophilic cells, and higher levels of urinary eosinophilic protein X. In contrast, subjects in the preterm group had significantly lower FEV_1, increased AHR, and increased levels of urinary leukotriene metabolite E4. In the term group, asthma and AHR were associated with inheritance, allergy, and cigarette exposure. For preterm subjects, this typical pattern of associations was either weaker or absent--current asthma was unrelated to either maternal smoking or with active smoking in adolescence. Instead, AHR in the preterm group was associated with BPD and with prolonged need for oxygen therapy during the neonatal period.

The typical pattern of factors associated with asthma may not apply to young patients with a history of preterm birth and BPD. The severity of BPD and the duration of oxygen treatment during the newborn period are the most important determinants of AHR after preterm birth. The respiratory abnormalities observed in children born before term may represent a distinct clinical entity, perhaps involving structural sequelae rather than airway inflammation.

COMMENT: *We have recognized for decades that premature infants with BPD may have an asthma-like illness later in childhood. In this important follow-up study, it would appear that these children have predominantly nonallergic mechanisms and genotype underlying their AHR. These observations have important prognostic and therapeutic implications. Not all children with AHR are created equal!*
A. M.

Halvorsen T, Skadberg BT, Eide GE, et al: Characteristics of asthma and airway hyper-responsiveness after premature birth.
Pediatr Allergy Immunol. 2005:16:487-494. ♦♦

Where There's Smoke, There's Fire!

MOST studies of exposure to second-hand smoke as a cause of asthma exacerbation have focused on children. This study evaluated the contribution of second-hand smoke to asthma exacerbations in adults.

The study was based on a cohort of 778 nonsmoking adults hospitalized for asthma, drawn from the membership of the Kaiser-Permanente managed care organization. One hundred eighty-nine patients wore a nicotine badge for 7 days, providing a direct measure of their exposure to second-hand smoke. One hundred thirty-eight patients provided hair samples for measurement of nicotine and cotinine levels, permitting measurement of exposure over the past 3 months.

Most patients were exposed to second-hand smoke--hair analyses suggested a 60% prevalence of exposure over the past month and an 83% prevalence over the past 2 to 3 months. Exposure was higher for ➤➤

patients with severe asthma requiring ICU admission. Subjects with the highest levels of nicotine exposure over the past week had higher asthma severity--mean increase in severity score for patients in the highest tertile of nicotine level was 1.56 points, controlling for other factors. Patients in the higher two tertiles of exposure over the past month had a higher prospective risk of hospitalization for asthma, hazard ratio 3.73.

Most adult patients hospitalized for asthma have recent exposure to second-hand smoke. Patients with higher levels of passive smoking have more severe asthma and are at higher risk of hospitalization. Asthma patients should be screened for and advised to minimize exposure to second-hand smoke.

COMMENT: *There is already an extensive literature demonstrating that passive smoking is associated with an increased risk of asthma in children and adults. This study demonstrates that subjects in the highest tertile of personal exposure to nicotine have more severe asthma. Subjects with higher levels of hair nicotine over the previous month had a higher risk of being hospitalized with asthma. These results certainly support efforts to prohibit smoking in public places.*
E. J. B.

Eisner MD, Klein J, Hammond SK, et al: Directly measured second-hand smoke exposure and asthma health outcomes.
Thorax. 2005;60:814-821. ♦♦

What Have We Learned About Anticholinergics?

GUIDELINES for treatment of acute severe or life-threatening asthma include the combined use of inhaled β_2-agonists and anticholinergics. However, this recommendation is based on a relatively small number of randomized trials. An updated review and meta-analysis of the effectiveness of the combination of β_2-agonists and anticholinergics is reported.

A search of the literature through April, 2005, identified 32 randomized controlled trials comparing the use of β_2-agonists and anticholinergics vs β_2-agonists alone for the treatment of acute asthma in the emergency department. The studies included a total of 3,611 patients, 1,564 pediatric and 2,047 adult; ipratropium bromide was the anticholinergic most frequently tested. Outcomes assessed included spirometric results in 26 studies and hospital admission in 20.

The combination of inhaled β_2-agonists and anticholinergics was associated with a reduction in hospital admission rate. The difference was significant in both children and adults--relative risks were 0.73 and 0.68, respectively. Meta-analysis also found significant improvement in spirometric parameters, measured 1 to 2 hours after treatment, in patients receiving the combination treatment.

The most recent available data support the combined use of β_2-agonists and anticholinergics for the treatment of acute asthma in the emergency department. Early use of this combination therapy yields a 30% reduction in hospital admission rate in adults as well as children. Adding an anticholinergic is more likely to be of benefit for patients with moderate to severe airway obstruction treated on multiple fixed-dose protocols.

COMMENT: *This meta-analysis confirms the current recommendations to treat acute asthma with a combination of inhaled short acting beta-2 agonists and anticholinergics, particularly for patients with acute severe asthma. Early administration leads to a 30% reduction in hospital admissions. Baseline severity of the asthma and aggressiveness of the anticholinergic protocol influenced the extent of the benefit achieved.*
E. J. B.

Rodrigo GJ, Castro-Rodriguez JA: Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis.
Thorax. 2005;60:740-746 ♦♦

Mast Cell Myositis: A Novel Concept

THE pathologic findings of asthma include hypertrophy of the airway smooth muscle and mast cell infiltration of the bronchial mucosa. Mast cell distribution and activation were assessed in varying compartments of the bronchial mucosa, including comparison of patients with allergic vs nonallergic asthma.

The investigators studied bronchial biopsy specimens from 11 patients with allergic asthma, 9 patients with nonallergic asthma, and 7 healthy controls. The tryptase-specific antibody AA1 was used to stain for mast cells, with extracellular deposition rated on a semi-quantitative scale. Mast cell density was compared in the epithelial, lamina propria, and smooth muscle compartments. The findings were analyzed in terms of airway remodeling.

Specimens from patients with allergic asthma showed significantly greater airway smooth muscle thickening, compared to patients with nonallergic asthma. Both asthmatic groups had increased mast cell numbers in all three compartments, compared with controls. However, extracellular deposition of mast cell deposition products in the lamina propria and smooth muscle compartments was higher in specimens from patients with allergic asthma. In this group, mast cell number and extracellular deposition of mast cell products were correlated with structural changes in the bronchial mucosa--specifically, with the thickness of the tenascin and laminin layers.

This study documents differences in the distribution of mast cells in the bronchial mucosa of patients with allergic vs nonallergic asthma. Allergic asthma is associated with increased numbers and activation of mast cells in the airway smooth muscle compartment, together with increased airway thickening. Together with previous studies, the results suggest that mast cells play a causal role in the structural airway changes taking place in allergic asthma.

COMMENT: *These authors studied the distribution of mast cells and signs of their activation in different compartments in the bronchial mucosa of patients* ➤➤

with allergic and nonallergic asthma in relation to airways remodeling. In this respect, it is tempting to speculate that within airway smooth muscle, mast cells may be activated and release inflammatory products that facilitate hyperresponsiveness and stimulate smooth muscle cell proliferation. These investigators show large differences between allergic and nonallergic asthmatics as to mast cell activation and smooth muscle thickness, suggesting a close relationship between mast cell infiltration of the smooth muscle layer and allergy. The concept of mast cell myositis is a novel one in the pathogenesis of asthma.
E. J. B.
Amin K, Janson C, Boman G, Venge P: The extracellular deposition of mast cell products is increased in hypertrophic airways smooth muscles in allergic asthma but not in nonallergic asthma.
Allergy. 2005;60:1241-1247. ♦♦

Praise the Lord and Pass the Epinephrine...Quickly!

TIMELY use of epinephrine is a critical intervention for children experiencing anaphylactic reactions. Despite the high potential for anaphylactic events to occur at schools, little is known about the rate of such events or whether schools are prepared to deal with them. Epinephrine use and other factors related to management of anaphylaxis in schools were assessed in a statewide study

School nurses in 109 Massachusetts school districts were asked to complete a "Report of EpiPen Administration" form each time epinephrine was administered at school. Forty-eight districts reported at least one use of epinephrine during the 2-year study period, including 22 districts reporting multiple administrations---from 2 to 24. Nearly half of the recipients were elementary school-age children. More the one-third of treated subjects had multiple allergies, most commonly to tree nuts and peanuts. Sixty percent of reactions resulted from eating some type of food, but the specific allergen was known in only 43% of food-related reactions.

In nearly one-fourth of cases, there was no known history of life-threatening allergy, and thus no specific care plan or doctor's order for epinephrine use. About three-fourths of the reactions met absolute indications for epinephrine use. Average time to epinephrine administration was 9 minutes for subjects with known allergic conditions and 14 minutes for those whose allergy was undiagnosed. Eight percent of subjects were not transported to an emergency department after receiving epinephrine.

Epinephrine administration in schools appears relatively frequent. In many cases, the affected student has no known history of allergic reactions. Most reactions occur after eating, although the specific allergen is often unknown. Massachusetts now requires that all epinephrine administrations occurring at school be reported to the public health department, which should produce additional useful epidemiologic data.

COMMENT: *As allergists we share rhinitis with ENTs and primary care physicians and asthma with pulmonologists, but food allergy and anaphylaxis are our own. This article evaluated the use of epinephrine in schools over a 2-year period. Several important points could be made from this article so I encourage all pediatric allergists to read it. First, the average time to epinephrine administration was 10 minutes. We would all agree this may be too long in some cases and that epinephrine should be more readily available. Second, at least 25% of all reactions were secondary to nut exposure. It would be interesting to see the rates of epinephrine rates in newer "peanut-free" schools. One would assume with improved awareness, the outcomes would be different.*
T. L. M.
McIntyre CL, Sheetz AH, Carroll CR, et al: Administration of epinephrine for life-threatening allergic reactions in school settings.
Pediatrics. 2005;116:1134-1140.

Recombinant C1INH: Just Around the Corner, or Over the Cliff?

PATIENTS with hereditary angioedema (HAE) have deficiency of C1 esterase inhibitor (C1INH), the plasma protein C1 inhibitor. The result is recurrent, potentially life-threatening episodes of submucosal and/or subcutaneous tissues. A recombinant human C1INH has recently been developed from the milk of transgenic rabbits. Initial experience with rhC1INH in patients with HAE is reported.

Twelve asymptomatic patients with HAE participated in the study. On two separate occasions, patients received the study medication at doses of 6.25 to 100 U/kg IV. Safety and tolerability were evaluated, and pharmacokinetic and pharmacodynamic analyses were carried out.

No adverse events were attributed to the administration of rhC1INH. Analysis of functional C1INH showed a dose-dependent increase in maximum concentration and time at a functional concentration of over 0.4 U/mL. After the 100 U/kg dose, functional C1INH level remained above 0.04 U/mL for a mean of 9.2 hours. Pharmacodynamic analysis showed an initial dose-dependent drop in mean normalized C4 concentration after infusion of the study drug. This was followed by a dose-dependent increase, peaking at 201% after the 100 U/kg dose. At this dose, clearance of rhC1INH was approximately 13 mL/min, with a half-life of 3 hours and distribution volume of 3 L. The drug's biologic activity occurred through a dose-dependent increase in C4 antigen, with a corresponding decrease in levels of cleaved C4.

Initial experience suggests that rhC1INH is a safe drug with relevant biologic activity in asymptomatic patients with HAE. Clearance occurs in dose-dependent fashion, with a half-life of approximately 3 hours. In appropriate doses, rhC1INH should provide functional C1INH levels for long enough to stop the progression of edema. Clinical trials in symptomatic HAE patients are needed. ➤➤

COMMENT: *Although HAE is uncommon, it is a debilitating, life-threatening condition that is devastating to affected families. These Dutch researchers report the pharmacokinetics and dynamics of a new recombinant human Cl esterase inhibitor. Although the half-life of this product is only 3 hours, the impressive results provide hope to our patients with HAE.*
S. M. F.

van Doorn MBA, Burgraaf J, van Dam T, et al: A phase I study of recombinant human Cl inhibitor in asymptomatic patients with hereditary angioedema.
J Allergy Clin Immunol. 2005;116:876-883. ♦♦

Allergy Is Not an All-or-Nothing Phenomenon

ON assessment of IgE-mediated sensitization to allergens, patients are typically classified as either sensitized or not. However, this dichotomous classification does not perform well in predicting the risk of clinical reactions. Quantitative IgE antibody measurements were analyzed for their ability to predict wheezing in preschool children.

The study included 512 children from a U.K. population-based birth cohort study. Children were followed up to age 5, including parental reports of wheezing, skin tests, lung function studies, and measurement of specific serum IgE levels. Levels of IgE antibodies to common allergens were analyzed as predictors of the occurrence and persistence of wheezing and of lung function parameters.

As levels of specific IgE antibodies to mite, cat, and dog increased, so did the risk of current wheezing. On summed analysis of all three antibodies, the probability of current wheezing increased by 1.33-fold per logarithmic unit increase. A similar association was noted for probability of reduced lung function. For sensitized children, the sum of specific IgE antibodies to mite, dog, and cat was the strongest predictor of current wheezing, odds ratio 1.28. Current wheezing was unrelated to wheal size on skin testing. The summed IgE levels at age 3 were also associated with the risk of persistent wheezing at age 5, with a 2.15-fold increase per logarithmic unit increase.

Quantitative analysis of specific IgE levels to common allergens is a significant predictor of wheezing and reduced lung function in preschool children. For children who wheeze in the first 3 years, the sum of specific IgE antibodies to mite, cat, and dog might be a clinically useful predictor of persistent wheezing.

COMMENT: *Can the probability of wheezing in children be predicted? These European researchers used data collected from a large birth cohort to answer this question. Levels of specific IgE to environmental allergens were useful to predict increasing risk of wheezing, although total IgE or even allergy skin tests were not. Interestingly, the odds ratios where more predictive if all three environmental allergen values were summed. Not only is the probability of wheezing in children associated with sensitization to environmental allergens, but the risk of reduced lung function increases with increasing levels of these allergen specific IgE values.*
S. M. F.

Simpson A, Soderstrom L, Ahlstedt S, et al: IgE antibody quantification and the probability of wheeze in preschool children.
J Allergy Clin Immunol. 2005;116:744-749. ♦♦

Maintenance and Reliever Therapy, All in One!

COMBINED treatment with an inhaled corticosteroid and a long-acting β_2-agonist has been a key advance in asthma therapy. Combining budesonide and formoterol for maintenance therapy and symptom relief might offer significant advantages, including the possibility of simplified therapy using a single inhaler. A 12-month randomized trial was performed to examine the efficacy of combined budesonide/formoterol therapy for asthma.

The open-label, dose-titration study included 2,143 adolescent and adult patients with asthma. The patients' mean FEV_1 was 73% predicted; mean inhaled corticosteroid dosage was 884 µg/d. Patients in the intervention group received budesonide/formoterol, two 160/4.5 µg inhalations twice daily, with additional inhalations as needed. Controls received salmeterol/fluticasone, 50/250 µg twice daily, plus salbutamol as needed. To parallel clinical practice, physicians were allowed to titrate the patient's maintenance dose after the first 4 weeks. The main outcome of interest was time to first severe asthma exacerbation.

Risk of severe exacerbation was 25% lower in the budesonide/formoterol group, with a similar reduction in risk of severe exacerbation excluding unscheduled visits. The annual rate of severe exacerbations was 0.24 events/patient/y with budesonide/formoterol vs 0.31 with salmeterol/fluticasone. Use of as-needed medications was 45% lower in the budesonide/formoterol group; inhaled corticosteroid dosage was comparable between groups. Both treatments were safe and yielded similar improvements in health-related quality of life.

A combination approach using budesonide/formoterol for maintenance and as-needed therapy may provide a simplified alternative for asthma treatment. Budesonide/formoterol can reduce the rate of severe exacerbations; most other outcomes are similar to those of salmeterol/fluticasone plus as-needed salbutamol. Budesonide/formoterol may allow single-inhaler therapy for asthma.

COMMENT: *This study was not blinded but included 2,143 adolescents and adults showing a significant decrease in the number of severe exacerbations and improvement in quality of life and FEV_1 when budesonide/formoterol was used in regular and as-needed therapy. The mean inhaled corticosteroid dose, expressed as beclomethasone dipropionate equivalents was lower in the budesonide group. This study supports three previously published blinded studies of over 5,000 patients. When the budesonide/formoterol combi-* ➤➤

nation becomes available in the United States, it could potentially allow for more effective control of moderate to-severe persistent asthma in that patients would only require one inhaler.
B. E. C.
Vogelmeier C, D'Urzo A, Pauwels R, et al: Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option?
Eur Respir J. 2005;26:819-828. ♦♦

Cleanliness Is Next to Godliness...Or Is It?

GOOD household sanitation--including measures to improve ventilation and air quality while avoiding dampness and allergen exposure--would be expected to decrease symptoms in asthmatic children. However, this assumption may be questioned in the era of the "hygiene hypothesis." The effects of domestic hygiene and dampness on allergic symptoms in children were investigated.

The study included 996 primary school-age children in Australia. Based on a parental questionnaire regarding home hygiene practices, each child's home was scored in terms of cleanliness and ventilation. Wheezing, asthma, and other allergic symptoms were assessed.

Homes with higher cleanliness scores had lower levels of molds, before as well as after adjustment for the age of the home. Homes with higher scores for ventilation also had less mold, fewer damp patches, and less condensation. In contrast, children whose homes had high cleanliness scores had increased rates of current wheezing and rhinoconjunctivitis. These associations remained significant even after adjustment for family history of asthma, passive smoke exposure, and home dampness.

Children living in cleaner homes may actually have higher rates of wheezing and rhinoconjunctivitis. This is despite the finding that homes with higher cleanliness scores have lower rates of mold and dampness. More research would be needed to demonstrate a causal relationship.

COMMENT: *For decades conventional wisdom has suggested that "cleanliness is next to Godliness." While this may be somewhat of an exaggeration, this paper suggests that poor hygiene practices are associated with less allergic airway disease. These observations may be provocative, but should not detract from well-founded environmental control measures in affected children, such as tobacco and allergen avoidance.*
A. M.
Zhang G, Spickett J, Lee A-H, et al: Household hygiene practices in relation to dampness at home and current wheezing and rhino-conjunctivitis among school age children.
Pediatr Allergy Immunol. 2005;16:587-592. ♦♦

CLINICAL TIDBITS

Allergic Rhinitis and Ear Pain in Flight

THE authors have noted an increase in ear pain among Japanese air force trainees undergoing hypobaric chamber training. A 9-year experience with hypobaric chamber training was reviewed to evaluate the possible association between ear pain and allergic rhinitis. In a series of more than 7,000 trainees, the rate of ear pain during hypobaric chamber training was 6.1%. Ear pain occurred most frequently in the spring. A subsequent survey study suggested that trainees with allergic rhinitis were more likely to complain of ear pain in the spring. Patients with allergic rhinitis are likely at increased risk of ear pain in response to pressure changes during air travel.

COMMENT: *These data confirm clinical observations that subjects with allergic rhinitis are at increased risk of ear pain--and I would add sinus pain--with barometric pressure change associated with flight, and probably with diving as well. This may not be a novel observation, but statistical confirmation of the association is noteworthy. The real question I face is what therapy is consistently effective in minimizing the problem.*
D. K. L.
Ohrui N, Takeuchi A, Tong A, et al: Allergic rhinitis and ear pain in flight.
Ann Allergy Asthma Immunol. 2005;95:350-353. ♦♦

Food Allergy and Eosinophilic Esophagitis

PATIENTS with eosinophilic esophagitis (EE) experience symptoms similar to those of gastroesophageal reflux disease, but do not respond to acid-reducing drugs. Skin prick and patch testing were performed to examine the role of food allergies in a series of 146 children with EE. In 39 cases, EE was clearly related to food allergy--follow-up biopsies were normal after elimination of the offending food, and became abnormal again after the food was reintroduced. Overall, 77% of patients had resolution of their EE after at least 6 weeks of dietary restriction based on the results of allergy testing. The authors present an algorithm of their approach to allergy testing and food elimination in patients with EE.

COMMENT: *The increasing prevalence and recognition of eosinophilic esophagitis will result in more patients referred to allergists/immunologists for evaluation. The published results of food testing by prick/percutanous skin testing or in vitro specific-IgE testing suggest that food sensitivity plays a role in a minority of patients. These investigators suggest that patch testing may need to be added to the evaluation to better detect responsible foods. A more aggressive approach with diet is a consideration in these challenging patients.*
D. K. L.
Spergel JM, Andrews T, Brown-Whitehorn TF, et al: Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests.
Ann Allergy Asthma Immunol. 2005;95:336-343. ➤➤

Allergen-Contaminated Nebulizers

A previous report described two patients with life-threatening asthma exacerbations apparently related to the contamination of their nebulizers with cockroach allergen. The prevalence of allergen contamination was assessed as part of a study of nebulizer use by inner-city children with asthma. Of 17 nebulizer reservoirs sampled, 5 had measurable levels of cat, dog, cockroach, and/or mouse allergen. Nebulizer setups placed as positive controls in homes with pets became contaminated with dog or cat allergen. Storing nebulizer setups in plastic bags may reduce the potential for allergen contamination.

COMMENT: *This report provides another potential explanation of why a patient may not respond to appropriate therapy. The clinical relevance of the levels of allergen detected is not known for the most part, but the possibility of inhaling allergen during an asthma treatment should be kept in mind. This is an allergen "sneak attack."*
D. K. L.
Bollinger ME, Butz A, Mudd K, Hamilton RG: Contamination of nebulizers with environmental allergens.
Ann Allergy Asthma Immunol. 2005;95:429-432. ♦♦

Computer Games and Spirometry

AN interactive computer game was developed to aid in teaching spirometry to preschool-aged children. The "multiple-target" game was designed to teach a full forced vital capacity maneuver in stepwise fashion. Using the game, healthy and asthmatic children aged 2.5 to 6.5 years were able to perform adequate spirometry tests compatible with American Thoracic Society/European Respiratory Society recommendations. In asthmatic children, severity scores were correlated with longer expiration times and lower values for forced expiratory flow at 50% of vital capacity. Computer games can be a valuable tool for coaching young children to perform spirometry.

COMMENT: *Using an animated computer game, these authors were able to obtain remarkably accurate spirometry measurements in asthmatic and nonasthmatic children as young as 2.5 years. Although additional validation of this coaching method is necessary, the availability of a routine objective assessment of lung function in the 2.5- to 5-year-old age group would be of tremendous value to practicing allergists.*
S. A. T.
Vilozni D, Barak A, Efrati O, et al: The role of computer games in measuring spirometry in healthy and "asthmatic" preschool children.
Chest. 2005;128:1146-1155. ♦♦

What Works Against Fire Ants?

DESPITE the increasing problem of systemic reactions to fire ant stings, few studies have evaluated strategies for personal protection. In experiments using dolls, any type of sock reduced the number of fire ants reaching the level of the skin and increased the time needed for ants to reach the skin. In contrast, insect repellants and other chemicals had little effect in deterring ants. Wearing socks or tights seems to provide a simple approach to protecting against fire ant stings.

COMMENT: *Sometimes simple is elegant! This paper provides us with a practical, cost-effective solution to a significant problem. Since the at-risk population appears to be increasing, physician awareness of personal protection measures will become more important.*
A. M.
Goddard J: Personal protection measures against fire ant attacks.
Ann Allergy Asthma Immunol. 2005;95:344-349. ♦♦

Montelukast in Cystic Fibrosis

MANY inflammatory mediators contribute to the pulmonary damage in cystic fibrosis (CF), including cysteinyl leukotrienes. A randomized, crossover trial was performed to assess the benefits of montelukast therapy for patients with CF. Compared to placebo, montelukast was associated with significant improvement in cough and wheezing scores as well as in FEV_1, peak expiratory flow, and forced expiratory flow between 25% and 75%. Serum and sputum inflammatory markers decreased as well, including eosinophil cationic protein and interleukin-8. Montelukast appears to reduce symptoms and improve pulmonary function in patients with CF.

COMMENT: *Since our CF patients are living longer, any methods of potentially improving quality of life are important. This small but provocative study suggests that we may have overlooked a simple and safe method of improving lung function in patients with CF. Why didn't I think of this?!*
A. M.
Stelmach I, Korzeniewska A, Stelmach W, et al: Effects of montelukast treatment on clinical and inflammatory variables in patients with cystic fibrosis.
Ann Allergy Asthma Immunol. 2005;95:372-380. ♦♦

Amantadine Resistance is a Scary Reality!

AMANTADINE and rimantadine are important drugs for the prevention and treatment of influenza A. Isolates of influenza A virus submitted to the World Health Organization's surveillance network were analyzed to assess trends in resistance to adamantine drugs. From the mid-1990s to the mid-2000s, the frequency of adamantane-resistant viruses increased by more than 30-fold. More than 60% of resistant viruses isolated since 2003 came from Asia. The rising incidence of adamantane-resistant influenza A virus underscores the need for caution in prescribing amantadine and rimantadine.

COMMENT: *These authors screened more than 7,000 influenza A field isolates for drug resistance. A significant increase in the proportion of resistant viruses was noted: from 0.4% in 1994-95 to 12.3% in 2003-04. As clinicians involved in immunity, we should be aware of the importance of recognizing the emergence and worldwide spread of drug-resistant viruses.*
E. J. B.
Bright RA, Medina M-j, Perez-Oronoz G, et al: Incidence of adamantine resistance among influenza A (H3N2) viruses isolated worldwide from 1994-2005: a cause for concern.
Lancet. 2005;366:1175-1181. ♦♦

REVIEWS OF NOTE

COMMENT: *The aim of this excellent review was to identify and assess comparative studies of the efficacy and effectiveness of influenza vaccines in individuals aged 65 years or older. The findings indicate that the effectiveness of trivalent inactivated influenza vaccines in the elderly is modest, irrespective of the setting, outcomes, population and study design. Further study is needed to determine the effect of vaccination in high-risk groups.*
E. J. B.
Jefferson T, Rivetti D, Rivetti A, et al: Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review.
Lancet. 2005;366:1165-1174. ♦♦

COMMENT: *This paper reviews natural T-regulatory cell biology and gives current concepts regarding T-regulatory cells in asthma, response to immunotherapy, and the hygiene hypothesis.*
B. E. C.
van Oosterhout AJM, Bloksma N: Regulatory T-lymphocytes in asthma.
R. J. M.
Eur Respir J. *2005.*;26:918-932. ♦♦

COMMENT: *A review of a timely topic that affects many patients in our offices every day. This evidence-based paper is complete with useful algorithms and, in my opinion, is a must-read.*
Ford CN: Evaluation and management of laryngopharyngeal reflux.
JAMA. 2005;1534-1540. ♦♦

COMMENT: *Glucocorticoids have been used as potent anti-inflammatory therapeutic agents for over 50 years, but not without drawbacks from the other edge of the sword. This article explains how recent research has teased out three different intracellular signaling mechanisms of the anti-inflammatory and immunosuppressive actions. It is not yet clear whether the desired effects and the undesirable side-effects occur by separate mechanisms. If so, however, one can imagine designer steroids that would target one of these mechanisms and have a more favorable therapeutic index.*
R. J. M.
Rhen T, Cidlowski JA: Antiinflammatory action of glucocorticoids--new mechanisms for old drugs.
N Engl J Med. 2005;353:1711-1723. ♦♦

COMMENT: *The concept of DNA-allergen vaccines is supported by an extensive body of science, animal data, and theory. Allergist/immunologists practicing today may not have the opportunity to use DNA-based immunotherapy, but knowing about this approach to immune modulation is an important part of our role as 21st century immunologists. This review is well-written and readable.*
D. K. L.
Tsalik EL: DNA-based immunotherapy to treat atopic disease.
Ann Asthma Allergy Immunol. 2005;95:403-410. ♦♦

COMMENT: *This short, concise, and well-referenced review of acute asthma management of children in the emergency department (ED) is worth reading. Probably few community-based allergists see children with acute asthma, themselves, in the hospital ED today. However, all of us should be aware of current management trends in this setting.*
J. A. A.
Chipps BE, Murphy KR: Assessment and treatment of acute asthma in children.
J Pediatr. 2005;147:288-294. ♦♦

COMMENT: *This important prospective study from the Netherlands better defines the nature of celiac disease (CD) today. The changing features of newly diagnosed CD are important to recognize. No longer is CD likely to be diagnosed in an infant less than age 2 who has chronic diarrhea, abdominal distention, and total growth failure. More often, the diagnosis is made in a child over 2 years old who is underweight for height with abdominal pain and possible lassitude, with or without diarrhea.*
J. A. A.
Steens RFR, Csizmadia CGDS, George EK, et al: A national prospective study on childhood celiac disease in the Netherlands 1993-2000: an increasing recognition and a changing clinical picture.
J Pediatr. 2005;147:233-238. ♦♦

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