

ALLERGYWATCH®

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

A Publication of The American College of Allergy, Asthma & Immunology

Volume 7, Number 5

September-October 2005

Prevention Is Better Than Cure!

ASTHMA and other atopic diseases result from genetic predisposition interacting with environmental factors. Environmental interventions for families at high genetic risk of asthma have focused on avoidance of individual risk factors. This article presents the 7-year outcomes of a multifaceted program for primary prevention of asthma in high-risk children.

The Canadian Childhood Asthma Primary Prevention Study included 545 infants at high genetic risk of asthma, having at least one first-degree relative with asthma or two first-degree relatives with other allergic diseases. The intervention program included measures to control exposure to house dust mite, pet avoidance, elimination of environmental tobacco smoke, and breast-feeding and/or partially hydrolyzed whey formula. Preventive measures were implemented before birth and continued through the first year of life; controls received usual care. When the children were 7 years old, they underwent out-

come evaluation including examination by a pediatric allergist with methacholine challenge testing and skin tests.

Complete assessment data were available for 380 children. The pediatric allergist diagnosed asthma in 14.9% of children in the intervention group compared with 23.0% of controls: adjusted risk ratio 0.44. When asthma was defined as wheezing without a cold plus bronchial hyperresponsiveness, prevalence was also lower in the intervention group: 12.9% vs 25.0%, adjusted risk ratio 0.39. Rates of other allergic disease outcomes—including allergic rhinitis, atopic dermatitis, positive skin test results, and bronchial hyperresponsiveness—were not significantly different between groups.

A program of avoidance measures instituted before birth and throughout infancy can reduce the prevalence of asthma in high-risk children. Other allergic disease outcomes appear unaffected; genetic susceptibility to bronchial hyperresponsiveness and atopy may be less responsive to allergen avoidance. Follow-up at age 11 to 12 will determine whether asthma is truly prevented or merely delayed. ➤➤

CONTENTS

- | | |
|--|--|
| 1 Prevention Is Better Than Cure! | 7 Prolonged Breast-Feeding Can Be Effective |
| 2 Informed Food Allergy Practice | 7 We Still Can't Choose Our Parents! |
| 3 Associations Between Different Allergens | 8 GERD Numbs Laryngeal Irritant Receptors |
| 3 The Nitty-Gritty on Nut Allergy | 8 Stay on the Watch for AERD |
| 4 Adverse Reactions during Surgery | 9 Asthma Risk Factors: Some Answers and More Questions |
| 4 Do Intradermal Skin Tests Have Worth? | 9 Is Nonallergic Asthma an Autoimmune Process? |
| 5 Some Answers on Immunotherapy | 10 Mometasone vs Beclomethasone and HPA-Axis Function |
| 5 SLIT Has Upper and Lower Airway Effects | 10 Reduced FEV ₁ and Cardiovascular Mortality |
| 6 Some Surprises, More Questions on SLIT | 11 Proteolytic Enzyme Activity in Severe Asthma |
| 6 Prenatal Allergen Exposure Is Key | 11 Croup: What Have We Learned? |
| 7 Breast May Not Be Best! | 12 ALLERGY AND IMMUNOLOGY REVIEWS OF NOTE |

The American College of Allergy, Asthma & Immunology expresses its appreciation to Aventis Inc., a member of the sanofi-aventis Group for its educational grant in support of AllergyWatch®.

EDITOR

Emil J. Bardana, Jr., M.D.
Portland, OR

ASSOCIATE EDITOR

Anthony Montanaro, M.D.
Portland, OR

ASSISTANT EDITORS

John A. Anderson, M.D.
Fort Collins, CO.

Tammy L. Heinly, M.D.
Germantown, TN

Stanley M. Fineman, M.D.
Marietta, GA

Dennis K. Ledford, M.D.
Tampa, FL

Gailen D Marshall, Jr., M.D., PhD
Jackson, MI

Richard J. Morris, M.D.
Minneapolis, MN

Stephen A. Tilles, M.D.
Seattle, WA

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

"AllergyWatch®" is an official publication and a registered trademark of The American College of Allergy, Asthma & Immunology and is published six times per year in one volume. Subscription rates: U.S., Individual \$90.00 Outside the U.S.: \$120.00, Residents, Fellows, Students within the U.S.: \$65.00, outside the U.S., add \$18.00, bulk subscription pricing available upon request of the publisher. Send subscription inquiries to AllergyWatch®, 85 West Algonquin Road, Suite 550, Arlington Heights, IL, 60005. Address editorial enquiries to: AllergyWatch®, c/o Emil J. Bardana, M.D., Editor, The Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, PV 320, Portland, Oregon 97201-3098. Telephone (503) 494-8531, Fax (503) 494-4323 or via email to bardanae@ohsu.edu. No portion of this publication may be reproduced in any manner either written or by retrieval system without the written permission of the Publisher. The reviews and commentary expressed within this publication are solely those of the editorial board and not those of the ACAAI; additional data and opinions should be obtained through reading the full original content. Copyrighted 2005 by The American College of Allergy, Asthma & Immunology. ISSN 1521-2440.

RATES of asthma and other allergic diseases continue to rise sharply, with major consequences for public and individual health. As studies continue to clarify the genetics of asthma, interventions to control environmental risk factors still offer the best approach to prevention. The author presents an update on current knowledge regarding primary prevention of asthma and allergy.

A wide range of environmental risk factors may influence the development of asthma and allergy, including dietary factors, aeroallergens, exposure to infections, and environmental tobacco smoke (ETS). However, it is difficult to show a direct link between allergen exposure and the development of allergic disease. Studies of primary prevention have focused on children at high risk based on family history, with preventive measures starting soon after birth or preferably during pregnancy.

Studies have shown that ETS is a clear risk factor, especially during pregnancy and early childhood—avoidance of ETS should be recommended to all parents. Having the mother avoid allergenic foods during pregnancy is of no benefit, although avoiding these foods during breastfeeding may have some effect. Breast-feeding for 4 to 6 months may reduce the risk of wheezing and atopic dermatitis in early childhood, but the longer-term benefits are unclear. Feeding hydrolyzed milk formula may prevent cow's milk allergy and atopic dermatitis, whereas the benefits of delaying solid food remain to be demonstrated. So far, there is no clear evidence that house dust mite avoidance prevents either sensitization or respiratory allergy. Studies of combined food and aeroallergen avoidance have yielded promising results, as have dietary probiotics.

Several effective approaches to primary prevention of asthma and allergy have been identified, but many questions remain to be answered. Among the priorities for further research are ways of identifying the children at highest risk of allergy, including the possibility of individualized preventive strategies; the optimal timing of interventions; the effects of pet allergen avoidance; and new immunomodulatory approaches.

COMMENT: *Do the avoidance measures we recommend really prevent allergic disease in children? These researchers from two Canadian cities used a well-designed prospective, randomized controlled study to answer this question. After 7 years, children in the intervention group—who were either breast-fed or fed hydrolyzed whey formula for 12 months and who lived in homes that instituted dust mite control and pet and tobacco smoke avoidance—were half as likely to develop asthma as non-intervention controls. Although it is somewhat surprising that the rates of allergic rhinitis and atopic dermatitis were not affected by the environmental control measures, these data still support our recommendations for families with a predilection for allergic disease. For those interested in an excellent review of the primary prevention literature, Dr Arshad's CME article in the same issue of this journal (J Allergy Clin Immunol. 2005;116:3-14) provides a good synopsis of the data.*

S. M. F.

Chan-Yeung M, Ferguson A, Watson W, et al: The Canadian Childhood Asthma Primary Prevention Study: Outcomes at 7 years of age.

J Allergy Clin Immunol 2005;116:49-55.

◆◆

Informed Food Allergy Practice

PEANUT allergy is an increasing and potentially fatal problem. Management of peanut and tree nut allergy is inconsistent, with many patients receiving inadequate treatment and experiencing further reactions. An approach to clinical management of peanut/tree nut allergy is evaluated.

The prospective follow-up study included 747 children with peanut and/or tree nut allergy seen at the authors' allergy clinic. Mean age was 6.3 years. Management included detailed advice regarding nut >>>

avoidance. Patients were also provided with an emergency treatment plan, with the choice of medications based on the severity of the child's worst reaction and the amount of nut exposure that caused it. All patients received oral antihistamines; an adrenaline injector was supplied to children who had ever had any type of airway involvement, those who reacted to trace amounts of nut, and those with ongoing asthma.

Of 615 children with a median follow-up of 3.3 years, 21% had a further reaction. Compared with the pre-enrollment period, there was a 60-fold reduction in the frequency of severe reactions and a 9-fold reduction in the rate of moderate reactions. None of the children with mild index reactions had a severe reaction during follow-up. Seventy-nine percent of the subsequent reactions were mild, requiring oral antihistamines only. There was just 1 severe reaction, which responded to adrenaline injection. In a case-control study, the only predictor of follow-up reactions was a history of more frequent and severe reactions.

An effective approach to management of pediatric peanut/tree nut allergy is described. Based on allergen avoidance and appropriate prescribing, it considers the clinical characteristics of the allergy and the child's individual needs. The authors' strategy may be applicable to other common food allergies, in which most cases are mild but there is a risk of severe reactions.

COMMENT: *Deciding whether to give different advice to food allergy patients reporting "mild" vs "severe" reactions is often quite difficult, especially as the prevalence of IgE-mediated clinical reactions to food increases. The authors of this study stratified peanut- and/or tree nut-allergic patients based on the severity of their prior reactions. Epinephrine was prescribed only if the patient reported a history of concomitant asthma, airway narrowing with prior reactions, or a reaction to a "low-dose" exposure to the food. After more than 25,000 patient-months of follow-up, the outcomes using this algorithm were impressive. Although there were neither oral challenges nor a control group, these results are a first step toward an evidence-based approach to the management of food allergy.*

S. A. T.

Ewan PW, Clark AT: Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice.

Clin Exp Allergy. 2005;35:751-756. ◆◆

Associations Between Different Allergens

MOST studies of allergic sensitization have addressed small numbers of allergens within a limited patient population. Most patients with atopy are sensitized to more than one allergen, but it is unclear whether sensitization to a particular allergen is related to other sensitizations. Sensitization to a wide range of allergens was assessed in a large U.K. birth cohort.

The study was based on the population-based Avon Longitudinal Study of Parents and Children, which included nearly 14,000 singleton infants surviving to age 4 weeks. At age 7, children underwent skin testing to a wide range of allergens. All were tested for allergy to house dust mite, grass pollens, cat, peanuts, tree nuts, and egg. In addition, the children were tested using one of three allergen panels: animal danders, foods, or aeroallergens. A wheal diameter of 3 mm diameter or larger was considered to indicate sensitization.

The analysis included skin test data on 6,412 children. Aeroallergens had the highest sensitization rates: 8.5% for grass pollens, 7.8% for *Dermatophagoides pteronyssinus*, 4.9% for cat, 3.6% for *Dermatophagoides farinae*, and 2.7% for dog. The rate of peanut sensitization was 1.4%, while tree nut sensitization was found in 1.0% of children. Of patients sensitized to any allergen, over 95% were also sensitized to grass pollens, *D. pteronyssinus*, or cat. Particularly strong associations were noted between pollens, animals, house dust mite, and tree nut allergens.

In this large cohort of British children, grass pollen, house dust mite, and cat are the most frequent allergic sensitizations. The results also suggest strong associations between allergens, within and across allergen groups. Nearly all allergic children are sensitized to grass, *D. pteronyssinus*, and/or cat.

COMMENT: *As part of the European Longitudinal Study of Pregnancy and Childhood, this sub-study involved prospective follow-up on a large birth cohort in the Avon region of the United Kingdom, including skin testing at age 7. Among children with positive skin tests, there was a remarkable prevalence of sensitization to cat, *D. pteronyssinus*, or grass pollen. Sensitization to one or more of these three aeroallergens was also strongly associated with sensitization to peanut, tree nuts, or eggs.*

S. A. T.

Relationship between aeroallergen and food allergen sensitization in childhood.

Clin Exp Allergy. 2005;35:933-940. ◆◆

The Nitty-Gritty on Nut Allergy

GRADED challenge is the current standard for diagnosis of food allergy. However, this is a time-consuming investigation that carries a risk of serious allergic reactions. Previous reports have suggested cutoff levels for skin prick testing and specific IgE measurement to improve the diagnostic utility of these allergy tests. Skin prick and specific IgE results were evaluated as predictors of the response to challenge testing for peanut allergy.

The prospective study included pediatric patients, up to 16 years old, undergoing peanut or tree nut challenge testing. Patients were drawn from a tertiary allergy clinic or from a community birth cohort. Challenge testing was offered to all children with a clinical history of peanut allergy, as long as they had no evidence of anaphylaxis. The skin prick and serum IgE results were evaluated for their ability to predict the response to peanut challenge. ►►

A total of 161 peanut challenges were performed in 157 patients. Data were available on the results of skin prick testing in 135 cases and specific IgE measurement in 126. A skin prick test response measuring 8 mm or larger was strongly associated with a positive response: positive predictive value 94.4%, specificity 98.5%. At a specific IgE level of 15 kU_A/L or higher, positive predictive value was 91.3% and specificity 96.8%. The tests' predictive value was unaffected by patient age, interval between testing and challenge, source of referral, or challenge type.

For children with suspected peanut allergy, a skin prick test response of 8 mm or larger or a specific IgE level of 15 kU_A/L or higher is a strong predictor of a positive response to challenge testing. These values seem generalizable to other groups of pediatric patients referred for evaluation of peanut allergy. Data from other sources suggest that only about one-fourth of peanut-sensitized children will have a skin test result of this magnitude, however.

COMMENT: These British researchers studied the results of peanut challenges in 157 children and adolescents with a history of nut allergy. Using statistical tools they were able to determine that a skin prick test response of 8 mm or larger or a specific IgE level of 15 kU/L or greater had high predictive value for a positive challenge result. There was a large immunologic "grey" area in which there was no certainty of either allergic or nonallergic sensitivity. The bottom line is that challenges are not needed if the skin test response is 8 mm or larger or if the RAST result is 15 kU/L or higher, but at lower levels clinical judgment is still critical.

S. M. F.

Roberts G, Lack G, et al: Diagnosing peanut allergy with skin prick and specific IgE testing.

J Allergy Clin Immunol. 2005;115:1291-1296. ♦♦

Adverse Reactions during Surgery

PATIENTS with hypersensitivity reactions during general anesthesia require testing to discover the causative agent and mechanism of the reaction. A large experience with hypersensitivity reactions to general anesthesia in children was analyzed, focusing on the frequency of IgE-mediated allergic reactions.

The 12-year experience included 68 children with hypersensitivity reactions to general anesthesia. Mean age was 8 years, 10 months. Forty-four percent of the children had a history of multiple surgeries for congenital abnormalities. Forty-six percent had a history of allergic diseases such as asthma or atopic dermatitis, while 13% had hypersensitivity to a single medication. Skin prick tests were performed, including testing for anesthetics, natural rubber latex, and neuromuscular blocking agents (NMBAs).

Based on the skin test results and clinical history, a diagnosis of IgE-mediated anaphylaxis was made in 75% of patients. Sixty-one percent of these reactions were caused by NMBAs. Cross-reactivity between NMBAs was common, especially atracurium and vecuronium. Other causal agents included latex, 27% of cases; colloids, 14%; opioids, 9%; and hypnotic agents, 12%. Informed by the results of testing, sub-

sequent surgeries in 20 patients were carried out without further incidents.

Most hypersensitivity reactions during general anesthesia in children are IgE-mediated allergic events, this experience suggests. Neuromuscular blocking agents are the most frequent cause, followed by latex. As outlined in this study, allergy testing is safe and feasible in this situation and can help to increase the safety of any subsequent operations.

COMMENT: Allergists are frequently asked to evaluate adverse reactions during surgery. This study evaluated anaphylactic reactions during surgery in 68 children over a 12-year period. IgE-mediated reactions were observed in 51 children, with 61% related to NMBAs and 27% to natural rubber latex. Significant shared antigenicity was noted among the NMBAs. Specific IgE for the quaternary ammonium ion of NMBA was evaluated by radioimmunoassay and skin testing and confirmed its presence in 50% of instances. The evaluation and selection of alternative safe drugs demonstrated the feasibility and safety of the authors' methodology.

E. J. B.

Karila C, Brunet-Langot D, Labbez F, et al: Anaphylaxis during anesthesia: results of a 12-year survey at a French pediatric center.

Allergy. 2005;60:828-834. ♦♦

Do Intradermal Skin Tests Have Worth?

THE diagnosis of clinical respiratory allergies depends on skin testing along with patient history. Based on the belief that intradermal skin tests are more sensitive for aeroallergen sensitivity, many allergists start with epicutaneous or percutaneous skin testing, proceeding to intradermal testing if the initial results are negative. This study evaluated the role of epicutaneous, percutaneous, and intradermal skin testing for the diagnosis of respiratory allergy.

The study included 68 patients with a history of allergic rhinoconjunctivitis and 40 controls without allergic symptoms. All subjects underwent skin testing using the skin prick and Multi-Test II (MTII) methods. Intradermal skin testing was performed only if these initial tests yielded negative results. Nasal challenges were performed in patients with positive results on intradermal tests but negative results on skin-prick testing and MTII.

The final analysis included 56 patients with a history of allergic symptoms and positive skin test results and 18 subjects with no allergy symptoms and negative skin test results. Compared with clinical history, the MTII approach offered consistently higher sensitivity than skin-prick testing for all aeroallergens. Sensitivity averaged 77% for MTI, compared with 62% for skin-prick testing. Of patients with negative MTII results, 17% had intradermal test results corresponding to the clinical history, but none had positive results on nasal challenge. The results of nasal challenges were comparable to those of negative controls and different from those of positive controls.

In the diagnosis of respiratory allergies, MTII offers better sensitivity than skin-prick testing, ►►

with similar specificity. The findings question the diagnostic yield of routine intradermal skin testing: patients with negative results on MTH are unlikely to show clinically relevant allergy on intradermal skin testing. False-positive results are common with intradermal testing.

COMMENT: *The debate over the utility of intradermal skin testing has existed since before my fellowship. This study clearly shows there is no demonstrable value of intradermal testing if both epicutaneous or percutaneous and multitestings are negative. Generally, multitestings are not used following epicutaneous/percutaneous testing; rather negative intradermal testing is used to "rule out" allergy whereas positive epicutaneous/percutaneous testing "rules in" allergy. This work does not change my philosophy, but it is a reminder that few treatment decisions should be based solely on positive intradermal allergy skin tests.*

D. K. L.

Schwindt CD, Hutcheson PS, Leu S-Y, et al: Role of intradermal skin tests in the evaluation of clinically relevant respiratory allergy assessed using patient history and nasal challenges.

Ann Allergy Asthma Immunol. 2005;94:627-633. ♦♦

Some Answers on Immunotherapy

INTERLEUKIN-9 (IL-9) has important effects on mast cell growth and differentiation. It is also involved in stimulating tissue infiltration by mast cells, a function that requires activation of the stem cell factor/c-Kit pathway. Expression of IL-9+ and c-Kit+ mast cells was evaluated in allergen-exposed patients with seasonal allergic rhinitis, along with the effects of subsequent immunotherapy.

Forty-four patients with severe summer hay fever and a positive skin test to timothy grass pollen were included in the study. Nasal biopsy specimens were obtained before and during pollen season. Patients were then randomized to receive 2 years of treatment with active allergen immunotherapy or placebo. Immunohistochemistry was used to measure IL-9+ and c-kit+ mast cells in the nasal biopsy specimens. Dual immunofluorescence was performed to identify cell types expressing IL-9 protein. The expression and phenotypes of IL-9 mRNA-positive cells were assessed as well.

Baseline studies showed a significant rise in c-Kit+ mast cells in nasal biopsies taken during pollen season. There was also a trend toward an increased number of IL-9 mRNA-positive cells, correlated with nasal EG2+ eosinophils and IL-5 mRNA-positive cells. T cells, eosinophils, neutrophils, and mast cells all expressed IL-9 protein.

In patients receiving active immunotherapy, the seasonal changes in c-Kit+ mast cells and IL-9 mRNA-positive cells were significantly inhibited, compared with the placebo group. Expression of IL-9 protein by nonendothelial cells was also reduced after successful immunotherapy.

This study confirms increased expression of IL-9 in the nasal mucosa of patients with seasonal allergic rhinitis during pollen season, a change that is corre-

lated with tissue infiltration by eosinophils and mast cells. Seasonal increases in c-Kit+, mast cells, and eosinophils are significantly reduced after 2 years of allergen immunotherapy. These changes may reflect changes in local IL-9 expression induced by immunotherapy.

COMMENT: *Interleukin-9 is a mast cell growth-enhancing Th2 cytokine that stimulates differentiation of mast cells and contributes to the allergic response in synergy with the stem cell factor/c-Kit pathway. These researchers further characterized the increase in these cytokines in the nasal mucosa of allergic patients during the grass pollen season in London. In those patients receiving allergen immunotherapy there was impressive inhibition of both c-Kit+ mast cells and the number of IL-9 positive cells. As we learn more about the mechanism of allergen immunotherapy we also learn more about the intricacies of the allergic response.*

S. M. F.

Nouri-Aria KT, Pelette C, Jacobson MR, et al: IL-9 and c-Kit+ mast cells in allergic rhinitis during seasonal allergen exposure: effect of immunotherapy.

J Allergy Clin Immunol. 2005;116:73-79. ♦♦

SLIT Has Upper and Lower Airway Effects

SEVERAL studies have established the clinical effectiveness of sublingual immunotherapy (SLIT) for patients with respiratory allergies. Questions remain about this therapy, including the mechanism of its effects on allergic inflammation and whether it has any effect on the lower airway. These issues were addressed in a large randomized trial of SLIT for birch pollen allergy.

The randomized, open trial included 79 adult patients with allergic rhinitis, with or without mild asthma, and confirmed allergy to birch pollen only. After a run-in pollen season, the patients were randomized to receive birch pollen SLIT or pharmacologic treatment only for the subsequent four seasons. In addition to clinical evaluation, outcomes analysis included pulmonary function tests, methacholine challenge studies, and nasal smears for eosinophil counts.

Only 52 patients completed the study, with a higher dropout rate in the control group than in the SLIT group. Compared with controls, patients receiving SLIT had a reduction in rhinitis symptoms, which became significant during the second pollen season. A reduction in bronchodilator use became significant during the third pollen season. Improvements in pulmonary function variables—including FEV₁, specific airways conductance, and maximal expiratory flow at 25% of forced vital capacity—were also observed during the second season of SLIT. The provocative dose of methacholine increased as well.

This long-term study documents the clinical efficacy of SLIT for patients with respiratory allergy to birch pollen. Sublingual immunotherapy has significant effects at the nasal level, including reduced eosinophilic infiltration; and at the bronchial level, with improvements in pulmonary function vari- ►►

ables.

COMMENT: Although we have seen numerous reports in the European literature of the efficacy of SLIT, this is one of the first to report both a sustained benefit and various immunologic changes. After a 6-month run-in, the treated patients received SLIT for 3 years, followed by 6 months off the therapy. There was impressive improvement in both rhinitis and asthma symptoms with SLIT. After the second year of treatment, various immunologic parameters including nasal eosinophils and methacholine challenge demonstrated improvement, which was sustained even after discontinuation of SLIT. Strengths of this study included the prolonged treatment period and the evaluation of immunologic parameters. Weaknesses included the high dropout rate, mainly from protocol deviations, and the nonblinded design, which was required by the review board. Sublingual immunotherapy seems to be a therapy most of us will be using in the future; it is important to have data that help to explain its benefits and effects.

S. M. F.

Marogna M, Spadolini I, Massolo A, et al: Clinical, functional, and immunologic effects of sublingual immunotherapy in birch pollinosis: a 3-year randomized controlled study.

J Allergy Clin Immunol 2005;115:1184-1188. ♦♦

Some Surprises, More Questions on SLIT

THE effectiveness of sublingual-swallow immunotherapy (SLIT) for allergic rhinitis is now well documented. However, the optimal allergen dosage needed to achieve clinical effect with SLIT is still unclear. Two allergen dosages were compared for their effects on the clinical and immunologic outcomes of SLIT.

The randomized trial included 71 children with rhinoconjunctivitis and grass pollen allergy. All received SLIT using the same three-grass extract, but one group received a 300 IR extract while the other received a 100 IR extract. The dosages used in these two groups were 375 and 80 times higher, respectively, than dosages used in conventional subcutaneous immunotherapy (SCIT). Clinical outcomes included symptoms, medications used, and side effects. Specific IgE and IgG4 in serum and nasal secretions were measured using the CAP system FEIA methods.

During grass pollen season, mean symptom medication scores were significantly higher for patients receiving SLIT with the 100 IR extract. Side effects were similar, affecting roughly one-fourth of patients in both groups. After 3 months of SLIT, no significant changes in serum-specific IgE or IgG4 occurred in either dose group. In contrast, seasonal increases in nasal IgE and IgG4 occurred only in the 100R dose group.

The clinical response to SLIT is significantly greater when a higher allergen dosage is used. In addition, seasonal blunting of nasal-specific IgE and IgG4 is noted only in patients receiving the higher of the two SLIT dosages used in this study. The local immunologic mechanisms of SLIT may differ from the

systemic mechanism of conventional subcutaneous immunotherapy.

COMMENT: There is growing scientific data supporting the efficacy of SLIT. However, to achieve clinical efficacy doses at least 100 higher than SCIT are required. These investigators used cumulative doses of SLIT that were 375 times higher than SCIT and showed greater clinical efficacy compared with cumulative dosages that were only 85 times higher than SCIT. No changes in serum-specific IgE or IgG4 were observed, but blunting of seasonal increases in IgE were noted in nasal secretions. The results suggest a local immunologic effect of SLIT quite different from SCIT. The bottom line also implies a much greater cost of SLIT over SCIT.

E. J. B.

Marcucci F, Sensi L, Di Cara G, et al: Dose dependence of immunological response to sublingual immunotherapy (SLIT).

Allergy. 2005;60:952-956. ♦♦

Prenatal Allergen Exposure Is Key

ALLERGIC sensitization may develop very early in life, possibly even before birth. A role of prenatal exposure is suggested by studies showing cat and house dust mite allergen in the fetal circulation. The effects of prenatal exposure to allergens on serum IgE levels at birth were evaluated in infants with a family history of allergy.

The study included 221 newborns at high risk of allergic disease, all having at least one first-degree relative with asthma. Between the fourth and sixth month of gestation, dust samples from the mother's mattress and family room were obtained for measurement of house dust mite, cat, and dog allergen. Relationships between these values and the infants' total IgE level at 3 to 5 days after birth were evaluated.

Blood samples were available from 174 infants. Of these, 24% had an elevated IgE level, 0.5 IU/mL or higher. Prenatal exposure to house dust mite allergen was related to IgE level in dose-response fashion: the rate of elevated IgE increased from 13% for infants in the lowest quartile of allergen exposure to 26% in the fourth quartile. This relationship was unaffected by sex, season of birth, maternal smoking, or breastfeeding before the blood sample was taken. Prenatal exposure to cat and dog allergen was unrelated to IgE level at birth.

In newborns with a family history of asthma, prenatal exposure to house dust mite allergen is related to total serum IgE level at birth. No such relationship is noted for pet allergens. In utero allergen exposure can independently affect the fetal immune system.

COMMENT: Mounting evidence supports the notion that early exposure to animal danders may protect from development of allergic disease. In this study it appears that pre-natal exposure to increasing amounts of dust mites in selected high-risk patients is associated with higher IgE levels at birth. The next step would be to determine whether strict environmental controls can prevent this phe- ➤➤

nomenon and whether it would diminish specific sensitization later in life.

A. M.

Schonberger HJ, Dompeling E, Knottnerus JA, et al: Prenatal exposure to mite and pet allergens and total serum IgE at birth in high-risk children.

Pediatr Allergy Immunol. 2005;16:27-31.

Breast May Not Be Best!

THERE is a long history of debate over the possible relationship between breast-feeding and the development of atopic disease early in life. Some studies have found that breast-feeding increases the risk of diseases such as atopic dermatitis and food allergies, while others have found no association. The relationship between exclusive breast-feeding and risk of atopic dermatitis in the first year of life was evaluated in a Swedish birth cohort.

From a cohort of nearly 22,000 infants, data on both dermatitis and breast-feeding during the first year of life were available on 8,346. The relationship between breast-feeding and atopic dermatitis was analyzed, with adjustment for potential confounders.

About 23% of infants had at least one episode of atopic dermatitis before their first birthday. The duration of exclusive breast-feeding was not significantly different for infants with vs without atopic dermatitis. "Short exclusive breast-feeding"—ie, less than 4 months—was unrelated to the risk of any atopic dermatitis or to the risk of three or more episodes. The findings were unaffected by adjustment for confounding variables, including family history of atopy. Having furred pets at home was associated with a lower risk of atopic dermatitis. Among infants with no family history of atopy, risk of atopic dermatitis was actually lower if the parents smoked.

Breast-feeding exclusively does not appear to affect infants' risk of atopic dermatitis during the first year of life. Exposure to furred pets may have a protective effect against early atopic dermatitis, whether or not the infant has a family history of allergy.

COMMENT: This large Swedish study examines an area of investigation rife with controversy. The investigators found no protective effect of breast-feeding, regardless of atopic genetic risk or duration of breast-feeding—two variables that were poorly controlled in previous studies. Despite these findings, the benefits of breast-feeding still outweigh any risk!

A. M.

Ludvigsson JF, Mostsrom M, Ludvigsson J, et al: Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants.

Pediatr Allergy Immunol. 2005;16: 201-208. ♦♦

Prolonged Breast-Feeding Can Be Effective

SEVERAL studies have suggested that breast-feeding reduces the risk of allergic disease via influences on the bacterial flora of the infant gut. The

ongoing debate over this issue has included limited data from developing countries. The effects of breast-feeding on the rate of allergic disease were evaluated in poor South African children.

The study included a 15% random sample of two Cape Town suburbs with very poor socioeconomic conditions and high population density. The occurrence of allergic disease among children aged 6 to 14 was evaluated using the International Study on Asthma and Allergies in Childhood questionnaire. Information on duration of breast-feeding, maternal smoking, and parental history of allergy was collected as well.

Information on duration of breast-feeding was available for 861 children, almost all of whom received at least some breast milk. Forty-four percent of the children were breast-fed for longer than 6 months—children in this group were poorer and had more siblings than those with shorter durations of breast-feeding.

Children who breast-fed for 6 to 12 months had a significantly lower overall rate of allergic disease, adjusted odds ratio 0.52, than those who breast-fed for less than 6 months. Children who breast-fed for longer than 12 months also had a lower rate of allergic disease, particularly hay fever. These inverse, linear associations remained significant for children with no parental history of allergic disease. However, among children whose mother or father had allergies, breast-feeding had no significant protective effect.

This South African study of low-income children indicates a lower rate of allergic disease among children who are breast-fed for longer than 6 months. However, the protective effect is significant only for children with nonallergic parents, not for those with a familial predisposition to allergies. Reducing the risk of allergy may be an additional benefit of recommendations to encourage prolonged breast-feeding for infants in developing countries.

COMMENT: The longstanding debate about the protective effects of breast-feeding against development of atopy has not been resolved. This study addressed the question in a poor South African population and found that prolonged (over 6 months) breast-feeding was protective against atopy only in children with nonatopic parents. No such protection was noted in at-risk children based on family history of atopy. Such data, if confirmed in other populations, may provide guidance for practitioners who are often asked for advice regarding the value of breast-feeding for allergy prophylaxis.

G. D. M.

Obihara CC, Marais BJ, Gie RP, et al: The association of prolonged breastfeeding and allergic disease in poor urban children.

Eur Respir J. 2005;25:970-977. ♦♦

We Still Can't Choose Our Parents!

MATERNAL asthma is a stronger risk factor for asthma and atopy than paternal asthma. Differences in the intrauterine environment are among the possible explanations for this differ- ►►

ence. Polymorphisms of the glutathione S-transferase *GSTP1* gene, which influences handling of reactive oxygen species, were evaluated as predictors of disease characteristics in asthmatic children.

The study included 145 unrelated families with an asthmatic child. All families were white and living in one county of Central England. Probands and parents underwent *GSTP1* genotyping studies. The effects of the children's and parents' *GSTP1* Val¹⁰⁵/Val¹⁰⁵ and Ala¹¹⁴/Ala¹¹⁴ genotypes on the children's lung function parameters were analyzed.

Children with the Val¹⁰⁵/Val¹⁰⁵ and Ala¹¹⁴/Ala¹¹⁴ genotypes demonstrated nonsignificant increases in pulmonary function variables. The fathers' genotype was unrelated to the children's lung function measures. However, maternal genotype was strongly related to several pulmonary function variables in the asthmatic children. The maternal Val¹⁰⁵/Val¹⁰⁵ genotype was associated with a FEV₁/FVC ratio of 105.2%, compared to 97.9% for the maternal Ile¹⁰⁵/Val¹⁰⁵ and Ile¹⁰⁵/Ile¹⁰⁵ genotypes. Mean FEV₁ was 109.0% for children of mothers with the Ala¹¹⁴/Val¹¹⁴ genotype, compared to 99.0% for the Ala¹¹⁴/Ala¹¹⁴ genotype. Corresponding FEV₁/FVC ratios were 104.1% and 98.2%. The associations remained significant after adjustment for variables such as maternal and child atopy, maternal smoking, and genotype transmission to the probands.

Functional polymorphisms of *GSTP1* in the mother are significant predictors of lung function variables in children with asthma. Maternal (but not paternal) genotype affects the offspring's asthma phenotype. The maternal *GSTP1* gene, or one closely linked to it, seems to be a distinct risk factor for expression of asthma in the child.

COMMENT: We have clearly appreciated that asthmatic moms confer a greater risk of asthma to their children than asthmatic dads. Since the detoxification of many drugs and the products of oxidative stress are in part mediated by glutathione S-transferase, this mechanism may partially explain these genetically conferred risk factors. Unfortunately we still can't choose our parents!

A. M.

Corroll WD, Lenney W, Strange CF, et al: Maternal glutathione S-transferase *GSTP1* genotype is a specific predictor of phenotype in children with asthma. *Pediatr Allergy Immunol.* 2005;16:32-39. ♦♦

GERD Numbs Laryngeal Irritant Receptors

SEVERAL factors can adversely affect laryngopharyngeal sensitivity (LPS), which plays a central role in preventing aspiration. Impaired LPS is one possible mechanism of the increased risk of asthma and other respiratory diseases in patients with gastroesophageal reflux disease (GERD). A new, objective technique of measuring LPS was used to compare LPS in patients with GERD and chronic cough vs healthy controls.

The study included 15 patients with GERD and chronic cough and 10 healthy subjects. Laryngopharyngeal sensitivity was assessed using fiberoptic endoscopic

evaluation of swallowing with sensory testing (FEESST), which delivers air pulses to the aryepiglottic folds to elicit a laryngeal adductor reflux (LAR). The lowest air pressure required to elicit the LAR was used as an indicator of LPS. Subjects underwent FEESST on two separate days, before and after laryngopharyngeal infusion of normal saline and 0.1 N hydrochloric acid, respectively.

At baseline, the mean LAR threshold was significantly elevated for patients with GERD and chronic cough: 9.5 mm Hg, compared with 3.68 mm Hg for controls. Hydrochloric acid infusion was associated with a significant increase in LAR threshold in healthy subjects, whereas saline infusion had no effect. Increases were also noted in the only 2 GERD patients with baseline LAR values of less than 10 mm Hg. There were no complications of the FEESST procedure.

Patients with GERD and chronic cough exhibit reduced LPS, based on a new objective measurement technique. Repeated exposure to acid may impair the sensory integrity of the upper airway, thus leading to an increased risk of aspiration.

COMMENT: Laryngopharyngeal sensitivity is important in prevention of aspiration. Patients with GERD are suspected of having a reduced LPS, but this has largely been unstudied. Using the unique FEESST method—in which air pulses at varying pressure are delivered to the aryepiglottic folds—these investigators compared normals to 15 patients with GERD. They found that GERD patients with cough had decreased LPS to stimulation compared to healthy subjects. This may be related to chronic exposure to acid with desensitization of irritant receptors. This, in turn, may increase the risk of microaspiration, adversely impacting cough, asthma and perhaps promoting the evolution of interstitial lung disease. Further study is needed to expand these important observations.

E. J. B.

Phua SY, McGarvey LPA, Ngu MC, Ing AJ: Patients with gastroesophageal reflux disease (GERD) and cough have impaired laryngopharyngeal mechanosensitivity.

Thorax. 2005;60:488-491. ♦♦

Stay on the Watch for AERD

IN patients with aspirin-exacerbated respiratory disease (AERD), nasal polyps and chronic hyperplastic eosinophilic sinusitis can be accompanied by intense infiltration of eosinophils. This intense eosinophilic infiltration may lead to fibrosis, hyperplasia, and airway remodeling. A CT score of sinus involvement was evaluated as an indicator of AERD.

Two groups of patients with moderate to severe asthma were studied: 21 with AERD, who experienced exacerbations after taking aspirin, and 19 with aspirin-tolerant asthma (ATA). All underwent sinus CT scanning, with severity of sinus involvement scored according to a validated scoring system: a CT score of 12 or higher indicated severe sinus disease. Markers of remodeling and airway inflammation were evaluated as well. >>>

The two groups were similar in terms of asthma severity, with postbronchodilator FEV₁ values of 94.3% predicted in the AERD group and 90.7% predicted in the ATA group. Mean CT score was significantly higher in patients with AERD: 16.9, compared with 6.2 in the ATA group. Percentage of patients with severe sinus involvement was 81% vs 26%, respectively. Nasal polyps were present in 90% of AERD patients vs 26% of ATA patients. Total lung capacity was greater in the AERD group, 107.9% vs 98.0%, consistent with increased air trapping. Other lung function and inflammatory variables were similar between groups, including diffusing capacity, exhaled nitric oxide, eosinophilia, and breath condensate pH.

Together with nasal polyps, the finding of hyperplasia on a sinus CT scan is an indicator of AERD. These features may help in detecting the presence of aspirin intolerance in an asthmatic patient. The results support the theory that AERD is associated with remodeling of both the upper and lower airways.

COMMENT: *The observation that severe sinus disease is associated with AERD is not new, as nasal polyps associated with aspirin sensitivity are the visible expression of chronic sinus inflammation. The idea that the severity of a sinus CT might allow prediction of AERD, even without a history of aspirin reactions, is of some merit. With the current interest in fungal hypersensitivity in subjects with severe sinus disease, we should not forget the beneficial possibility of prostaglandin modification with aspirin desensitization in such subjects, provided that AERD is confirmed.*

D. K. L.

Mascia K, Borish L, Patrie J, et al: Chronic hyperplastic eosinophilic sinusitis as a predictor of aspirin-exacerbated respiratory disease.

Ann Allergy Asthma Immunol. 2005;94:652-657. ♦♦

Asthma Risk Factors: Some Answers and More Questions

PREVIOUS studies have identified risk factors for childhood-onset asthma, as well as for persistence of childhood asthma into adulthood. It is important to understand which asthma risk factors may affect specific population subgroups. Long-term follow-up data were used to seek risk factors for asthma developing in childhood vs adolescence and in males vs females.

The analysis included data on a birth cohort of 1,037 New Zealand children followed up from birth to age 26. The main outcome of interest was recurrent wheezing, defined as wheezing reported on at least two assessments. Potential risk factors for onset of wheezing during childhood (before age 10) and during adolescence (after age 10) were analyzed separately for males and females.

Recurrent wheezing developed before age 26 in 23.7% of subjects, with similar proportions of males and females. Childhood-onset wheezing was more frequent in males whereas adolescent-onset wheezing was more frequent in females. Most adolescent-onset

wheezing occurred between age 10 and 18. For both males and females, development of wheezing before age 26 was associated with a lower FEV₁/FVC ratio, a higher likelihood of atopy at age 13 and 21, a positive methacholine challenge at age 9, diagnosis of asthma, and smoking at age 15.

On multivariate analysis, childhood-onset wheezing was associated with maternal atopy: hazard ratio (HR) 1.48 for boys vs 2.37 for girls. Paternal atopy was a significant risk factor for childhood wheezing in boys, HR 1.72, but not in girls. Neither maternal nor paternal atopy affected the risk of adolescent-onset wheezing in males. However, maternal atopy was a significant risk factor for adolescent-onset wheezing in females, HR 2.08. On combined analysis of childhood- and adolescent-onset wheezing, paternal atopy was a stronger risk factor in females than males: HR 1.62 vs 1.35, respectively.

Some differences in the risk of childhood- vs adolescent-onset wheezing are noted for males vs females. Maternal atopy is a stronger risk factor for males in childhood but for females in adolescence; paternal atopy is a significant risk factor mainly for females. Atopy and airway hyperresponsiveness are risk factors for childhood wheezing in both sexes, but atopy is a risk factor for adolescent wheezing only in males.

COMMENT: *Identifying risk factors for developing asthma, especially in children, is potentially important information in providing early effective therapy or even prophylaxis. Although family history is a known risk factor, this study adds more specific information about the specific effects of paternal vs maternal atopy on male vs female asthma risk, as well as onset in childhood vs adolescence. Such information begs more long-term, longitudinal studies that may involve interventional strategies.*

G. D. M.

Mandhane PJ, Greene JM, Cowan JO, et al: Sex differences in factors associated with childhood- and adolescent-onset wheeze.

Am J Respir Crit Care Med. 2005;172:45-54. ♦♦

Is Nonallergic Asthma an Autoimmune Process?

THE pathophysiology of nonallergic asthma remains unknown. Although inflammatory airway changes have been described in this group of patients, no triggering event that initiates bronchial inflammation has been identified. Chronic urticaria, once regarded as an idiopathic condition, is now thought to be of autoimmune origin in most patients. This study looked for evidence of circulating histamine-releasing factors in the serum of patients with nonallergic asthma.

The study included 24 patients with nonallergic asthma, mean age 47.2 years. Twenty-seven patients with respiratory allergic disease and 3 healthy subjects were studied for comparison. Skin testing was performed using the patients' autologous serum. In addition, an in vitro basophil histamine-release assay was performed using autologous basophils and basophils from normal donors.

Responses to the autologous serum skin test ►►

were positive in 58% of patients with nonallergic asthma, compared to none of the tested controls. In most of the patients with positive skin test results, wheal diameter was 5 mm or larger. However, just 1 of 12 serum samples from patients with a positive skin test induced histamine release from autologous basophils in vitro. In another case, the serum sample induced histamine release from membrane IgE-stripped autologous basophils only. Many of the patients with nonallergic asthma experienced symptoms of rhinitis as well, suggesting involvement of both the upper and lower airway.

Most patients with nonallergic asthma have a positive skin test reaction to their own serum. However, in vitro studies find only limited evidence of histamine-releasing autoantibodies in sera from these patients. Some yet-to-be-identified autoantibodies or histamine-releasing factors may trigger inflammatory airway changes in patients with nonallergic asthma.

COMMENT: *The association between total IgE level and both allergic and nonallergic asthma has been known for some time, but thus far the link with nonallergic asthma has been mysterious. Realizing that IgE upregulates its own high-affinity receptor on mast cells and basophils, the authors of this study hypothesized that nonallergic asthma may be an autoimmune disease that involves autoantibody-induced degranulation of mast cells and/or basophils. Analogous to autoimmune forms of chronic urticaria, the nonallergic asthma patients were much more likely to have positive autologous skin tests than control subjects. These results support the authors' hypothesis, and will no doubt stimulate further studies to better characterize this phenomenon. However, as pointed out in the accompanying editorial, the provocative findings by no means prove that this histamine-releasing activity is an essential component of the pathophysiology of nonallergic asthma. (See also the accompanying editorial, Clin Exp Allergy. 2005;35:835-837.)*

S. A. T.

Tedeschi A, Comi AL, Lorini M, et al: Autologous serum skin test reactivity in patients with nonallergic asthma.

Clin Exp Allergy. 2005;35:849-853. ♦♦

Mometasone vs Beclomethasone and HPA-Axis Function

IMPAIRMENT of hypothalamic-pituitary-adrenal (HPA) axis function is an important adverse effect of inhaled corticosteroid therapy. Mometasone furoate dry powder inhaler (MF-DPI), at a 400 µg dose, is effective in the treatment of asthma with a reduced potential for HPA axis dysfunction. The HPA axis effects of MF-DPI were compared with those of other inhaled corticosteroids.

The randomized, controlled trial included 53 adult patients with mild asthma and normal morning serum cortisol concentrations at baseline. One group received MF-DPI 400 µg, 1 puff/d each morning. The other two groups received beclomethasone propionate (BDP) via metered-dose inhaler, one with hydrofluoro-

ralkane (HFA) propellant (HFA-BDP: 200 µg, 2 puffs bid) and one with chlorofluorocarbon (CFC) propellant (CFC-BDP): 400 µg, 2 puffs bid). Treatment continued for 14 days; effects on area under the 24 hr serum cortisol concentration curve (AUC_{0-24}) and on 24 h urinary free cortisol excretion were monitored.

The median decrease in serum cortisol concentration AUC_{0-24} was 9% in patients assigned to MF-DPI, compared with 23% in those taking HFA-BDP and 24% in those taking CFC-BDP. Mometasone furoate was also associated with a lesser reduction in urinary free cortisol excretion. Patients taking MF-DPI also tended to have higher values for morning and evening peak expiratory flow. Treatment-related adverse events were higher in the MF-DPI group; all were mild and none required discontinuation of treatment.

In patients with asthma, MF-DPI had a lesser effect on HPA-axis function than two different forms of BDP. This advantage reflects the lower systemic bioavailability of mometasone furoate and the use of a dry powder inhaler. More study is needed to determine the long-term benefits of MF-DPI treatment.

COMMENT: *Regarding safety endpoints, it is generally difficult to show significant differences between equivalent doses of different inhaled corticosteroids. Using a once-daily dry powder inhaled dose of mometasone furoate similar to that which will soon be launched in the United States, the authors demonstrated a significant difference in serum cortisol concentrations area under the 24 hr serum cortisol concentration curve between mometasone and two comparable formulations of beclomethasone propionate. Although this was only a 14-day study, if the results can be replicated in longer-term studies, mometasone furoate may remain in the running for the highly sought-after label of "safer steroid."*

S. A. T.

Chrousos GP, Ghaly L, Shedden A, et al: Effects of mometasone furoate dry powder inhaler and beclomethasone dipropionate hydrofluoroalkane and chlorofluorocarbon on the hypothalamic-pituitary-adrenal axis in asthmatic subjects. ♦♦

Chest. 2005;128:70-77.

Reduced FEV₁ and Cardiovascular Mortality

MOST patients with reduced FEV₁ values have conditions such as chronic obstructive pulmonary disease or asthma, which are associated with persistent inflammation. Population studies have found that subjects at the lowest levels of FEV₁ have the highest values for inflammatory markers such as C-reactive protein (CRP). The relationship between reduced FEV₁ and risk of death from cardiovascular causes was assessed.

The analysis included data on 1,861 subjects from the first National Health and Nutrition Examination Survey, aged 40 to 60 years at enrollment in 1971-75. Spirometry was performed to measure FEV₁. The association between FEV₁ and death from cardiovascular and ischemic heart disease was evaluated, with adjustment for smoking.

Forty-five percent of all deaths were from car- ➤➤

diovascular causes, three-fourths of these from ischemic heart disease. The risk of cardiovascular death or hospitalization increased as FEV₁ decreased: cardiovascular mortality was more than tripled for subjects in the lowest vs highest quintile of FEV₁, relative risk 3.36. The association was even stronger for death from ischemic heart disease, relative risk 5.65. A meta-analysis of large cohort studies that adjusted for smoking found a pooled relative risk of 1.77.

Epidemiologic data link reduced FEV₁ to increased cardiovascular mortality. This pulmonary function measure may provide a useful marker of cardiovascular risk, independent of smoking.

COMMENT: *Reduced FEV₁, independent of cigarette smoking, is associated with an increase in cardiovascular mortality. The increase is up to 5-fold when stratified across FEV₁ values. Several factors may play a role in this link. These include obesity and its role in both conditions, as well as inflammatory mediators and their role in atherosclerosis and obstructive lung diseases. Inflammatory markers such as CRP are elevated in patients with both conditions. Recognizing this link, could we then follow CRP levels in addition to FEV₁ to identify those asthmatic patients at risk of a cardiovascular event?*

T. A. H.

Sin DD, Wu LL, Man SFP: The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature.

Chest. 2005;127:1952-1959. ♦♦

Proteolytic Enzyme Activity in Severe Asthma

ASTHMA patients with asthmatic mucus hypersecretion (AMH) have an accelerated rate of decline in lung function. Matrix metalloproteinases (MMPs) contribute to airway remodeling in asthma. This study assessed MMP-9 activity as a marker of AMH and severe asthma.

The study included 22 patients with asthma and 7 normal controls. On evaluation including lung function testing and bronchoscopy, 8 patients were classified as having AMH, based on the presence of mucus plugging. Six patients had mild/moderate asthma while 8 had severe asthma. Mean FEV₁ in the AMH group was similar to that of the patients with severe asthma but lower than in patients with mild/moderate asthma or normal controls.

On zymographic analysis of bronchoalveolar lavage fluid (BALF), MMP-9 was also higher in patients with AMH or severe asthma than in those with mild/moderate asthma. Tissue inhibitor of metalloproteinase (TIMP)-1 was also higher in the AMH and severe asthma patients; the ratio of MMP-9 to TIMP-1 was not significantly different between groups. The MMP-9 activity and MMP-9/TIMP-1 ratio were unrelated to FEV₁% predicted, and levels of MMP-9 and TIMP-1 in BALF were unrelated to serum levels.

Patients with AMH and severe asthma have similar increases in proteolytic enzyme activity in BALF. Patients with AMH may represent part of the spectrum of severe asthma. High levels of MMP-9 and

TIMP-1 may contribute to airway remodeling and deteriorating lung function in AMH and severe asthma.

COMMENT: *Identifying those patients at risk for rapid loss of lung function and airway remodeling is increasingly puzzling to providers. This study did demonstrate a relationship between AMH and severe asthma, with an increase in proteolytic enzyme activities. Levels of MMP-9 were elevated in BAL fluid in both groups, compared to nonasthmatic subjects. Unfortunately, there was no correlation between levels in BALF and serum or induced sputum levels of MMP-9. Therefore, MMP-9 could not be easily used to identify patients at greatest risk of fixed obstruction or those in whom metalloproteinase inhibitors may have a role.*

T. A. H.

Ko FWS, Diba C, Roth M, et al: A comparison of airway and serum matrix metalloproteinase-9 activity among normal subjects, asthmatic patients, and patients with asthmatic mucus hypersecretion. Chest. 2005;127:1919-1927.

Croup: What Have We Learned?

CROUP is the main cause of airway obstruction in infants and young children. Although croup is known to be a seasonal disease, most studies of this issue have included small samples and relatively short study periods. Seasonal patterns in hospitalization for croup were evaluated over 14 years' follow-up.

The population-based study included hospitalizations for croup in Ontario between 1988 and 2002. The analysis included a total of 44,820 children, all 0 to 4 years old and eligible for universal health coverage. Seasonal patterns of hospitalization for croup were analyzed, including the effects of patient age and sex.

Sixty-nine percent of patients were boys. Peaks occurred in October of odd-numbered years, with minor February peaks in alternate years. Troughs occurred in July and August of each year. Infants in the first year of life had the highest hospitalization rates, especially boys. There was a very sharp increase in croup hospitalizations in October 1993, with a downward trend thereafter.

Long-term analysis shows a clear biennial pattern in hospitalization for croup, with significant variations by age and sex. Croup hospitalizations have been decreasing since 1993-94, possibly reflecting the increased use of corticosteroid treatment for croup in the emergency department. The findings may be useful in further studies of croup treatment and possibly prevention.

COMMENT: *A very important outcome of a huge long-term study involving children hospitalized for croup (over 44,000 Canadian children aged 0 to 4 years, studied over 14 years) was the finding of a dramatic decrease in the numbers hospitalized between 1993 to the end of the study in 2002. The investigators as well as the author of the commentary (Pediatrics. 2005;116:230-231) advance convincing evidence that the use of corticosteroids as a standard of care for croup from 1992 to the present is the* ►►

reason for the decreased need for hospitalization in these children.

J. A. A.

Segal AO, Crighton EJ, Moineddin R, et al: Croup hospitalizations in Ontario: a 14-year time series analysis.

Pediatrics. 2005;116:51-55. ♦♦

REVIEWS OF NOTE

COMMENT: This exhaustive review of the eosinophilic lung disorders will serve the clinician well in the evaluation of such patients. The major challenge in these disorders is to distinguish eosinophilic lung disorders of known causation (parasitic, infectious, drug, toxic, and radiation) from those of undetermined causation.

E. J. B.

Cottin V, Cordier J-F: Eosinophilic pneumonias. Allergy. 2005;60:841-857. ♦♦

COMMENT: These authors review the relevance of leukotrienes to allergic inflammation. The review

also highlights the role of leukotriene receptor antagonists as monotherapy or in combination for the treatment of allergic rhinitis.

A. M.

Peters-Golden M, Henderson WR: The role of leukotrienes in allergic rhinitis.

Ann Allergy Asthma Immunol. 2005;94:609-618. ♦♦

COMMENT: Using subcutaneous immunotherapy as a comparator, this critical review summarizes the literature supporting the use of sublingual immunotherapy for rhinoconjunctivitis. The author concludes that sublingual immunotherapy falls short on several fronts, including the magnitude of its effect, the longevity of its effect, and the relative lack of data supporting its efficacy in children.

S. A. T.

Sublingual immunotherapy for allergic rhinoconjunctivitis--the seeming and the real.

Int Arch Allergy Immunol. 2005;137:181-186. ♦♦

COMMENT: This comprehensive review describes the most frequent variants of lung disorders in patients with various types of autoimmune disorders.

E. J. B.

Crestani B: The respiratory system in connective tissue disorders.

Allergy. 2005;60:715-734. ♦♦

American College of Allergy, Asthma & Immunology

85 West Algonquin Road, Suite 550
Arlington Heights, IL 60005-4425

PRSRT-STD
US POSTAGE
PAID
PERMIT NO 4453
ATLANTA, GA