AllergyWatch®

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

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Exhaled Nitric Oxide Measurement Is More Sensitive Than Conventional Asthma Tests

VARIOUS tests have been recommended to confirm the diagnosis of asthma, most seeking to demonstrate variable airflow obstruction and responsiveness to bronchodilators or corticosteroids. However, these tests have low sensitivity, among other shortcomings. New alternatives for asthma diagnosis include measurement of exhaled nitric oxide and induced sputum cell counts as indicators of airway inflammation. This study compared the performance of exhaled nitric oxide measurement and induced sputum analysis with conventional diagnostic tests for asthma.

Forty-seven patients referred for evaluation of asthma underwent a comprehensive series of tests in a fixed sequence. Over a series of three visits, the patients underwent exhaled nitric oxide measurement, skin allergy testing, spirometry, assessment of airway responsiveness to bronchodilator, hypertonic saline challenge, induced sputum analysis, serial peak flow recordings, and a trial of oral prednisolone. The diagnostic performance of the various tests was assessed.

Asthma was diagnosed in 36% of patients. Of the 17 patients with asthma, 15 had symptoms plus evidence of bronchial hyperresponsiveness while 2 had symptoms plus bronchodilator reversibility, without bronchial hyperresponsiveness. Three-fourths were atopic. Of the patients without asthma, the most frequent diagnoses were chronic rhinosinusitis, postviral respiratory syndrome, and gastroesophageal reflux disease.

Lung function values were significantly lower in asthma patients than in nonasthmatic patients, while exhaled nitric oxide levels and sputum eosinophil counts were significantly higher. In contrast, there was no significant difference in peak flow or spirometric responses to oral prednisolone. Diagnostic sensitivity was 88% for exhaled nitric oxide measurement and 86% for sputum eosinophil count, compared with values of 0% to 43% for conventional tests.

In suspected asthma, exhaled nitric oxide measurement and induced sputum analysis offer higher➤➤

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- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Thorax
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- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal

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diagnostic accuracy than conventional tests. Even at higher cutoff points, pulmonary function tests have low sensitivity. Exhaled nitric oxide measurement promises an easier approach to confirming the diagnosis of asthma with an increased level of confidence.

COMMENT: *Accurate diagnosis of asthma is important for early intervention and proper management. Conventional methods (such as peak flow and spirometry at baseline and after corticosteroids) suffer from poor sensitivity, and tests such as methacholine challenge are labor-intensive and expensive. This study investigated 47 consecutive patients whose clinical presentation was suggestive of asthma. Both peak expiratory flow rate and spirometry had sensitivities of less than 50%, while exhaled nitric oxide and sputum eosinophil quantitation had high sensitivities of almost 90%. Given the new generation of clinical instruments designed to detect exhaled nitric oxide, this could be a useful clinical tool for easy detection or confirmation of suspected asthma.*
G. D. M.

Smith AD, Cowan JO, Filsell S, et al: Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests.
Am J Respir Crit Care Med. 2004;169:473-478. ♦♦

Study Analyzes Asthma-Related Deaths During Sports

ASTHMA is known to be frequent among competitive athletes, but few studies have looked at asthma as a potential cause of death during sports. A large series of deaths during athletic activities were analyzed to assess the role of asthma.

Using a press clipping service, the investigators identified 263 deaths occurring during or immediately after a sporting or athletic event between 1993 and 2000. For each death identified as potentially related to asthma, an autopsy report was sought. The investigators also attempted to make contact with the decedent's family to request information about the death and the subject's sports participation and medical history, including any medications taken. News reports and other secondary sources of information were used to help confirm whether the death was caused by asthma.

The analysis identified 61 potentially asthma-related deaths. Just 10 of the families were willing and able to provide additional information. The subjects were 42 males and 19 females. About 80% of the victims were under 21 years old when they died, while more than 40% were between 10 and 14 years old. Two-thirds were white and one-third black. Ninety-one percent had a medical history of asthma.

Fifty-seven percent of the subjects were competitive athletes. Of these 35 subjects, 18 died while participating in organized sports activities: during practice in 14 cases and during competition in 4. Basketball was the most frequently involved sport, 21% of deaths; followed by track/running, 12%; and gym class, 10%. Just 5% of subjects were known to be taking long-term asthma controller medications.

The findings lend new insights into the characteristics of asthma deaths associated with athletic activities. The typical victim is a young, white male with a history of mild intermittent or persistent asthma. The study confirms that sudden, fatal asthma exacerbations can be triggered by sports participation in both recreational and competitive events.

COMMENT: *Exercise-induced asthma can be the mildest form of asthma--but this paper reminds us that asthma must never be taken lightly. Using stringent criteria, the investigators analyzed 61 deaths from exertional asthma, which occurred disproportionately in white males aged 10 to 20 years. Very few deaths (5%) occurred in subjects taking controller medications. None of the patients were retrospectively classified as severe asthmatics before death. Basketball and track were the most common* ➤➤

activities at the time of death. Underperception of asthma severity, and/or lack of medication adherence, might be a fatal flaw even in mild asthmatics.
R. J. M.
Becker JM, Rogers J, Rossini G, et al: Asthma deaths during sports: report of a 7-year experience.
J Allergy Clin Immunol. 2004;113:264-267. ♦♦

Treatment for Allergic Rhinitis Improves Outcomes of Asthma

PATIENTS with asthma have a high frequency of concomitant allergic rhinitis, and studies suggest that the nasal disease affects lower airway symptoms and lung function in these patients. The possible effects of treatment for allergic rhinitis on the rate of asthma exacerbations remain unknown. The relationship between intranasal corticosteroid and antihistamine therapy and asthma exacerbation rate was analyzed in a nested case-control study.

Enrollees in a large managed-care plan were reviewed to identify 361 members who received emergency department (ED) and/or hospital treatment for asthma. These patients were matched to 1,444 controls with allergy and asthma. Rates of intranasal corticosteroid and second-generation antihistamine use were compared for the 12-month period before the index visit.

In the year before the index visit, case patients received significantly more asthma medications and utilized more hospital care for asthma visits than controls Patients who used either intranasal corticosteroids or second-generation antihistamines had a significantly lower rate of asthma-related ED visits, adjusted odds ratio (OR) 0.51. These medications were also associated with a lower rate of asthma hospitalizations, OR 0.34. For users of nasal corticosteroids, the adjusted ORs were 0.75 and 0.56, respectively. The trends were nonsignificant for users of second-generation antihistamines only. However, patients who used both types of medications achieved the greatest reductions, with ORs of 0.37 for ED visits and 0.22 for hospitalizations.

Asthma patients who receive medications for allergic rhinitis appear to have lower rates of ED visits and hospitalizations for asthma. Using both intranasal corticosteroids and second-generation antihistamines appears to yield the greatest risk reductions. Randomized trials are needed to confirm these benefits.

COMMENT: *There has been an escalation in the medical literature about the importance of the link between upper and lower airway disease. This report used data from managed care organizations analyzing emergency room visits and hospitalizations for asthma with the use of medications for allergic rhinitis. Not only did the use of antihistamines or intranasal steroids reduce the risk of ED visits or hospitalizations for asthma, but the combined use of both lowered the risk even more. This study adds strength the to concept that there is one airway and that we shouldn't neglect treatment of the nose when asthma is also a problem.*
S. M. F.
Corren J, Manning BE, Thompson SF, et al: Rhinitis therapy and the prevention of hospital care for asthma: a case-control study.
J Allergy Clin Immunol. 2004;113:415-419. ♦♦

SCIT and SLIT Are Similarly Effective for Birch Pollen Allergy

SUBCUTANEOUS immunotherapy (SCIT) has documented long-term benefits in the treatment of allergic disorders. More recent studies have shown that sublingual immunotherapy (SLIT) is also effective, with advantages over SCIT in side effects and convenience. The clinical efficacy and systemic side effects of SCIT and SLIT were compared in a randomized, placebo-controlled trial.

The 3-year trial included 71 adults with rhinoconjunctivitis and confirmed birch pollen allergy. In double-blind fashion, they were randomized to receive SLIT plus placebo subcutaneous injections; SCIT plus placebo sublingual drops; or subcutaneous plus sublingual placebo. Efficacy and safety outcomes were assessed in a baseline birch pollen season and in two consecutive treatment seasons. The groups were comparable in baseline disease severity and patient age and sex.

Fifty-eight patients were available for efficacy assessment after the first season of treatment. Median disease severity was reduced to one-half of the placebo level in the SLIT group and to one-third of the placebo level in the SCIT group. Because of very high pollen levels during the first treatment season, rhinoconjunctivitis symptoms and medication scores increased for most patients in the placebo group. In contrast, most patients in the SCIT and SLIT group had reductions in these outcomes. The difference between SCIT and SLIT was not significant, and the benefits were considered clinically as well as statistically significant.

The rate of grade 2 systemic side effects was similar across the three groups. There were several cases of grade 3 or 4 systemic reactions in the SCIT group, compared with none in the SLIT group. In the first treatment year, the average cumulative allergen dose was 175 times higher with SLIT than with SCIT.

For patients with birch pollen rhinoconjunctivitis, both SCIT and SLIT are clinically effective, compared with placebo. This small trial finds no significant difference in efficacy between the two forms of immunotherapy, whereas SLIT avoids grade 3 or 4 side effects. More study is needed to compare the long-term efficacy and cost-effectiveness of SCIT and SLIT.

COMMENT: *This study represents the first randomized, placebo-controlled, double-blind, double dummy study comparing sublingual with subcutaneous immunotherapy in allergic rhinitis patients. Compared to prior studies of this issue, this study is designed with a placebo arm with a baseline assessment before randomization. Patients were distributed according to symptom severity. Unfortunately, the low pollen* ➤➤

count pre-empted evaluations in the third year of the study. No significant difference was observed between SLIT and SCIT with respect to symptom scores and drug intake compared to baseline. Sublingual immunotherapy had a better safety profile. Some key questions remain unanswered. Will this work in allergic asthma? Will such therapy reduce the later development of asthma? Will SLIT work in polysensitized individuals? What is the long-term efficacy after termination? Is this economically feasible? At the end of two years the accumulated mean dose was 11,182 µg of Bet v 1 for SLIT-treated and 51 µg Bet v 1 for SCIT-treated patients.
E.J.B.
Khinchi MS, Poulsen LK, Carat F, et al: : Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study.
Allergy. 2004;59:45-53. ♦♦

Higher Antioxidant Levels May Protect Against Childhood Asthma

PREVIOUS studies of the relationship between antioxidant vitamins and asthma in adults of children have yielded inconsistent results. The relationship between childhood asthma and serum antioxidant levels was assessed.

The analysis included data on 7,505 children, aged 4 to 16 years, form the Third National Health and Nutrition Examination Survey. The relationship between higher serum levels of vitamin E, β-carotene, vitamin C, and selenium and childhood asthma was analyzed by logistic regression. The effect of exposure to environmental tobacco smoke on this relationship was assessed as well.

Serum vitamin E level had no significant effect on asthma. The other antioxidants studied had modest effects on asthma risk--odds ratios associated with a 1-standard deviation increase in serum level were 0.9 for β-carotene, 0.8 for vitamin C, and 0.9 for selenium. Based on serum cotinine measurements, subjects exposed to passive tobacco smoke derived a greater protective effect from higher serum selenium levels: odds ratio 0.5 per 1-standard deviation increase.

In children and adolescents, higher serum levels of some antioxidants have a modest protective effect against asthma. The protective effect of selenium appears higher for youth exposed to environmental tobacco smoke. The findings support further study of the potential role of serum antioxidants in asthma prevention.

COMMENT: *This large epidemiologic study involving over 7,000 children examined the relative levels of vitamin E, vitamin C, β-carotene, and selenium as protectants against asthma. Serum vitamin E had no impact in this cohort. There was mild (10% to 20%) protection associated with higher β-carotene, selenium and vitamin C levels. However, in children exposed to secondhand smoke in the home, selenium levels appeared to be correlated with significant protection (up to 50%) against the development of asthma. These data suggest a potentially simple and inexpensive method of reducing asthma risk with antioxidant dietary supplementation.*
G. D. M.
Rubin RN, Navon L, Cassano PA: Relationship of serum antioxidants to asthma prevalence in youth.
Am J Respir Crit Care Med. 2004;169: 393-398. ♦♦

Are Dose Adjustments Necessary After Local Reactions to Immunotherapy Shots?

FOR patients receiving immunotherapy, it is generally believed that the occurrence of local reactions predicts an increased risk of systemic reactions to subsequent injections. In some protocols, when an injection produces a local reaction, the next dose is decreased in an attempt to prevent a systemic reaction. The effects of such dose adjustments on the risk of systemic reactions were assessed.

The analysis included a total of 7,942 immunotherapy injection visits to the author's military allergen clinic over a 4-year period. For the first 2 years of the experience, when a patient had a local reaction to an injection, an adjustment was made to repeat or reduce the next dose, according to protocol. In the latter 2 years, no adjustment was made in this situation. The total number of shot visits was 3,250 during the dose-adjustment protocol and 4,692 during the no-adjustment protocol.

The rate of systemic reactions was not significantly different: 1.11% during the dose-adjustment period and 0.85% during the no-adjustment period. The systemic reaction rate was about the same at outlying allergy clinics, where a dose-adjustment protocol remained in place throughout the study period.

This experience questions the practice of dose adjustment after local reactions to immunotherapy injections. Under a no-adjustment protocol, the rate of systemic reactions remains unchanged, while reducing the likelihood of dosing errors and minimizing the number of injections needed to reach a therapeutic dose.

COMMENT: *This article is important for practicing allergists/immunologists to consider when formulating practice policy with respect to immunotherapy. Neither the frequency nor the severity of local reactions to immunotherapy was of value in predicting the likelihood of systemic reactions. This finding is the same as in a prior immunotherapy study and in the large data set from published hymenoptera studies. Local reactions are probably only an issue for patient comfort, even though we spend a significant amount of time making adjustments presumably for safety. Time to reconsider.*
D. K. L.
Kelso JM: The rate of systemic reactions to immunotherapy injections is the same
whether or not the dose is reduced after a local reaction.
Ann Allergy Asthma Immunol. 2004;92:225-227. ♦♦

What Are the Risk Factors for Early- vs Late-Onset Childhood Wheezing?

ALTHOUGH some childhood wheezing is transient in nature, many children will go on to develop problematic asthma. Recent reports suggest that early- and late-onset persistent wheezing are variations on the same persistent phenotype of childhood asthma. A British birth cohort was investigated to identify inherited and environmental factors associated with early- vs late-onset childhood wheezing.

The whole-population cohort included 1,456 children born on the Isle of Wight in 1989. They were followed up at frequent intervals through 10 years of age, including skin-prick testing at age 4.

One hundred twenty-five children who began wheezing in the first 4 years of life and were still wheezing at age 10 were classified as late-onset persistent wheezers. Another 81 children who started wheezing after age 4 but were still wheezing at age 10 were classified as late-onset persistent wheezers. Genetic and environmental risk factors for these wheezing phenotypes were analyzed by multivariate logistic regression.

All of the risk factors independently associated with late-onset persistent wheezing were inherited: parental asthma, family history of rhinitis, and eczema or atopy at age 4. Several inherited risk factors for early-onset persistent wheezing were identified, including eczema at age 2, food allergy at age 4, maternal or sibling asthma, maternal urticaria, and atopy at age 4. In addition, certain environmental factors were linked to early-onset asthma: low social class, recurrent chest infections at age 2, and parental smoking at age 2.

Inherited variables appear to be the most important risk factors for persistent childhood wheezing. In addition, environmental factors may be important contributors to the development of early-onset persistent wheezing. Where genetic risk factors are present, the absence of these environmental factors may delay the onset of childhood wheezing, but is unlikely to prevent it.

COMMENT: *What distinguishes young wheezers with limited episodes of wheezing from persistent asthmatics with inflammatory changes and the potential for pulmonary remodeling? These investigators examine a birth cohort of 1,456 infants and continue following these children for 10 years, in order to identify risk factors involved in both the early and late onset of childhood asthma. They compare their results to both the Tucson Children's Respiratory Study and the Childhood Asthma Management Program. These investigators find genetics, especially other allergic conditions in the child and maternal asthma, to be the most important factors in development of childhood asthma. Environmental factors, including respiratory infections, environmental tobacco smoke, and allergen exposure, contribute to the development of asthma at a younger age. This study may help to explain what many of us see daily in practice--large increases in the number of young children with asthma. The next step, as suggested in this study, is to identify therapeutic interventions to stop this trend.*
A. L. L.

Kurukulaaratchy RJ, Matthews S, Arshad SH: Does environment mediate earlier onset of the persistent childhood asthma phenotype?
Pediatrics. 2004;113:345-350. ♦♦

ED Management of Food Allergies Doesn't Match Guidelines

ANAPHYLAXIS may be caused by food allergies. Many patients with anaphylactic reactions will be treated in the emergency department (ED), but little is known about the management they receive. The ED management of patients with allergic reactions to foods was assessed.

The analysis included a random sample of 678 patients treated for food allergies at 21 North American EDs. Fifty-seven percent of the patients were female; average age was 29 years. Nuts and shellfish were the most common precipitating foods. The patients' ED management was analyzed and compared with recommended guidelines.

Just 0.5% of patients underwent peak expiratory flow recording in the ED. A complete blood count was obtained in 6% of patients, ECG in 5%, and chest radiograph in 3%. Treatment included antihistamines in 72% of patients, systemic corticosteroids in 48%, and inhaled albuterol or other respiratory treatments in 33%. Ninety-seven percent of patients were discharged home; median length of ED stay was 145 minutes.

Only 40% of patients were instructed to avoid the food causing the reaction. Epinephrine was used in 16% of patients; even among patients with severe reactions, only 24% received epinephrine. Twelve percent were referred to an allergist. Overall, just 2% of patients received all three of these recommended preventive measures.

For patients with acute allergic reactions to foods--including those with anaphylaxis--ED management appears inconsistent with recommended guidelines. The authors urge educational efforts for ED staff, including involvement by the allergy community.

COMMENT: *Anaphylaxis might be the Rodney Dangerfield of potentially fatal medical conditions. Time and again, studies show it gets little respect. This study reviewed 678 episodes of ED treatment for acute food-related allergic reactions, half of which were anaphylactic. Shockingly (pun intended), only 16% of patients received epinephrine in the ED (22% of those with anaphylaxis), only 16% got a prescription for self-injectable epinephrine, and just 12% were referred to an allergist. Why aren't ED physicians doing "the right thing" for these patients?*
R. J. M.
Clark S, Bock SA, Gaeta TJ, et al: Multicenter study of emergency department visits for food allergies.
J Allergy Clin Immunol. 2004;113:347-352. ♦♦

Postmenopausal Hormone Use Increases Asthma Risk

THE relationship of female reproductive hormones with asthma and chronic obstructive pulmonary disease (COPD) remains unclear. One report suggested a possible link between use of postmenopausal hormone replacement therapy and asthma. Data from the Nurses' Health Study were used to analyze the association between hormone replacement therapy and newly diagnosed asthma and COPD.

Over 120,000 female registered nurses, aged 30 to 55 years, enrolled in the study in 1976. Follow-up questionnaires were used to assess new physician diagnoses of asthma and/or COPD. These outcomes were examined for association with reported use of postmenopausal hormones. Degree of diagnostic certainty was assessed using data on medication use and pulmonary function results.

In a total 546,259 person-years of follow-up, a physician diagnosis of asthma was reported by 10,496 women and COPD by 8,105, with 3,066 overlapping cases. Asthma risk was significantly elevated for women reporting current use of estrogen only. The multivariate rate ratio was 2.29 (95% confidence interval 1.59 to 3.29), compared to women reporting no hormone use. Asthma risk was similarly elevated for women who currently used estrogen plus progestin. As diagnostic certainty increased, so did the rate ratios for association with asthma. Newly diagnosed COPD was no different for women who did and did not use hormones.

These prospective follow-up data suggest an increased risk of newly diagnosed asthma among postmenopausal women taking hormone replacement therapy. However, no relationship between hormone replacement and COPD is apparent.

COMMENT: *In this provocative observation, postmenopausal estrogen use appears to be associated with increased asthma risk. Given the increasing body of evidence on the potential hazards of estrogen replacement therapy, clinicians must examine this additional risk. As the authors point out, much more work is needed before a causal relationship can be determined.*

A. M.

Barr RG, Wentowski CC, Grodstein F, et al: Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease.

Arch Intern Med. 2004;164:379-386. ♦♦

Seizures Caused by EMLA Cream in a Young Child: Case Report

EUTECTIC mixture of local anesthetics (EMLA) is widely used to achieve topical anesthesia for superficial procedures. Most adverse effects are local and mild. A toddler with seizure occurring after application of EMLA cream to a large area is reported.

The 3-year-old girl, who had a history of eczema, was to undergo allergy skin testing. The parents were instructed to apply a 5 g tube of EMLA cream to her back then cover it with plastic wrap, to be removed at the allergist's office. On the way to the appointment, the child became nonresponsive, then developed a seizure. She had a raised erythematous rash on her back. Emergency medical services transported her to the hospital, where perioral and distal extremity cyanosis were noted. Mild bradycardia and hypotension developed; the patient was placed on 100% oxygen and admitted to the pediatric ICU. Laboratory findings included an oxyhemoglobin level of 80%, methemoglobin of 17.7%, and lidocaine level of 3.0 µg/L. The abnormalities resolved by the next morning, and the patient was discharged.

In this small child, application of EMLA cream over a large area caused seizure, cyanosis, and other symptoms, consistent with lidocaine toxicity and methemoglobinemia. This case serves as a reminder that even topically applied medications can have serious toxic effects.

COMMENT: *Warning! If you are using EMLA cream in order to reduce pain before allergy skin testing in small children, carefully read this report! Even though this technique has been studied by allergists for effects on allergy wheal-and-flare skin test reactions, serious toxic effects can occur. In this case report, a very large surface area (whole back) was covered with EMLA cream and covered with plastic wrap (in a child with eczema). The systemic absorption of local anesthetic was significant and resulted in not only a local reaction but also cyanosis, shock, seizures, and methemoglobinemia.*

J. A. A.

Parker JF, Vats A, Bauer G: EMLA toxicity after application for allergy skin testing.

Pediatrics. 2004;113:410-411. ♦♦

Tonsillectomy Benefits Patients with Chronic Cough and Enlarged Tonsils

IN about one-fifth of cases, the cause of chronic cough may remain unknown even after extensive testing and treatment trials. Some patients with chronic cough are observed to have enlarged tonsils, although this is not an accepted cause of cough. The effects of tonsillectomy in this group of patients with otherwise unexplained chronic cough are reported.

Of 236 patients with chronic cough seen over a 2-year period, 8 had unexplained chronic cough with tonsillar enlargement. There were 6 women and 2 men, mean age 37 years; cough had been present for a mean of 7 years. All 8 patients underwent tonsillectomy; outcomes were compared with those of 6 patients with enlarged tonsils but without chronic cough.

Postoperatively, all patients had improvement in their chronic cough. On a 0-to-100 visual analog scale, cough severity decreased from 57 mm at baseline to 27 mm 3 months after tonsillectomy. Compared with controls, the patients with chronic cough and tonsillar enlargement had elevated capsaicin cough reflex sensitivity at baseline. This outcome also improved after tonsillectomy. ➤➤

For patients with unexplained chronic cough and tonsillar enlargement, tonsillectomy may yield clinical improvement. Although further study is needed, tonsillectomy may play a useful role in selected patients with chronic cough, after other causes are ruled out.

COMMENT: *This small study addresses an often-overlooked possibility for patients with chronic cough syndrome. The authors looked at 8 consecutive patients with chronic cough and enlarged tonsils who underwent tonsillectomy. Six other patients without chronic cough who underwent tonsillectomy were the control subjects. Cough was assessed with a visual analog scale and capsaicin sensitivity. There was a dramatic improvement in both visual analog score and decreased capsaicin sensitivity in the treatment group compared to the control group. This should alert the practitioner to look for tonsillar enlargement in patients with chronic cough.*
G. D. M.
Birring SS, Passant C, Patel RB, et al: Chronic tonsillar enlargement and cough: preliminary evidence of a novel and treatable cause of chronic cough.
Eur Respir J. 2004; 23:199-201. ♦♦

Minority Race and Male Sex Among Factors Affecting Infants' AD Risk

LITTLE is known about the inherited and genetic risk factors for early-childhood atopic dermatitis (AD). Most studies of this issue have been small, assessed selected variables only, and been retrospective in nature. Prospective data were used to assess perinatal predictors of developing AD in the first 6 months of life.

The analysis included data on 1,005 mothers and children from the prospective cohort study Project Viva. Information on potential predictors was gathered when the women were enrolled in the study at their obstetrician's office. The outcome of interest was a health care provider's diagnosis of eczema or AD by the time the infant was 6 months old.

Seventeen percent of infants developed AD within the first 6 months of life. Risk was more than doubled for infants born to black or Asian mothers--adjusted odds ratios (ORs) 2.41 and 2.58, respectively--compared with infants born to white mothers. Risk was higher in boys than girls, OR 1.76. Older gestational age at birth was a risk factor, OR 1.14 per additional week; birth weight for gestational age was not. Parental history of eczema was a significant predictor, especially maternal history: OR 2.67. A wide range of other factors, including social, feeding, and environmental variables, were unrelated to AD risk.

Infants' risk of developing AD during the first 6 months of life is affected by a wide range of factors, including race, sex, gestational age at birth, and family history of atopy. It is hoped that a better understanding of the genetic and perinatal risk factors for early-childhood AD can help to target early interventions.

COMMENT: *This large prospective cohort study in Boston clearly showed a twofold risk of AD in infants of black and Asian mothers, compared to infants of white mothers. The data on AD in Hispanic infants indicated no increased risk, but involved a smaller number of subjects. I felt that another important finding was that the risk of developing AD was 1.7 times higher in male than in female infants. Many previous international studies have reported that AD is more often seen in female infants.*
J. A. A.
Moore MM, Rifas-Shiman SL, Rich-Edwards, et al: Perinatal predictors of atopic dermatitis occurring in the first six months of life.
Pediatrics. 2004;113:468-474.

Presenting Symptoms Don't Predict Severity of Reactions to Food Challenge

ALLERGIC reactions to food range from mild skin reactions to life-threatening anaphylaxis. Few studies have sought to identify predictors of the severity of subsequent reactions. A large experience of children with food allergy was analyzed to determine whether characteristics of an initial reaction to food can predict the severity of reaction on subsequent food challenge.

The 5-year experience included 998 challenges performed in children with food allergies at one children's hospital. Of these, 413 challenges were positive and 585 negative. Eighty-three percent of the positive challenges were to milk, egg, or peanut.

Data on the specific food involved and the children's presenting symptoms were analyzed to identify predictors of the response to food challenge. Cutaneous reactions were the most frequent presentation of food allergy, followed by multiple organ system reactions. In response to food challenge, multiorgan reactions were more likely to be caused by peanut, milk, or egg than by soy or wheat.

When challenged with the food that had caused their presenting symptoms, children were more likely have symptoms similar to their initial symptoms than to have a different type of reaction. Nevertheless, multiorgan reactions occurred in patients with all types of previous reactions. Egg was the food most likely to cause a different type of reaction on repeat challenge.

In this large experience with food challenges in allergic children, milk, egg, and peanut are the foods most likely to elicit a positive response and to produce multiple organ system reactions. For most patients, the reaction to open food challenge will be similar to the initial symptoms of food allergy. However, patients with any type of presenting symptom may experience severe reactions on repeat challenge. Since there is no way to predict the severity of subsequent reactions, all patients presenting with food allergies should be trained in emergency use of epinephrine.

COMMENT: *The diagnosis and management of food allergies continues to be a daunting challenge for the allergist. This retrospective analysis of an important database of well-performed food challenges reminds us that, despite a history of limited cutaneous* ➤➤

responses to an offending food allergen, more serious multi-organ involvement may occur on re-exposure. A thoughtful accompanying editorial reminds us of the need for vigilance in managing children and adults with food allergy.
A. M.
Spergel JM, Beausoleil JL, Fiedler JM, et al: Correlation of initial food reactions to observed reactions on challenges.
Ann Allergy Asthma Immunol. 2004;92:217-224. ♦♦

Preseason Treatment with Montelukast Plus Cetirizine Reduces AR Symptoms

MONTELUKAST has recently been approved for the treatment of allergic rhinitis (AR). Previous studies suggest that concomitant treatment with montelukast and loratadine yields greater symptom improvement than either treatment alone. Although antihistamines can prevent AR symptoms, the possible preventive effects of leukotriene receptor antagonists are unknown. This randomized trial assessed the prophylactic efficacy of cetirizine and montelukast, alone and in combination, in patients with AR.

Sixty young adults with seasonal AR were randomized to treatment with placebo; montelukast 10 mg; cetirizine, 10 mg; or montelukast plus cetirizine. Treatment was for 12 weeks, beginning 6 weeks before the start of grass pollen season. Patients self-recorded symptoms during pollen season.

The combination of montelukast and cetirizine was associated with significant reductions in symptoms during pollen season, including sneezing, ocular and nasal itching, rhinorrhea, and congestion. For ocular itching, nasal itching, and rhinorrhea, the combination was more effective than cetirizine alone. In addition, montelukast plus cetirizine was associated with a significant delay in the occurrence of AR symptoms.

Thirty-one patients underwent nasal lavage before treatment and at the end of the study. Eosinophil cationic protein level increased during pollen season for all groups except those taking montelukast plus cetirizine. There were no significant differences in mast cell tryptase levels.

For patients with seasonal AR, starting combined montelukast and cetirizine treatment 6 weeks before pollen season significantly reduces symptoms and inflammation of the nasal mucosa. This prophylactic effect does not occur in patients taking antihistamine or antileukotriene treatment only.

COMMENT: *A number of studies have addressed the effectiveness of combination therapy with histamine and leukotriene receptor antagonists in AR. There have been conflicting results, presumably resulting from variances in sample size and pollen counts. This study finds that using histamine and leukotriene-receptor antagonists for 6 weeks before pollen season is effective in preventing AR symptoms and reducing allergic inflammation in nasal mucosa. However, the study suffers from the small number of subjects and variable pollen counts, which were not factored into the analysis. This study does tell us that starting early before onset of the season is likely to yield the best results. However, whether combination therapy is really justified remains an unsettled question.*
E. J. B.
Kurowski M, Kuna P, Górski P, et al: Montelukast plus cetirizine in the prophylactic treatment of seasonal allergic rhinitis: influence on clinical symptoms and allergic inflammation.
Allergy. 2004;59:280-288. ♦♦

Exhaled NO Reflects Inflammation and Remodeling in Refractory Asthma

THE course and clinical findings of refractory asthma vary widely, reflecting differing pathologic patterns. Exhaled nitric oxide (NO) provides a noninvasive measure of eosinophilic inflammation in children with refractory asthma. This study sought to determine whether exhaled NO was also affected by airway remodeling in refractory asthma.

The prospective analysis included 28 children with refractory asthma, based on airflow limitation and/or clinical exacerbations despite high-dose inhaled steroid therapy. Median age was 11 years; all children were atopic. In addition to pulmonary function testing and bronchoscopy with bronchoalveolar lavage and bronchial biopsy, the patients underwent multiple-flow analysis of exhaled NO. Values for alveolar NO concentration and maximal conducting airway NO output were correlated with the other test results.

Exhaled NO values were significantly correlated with measures of inflammation and Th1/Th2 balance. In addition, NO measurements were correlated with various indicators of airway remodeling: alveolar NO concentration was correlated with the level of transforming growth factor-β in bronchoalveolar lavage fluid, while maximal NO output from the conducting airways was correlated with reticular basement membrane thickness. Alveolar NO was also significantly correlated with the percentage of predicted MEF_{25-75}.

In children with refractory asthma, multiple-flow analysis of exhaled NO may provide useful information on both airway remodeling and inflammation. Adding NO measurement to pulmonary function testing may provide a useful approach to noninvasive monitoring in this group of children. The findings are limited by the absence of a healthy control group.

COMMENT: *There is still no consensus regarding the optimal marker to use in following asthmatic patients. Although we are most concerned about the ultimate development of airway remodeling, the only way to conclusively determine this involves bronchial biopsy and measurement of basement membrane thickening. Exhaled NO has been shown to correlate with intrapulmonary inflammatory changes. These French researchers found a correlation between exhaled NO and evidence of remodeling in children who had diagnostic bronchoscopy for persistent asthma. For* ➤➤

years, pulmonary function testing has been our benchmark measurement for chronic asthma. The use of exhaled NO may become increasingly important in the near future.
S. M. F.
Mahut B, Delclaux C, Tillie-Leblond I, et al: Both inflammation and remodeling influence nitric oxide output in children with refractory asthma.
J Allergy Clin Immunol. 2004;113:252-256. ♦♦

CTLA-4 Polymorphism Affects IgE Level And Allergic Disease In Women, But Not Men

POSSIBLE genetic reasons for the greater severity of allergic diseases in women vs men are unknown. Polymorphisms of the cytotoxic T lymphocyte antigen 4 (CTLA-4) and interleukin (IL)-4 promoter genes were studied for gender differences in their relationship with allergic disease.

The cross-sectional study included 1,333 Taiwanese adults, aged 19 to 49 years: 667 men and 666 women. Based on history of allergy and detection of specific IgE to common allergens, 23.3% of subjects were classified as having allergic disease. DNA studies were performed for the +49 A/G polymorphism of the CTLA-4 gene and the -590 polymorphism of the IL-4 promoter gene. The DNA findings were correlated with gender discrepancies in allergic diseases and total IgE levels.

Women with the A/A genotype in the CTLA-4 (+49) position had the highest total IgE level: 154.9 kU/L, compared to 107.1 kU/L for those with the A/G genotype and 79.8 kU/L for those with the G/G genotype. Mean log values were 1.79, 1.65, and 1.54 kU/L, respectively. In contrast, the CTLA-4 (+49) polymorphism was unrelated to total IgE level in men. This polymorphism also showed a gender-dependent association with atopic disease: women with allergic rhinitis were significantly more likely to have the A/A genotype than those without atopic diseases. The IL-4 promoter (-590) genotype was unrelated to total IgE or allergic diseases in either sex.

In women but not men, the A/A genotype of CTLA-4 (+49) is linked to increased total IgE levels and a higher prevalence of allergic rhinitis. Total IgE levels are lowest for women with the G/G genotype of the same polymorphism. The findings may have implications for the greater severity of allergic diseases in women.

COMMENT: *While it has been clear for some time that there are gender differences in the prevalence and severity of atopic diseases, the molecular basis for these differences is unknown. CTLA-4 is a T-cell regulatory molecule with a polymorphism (+49) that has been shown to be associated with Graves' disease and Addison's disease. The current study enrolled 667 male and 666 female Taiwanese subjects and found that CTLA-4 polymorphism was associated with both allergic rhinitis and elevated IgE in women, but not men. This is the first demonstration of a gender-linked genetic relationship with an allergic disease.*
S. A. T.
Yang KD, Liu C-A, Chang J-C, et al: Polymorphism of the immune-braking gene (CTLA-4) (+49) involved in gender discrepancy of serum total IgE levels and allergic diseases. **Clin Exp Allergy.** 2004;34:32-37. ♦♦

Trials Question Benefits of Bed Covers for Mite-Allergic Patients

THE benefits of allergen-avoidance measures for mite-sensitized patients remain unproven. Bedding is the most common target for mite allergen-reduction interventions. The effectiveness of allergen-impermeable bed covers for mite-sensitized asthma patients was evaluated in a randomized trial.

Three hundred fifty-four adult asthma patients from London general practices and clinics were randomized to receive real or sham allergen-impermeable bed covers. Dog- or cat-sensitized patients with a pet in the home were excluded. Patients were to use the covers for 1 year, with no additional mite-reduction interventions. Outcome measures included mattress Der p 1 levels, symptoms, medications use, and peak flow records.

The mattress Der p 1 level decreased by a mean of 25.7 µg/g in patients receiving real bed covers vs 4.5 µg/g in those receiving sham covers. However, at the end of the study, there was no significant difference in allergen levels between groups. The peak flow and symptom results were also similar between groups.

In adult asthma patients sensitized to dust mite, the use of allergen-impermeable bed covers alone is not an effective intervention. Mite allergen levels and asthma symptoms are not significantly different than in sham-treated controls. The researchers encountered greater than expected difficulty in recruiting mite-sensitized patients with mild to moderate asthma.

COMMENT: *This randomized, controlled trial examines the effects of impermeable mattress and pillow covers in dust-mite-allergic subjects with asthma. The results suggest that this intervention does not help. The failure to show clinical improvements may have been due to the fact the placebo mattress and pillow covers also reduced the amount of recoverable Der p 1 in mattress dust, or perhaps because the intervention failed to include other mite-avoidance measures. However, this study is only one of a series of recent controlled investigations whose results challenge our longstanding standards of practice regarding dust mite environmental control measures. (See review by the same author, Clin Exp Allergy. 2004;34:268).*
S. A. T.
Luczynska C, Tredwell E, Smeeton N, Burney P: A randomized controlled trial of mite allergen-impermeable bed covers in adult mite-sensitized asthmatics.
Clin Exp Allergy. 2003;33:1648-1653. ♦♦

CURRENT clinical guidelines for asthma include the use of bedding encasement to reduce exposure to dust mite antigen. However, not all trials have ➤➤

shown significant clinical improvements in patients using bed covers. A qualitative and quantitative review of previous studies of the effectiveness of bedding encasement for asthma patients is presented.

The author performed a "narrative review" of clinical trials of bedding encasement as an intervention for patients with asthma, along with a quantitative analysis of the relationship between changes in allergen exposure and bronchial hyperresponsiveness. The review included 33 clinical trials of allergen avoidance for asthma patients that evaluated some type of bedding encasement.

Four studies including adequate exposure and BHR data concluded that bedding encasement led to significant reductions in mite allergen exposure and in BHR. However, another 10 studies showed significant reductions in allergen exposure, but no significant change in BHR. Five more studies with adequate data found no significant improvement in either outcome. In collective analyses, the benefits of bed covers appeared modest and nonsignificant. A moderate effect on allergen exposure and BHR appeared to be present for subjects with high initial exposure levels: over 2 µg of type 1 antigen per gram of settled dust.

Previous studies of bedding encasement for asthma patients find no consistent benefit in terms of reducing exposure to dust mite allergen or improving objective lung function. From a public health standpoint, the results suggest that bed covers are a "variably effective" intervention that may be best targeted to specific subgroups of patients who are likely to benefit.

COMMENT: *The mainstream approach of reducing dust mite exposure in symptomatic dust-mite-allergic patients has been under attack recently. This review evaluates the effects of encasing the mattress and pillow on asthma and BHR. The authors conclude that "its effectiveness is inconsistent and appears to be, at best, modest." While it is unlikely that new practice parameters will suggest skipping dust mite environmental control measures in sensitized patients, it is appropriate to "stay tuned" to this area as further evidence emerges.*
S. A. T.
Recer GM: A review of the effects of impermeable bedding encasements on dust-mite allergen exposure and bronchial hyper-responsiveness in dust-mite-sensitized patients. **Clin Exp Allergy.** 2004;34:268-275. ♦♦

Peach LTP-Specific IgE Indicates Risk of Reaction to Non-Rosaceae Foods

IN areas with low rates of birch pollen allergy, lipid transfer protein (LTP) is the main Rosaceae allergen. Lipid transfer protein is a widely cross-reactive panallergen found in a wide range of plant species, but patterns of cross-reactivity to foods unrelated to Rosaceae remain unclear. Patients sensitized to LTP were studied to assess the relationship between peach LTP-specific IgE and cross-reactivity with various non-Rosaceae foods.

Forty Rosaceae-allergic patients monosensitized to LPT underwent measurement of peach LTP-specific IgE. All were free of sensitization to other cross-reactive allergens, with negative skin-prick test results to birch and mugwort. Further skin-prick tests were performed using various plant foods botanically distinct from Rosaceae.

Levels of IgE to peach LTP were strongly correlated with the number of non-Rosaceae foods to which the patients reacted. Higher levels of peach LTP-specific IgE were noted for patients with positive skin-prick responses to nuts, 72% of patients; peanut, 67%; maize, 31%; rice, 36%; onion, 35%; orange, 28%; celery, 27%; and tomato, 29%. Patients with higher peach LTP IgE levels also reported reactions to more non-Rosaceae foods.

Rosaceae-allergic patients with high levels of peach LTP-specific IgE show high cross-reactivity with different types of non-Rosaceae plant foods. Thus high levels of IgE to peach LTP may indicate a high risk of reactions to a wide range of fruits, vegetables, and other plant foods.

COMMENT: *A variety of proteins are responsible for cross-reactions or oral allergy syndrome among foods that may differ botanically. Profilin, pathogenesis-related proteins, and LTPs are responsible for many of these cross-reactions. This research group has determined that peach is the best testing allergen to identify LTP sensitivity, which could result in reactions to Rosaceae (apple, apricot, almond, peach, pear, plum, cherry) and other foods. The challenge of food reactions is anything but peachy.*
D. K. L.
Asero R, Mistrello G, Roncarolo D, Amato S: Relationship between peach lipid transfer protein specific IgE levels and hypersensitivity to non-Rosaceae vegetable foods in patients allergic to lipid transfer protein.
Ann Allergy Asthma Immunol. 2004;92:268-272. ♦♦

SIT Reduces Early and Late Asthmatic Reactions

THERE are few placebo-controlled data on how allergen specific immunotherapy affects the early- and late-phase asthmatic reactions. Nineteen asthmatic patients with birch pollen allergy were randomized to receive 1 year of active SIT or placebo treatment. At the end of treatment, both groups underwent allergen and methacholine challenge studies, plus measurement of serum total eosinophil count and eosinophil cationic protein.

Bronchial allergen challenge induced an early asthmatic reaction in all patients and a late reaction in 16 of 19. For patients who received active SIT, the allergen dose required to induce the early-phase reaction increased significantly. In addition, active SIT was associated with a significant reduction in the size of the late-phase reaction. When tested 24 hours after allergen challenge, placebo-treated patients showed significant increases in methacholine sensitivity, total ➤➤

eosinophil count, and serum eosinophil cationic protein. These changes did not occur in patients receiving SIT.

For asthma patients allergic to birch pollen, 1 year of SIT is associated with significant reductions in both the early- and late-phase asthmatic reactions. The findings confirm the anti-inflammatory effects of SIT compared with placebo treatment, including reduced eosinophil numbers and activation and reduced nonspecific methacholine reactivity.

COMMENT: *Previous studies have demonstrated that SIT inhibits late-phase reactions in the skin, nose and lower airways. Previous studies of the lower airways were principally conducted in children allergic to house dust mite or* Alternaria alternata. *In this small but controlled study, the frequency of late asthmatic responses was high before treatment. Following SIT with birch pollen, the late asthmatic response decreased following allergen challenge, as assessed by a reduction in bronchial hyperreactivity and by the number and activation of eosinophils. This confirms the anti-inflammatory effect of SIT.*
E. J. B.
Arvidsson, MB, Löwenhagen O, Rak S: Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. **Allergy.** 2004;59:74-80.

Severe Reactions to Insect Bites Misdiagnosed as Cellulitis: Case Report

MOST hypersensitivity reactions to insects involve Hymenoptera stings, although reactions to various biting insects, such as Diptera, may occur as well. The black fly, order Simuliidae, plays a key role in transmission of onchocerciasis and other vector-borne illnesses. A child with repeated severe hypersensitivity reactions to Simuliidae bites is reported.

At age 3, the child was diagnosed as having cellulitis following a black fly bite, and antibiotics were prescribed. Four days later, she developed ataxia with peripheral weakness and was diagnosed as having acute inflammatory demyelinating polyneuropathy, or Guillain-Barré syndrome. She went on to require mechanical ventilation, but recovered with a mild neurologic deficit. The next year, she again developed a local reaction to black fly bites. Over the next few days, facial puffiness and edema developed, leading to a diagnosis of minimal change nephrotic syndrome. She recovered with 2 years of prednisolone therapy.

Over the next several years, the patient had repeated episodes of "cellulitis" after black fly bites. The lesions generally cleared within a few weeks, and were thought to respond better to intravenous than to oral antibiotics.

By age 8, some form of immunodeficiency causing recurrent cellulitis was suspected. Immunologic studies showed normal levels of IgG, IgA, and IgM. However, the patient's IgE level was very high, decreasing gradually in the months after a "cellulitis" episode. The pattern of springtime reactions after black fly bites led to skin testing, with negative responses to various flies of the order Diptera. However, testing with a Simuliidae whole-body extract yielded a strongly positive reaction with no delayed responses. Control subjects did not react even to high doses of the Simuliidae extract.

In this complex case, severe hypersensitivity reactions to Simuliidae bites appear to have been repeatedly misdiagnosed as cellulitis. These episodes led to unnecessary antibiotic treatment, and ultimately to immunologic workup for suspected immunodeficiency. Recognizing severe local reactions to insect bites and stings can prevent morbidity and inappropriate treatments.

COMMENT: *Large local reactions to biting and stinging insects can be a clinical challenge. Patients often are hesitant to accept simple reassurance when these local reactions are severe. Antibiotic therapy is frequently overused, as these reactions resemble cellulitis. The present case report emphasizes this point, as the affected subject was felt to have recurrent bacterial cellulitis but in reality was suffering from local reactions from a biting insect. Immunotherapy is generally not recommended for this type of local allergic reaction, but there may be exceptions.*
D. K. L.
Orange JS, Song L, Twarog FJ, Schneider LC: A patient with severe black fly (Simuliidae) hypersensitivity referred for evaluation of suspected immunodeficiency.
Ann Allergy Asthma Immunol. 2004;92:276-280. ♦♦

REVIEWS OF NOTE

COMMENT: *Despite the fact that fungi comprise an estimated 25% of the earth's biomass and surround most of us daily, much remains to be proven in the area of mold's effects on human health. The popular news media have spotlighted--some would say sensationalized--the issue of mold allergy and/or toxicity. This article succinctly reviews the available literature on human health effects, summarizes areas of controversy, and generally finds published claims of indoor-mold-induced illness to be lacking scientific foundation.*
R. J. M.
Terr AI: Are indoor molds causing a new disease?
J Allergy Clin Immunol. 2004;113:221-226.

COMMENT: *This meta-analysis provides one more piece of evidence reassuring us of the safety of inhaled corticosteroids. In my opinion, osteoporosis remains a concern because the condition is life-altering and only partially responsive to therapy. Despite the absence of a statistical decrease in bone density in inhaled corticosteroid users, individuals may be affected without differences in the mean data. The other point is the duration of the trials in this analysis was at least one year, which may not be sufficient to detect changes in bone density or fractures. The bottom line is to use the lowest effective dose and consider corticosteroid-sparing therapies.* ➤➤

D. K. L.
Halpern MT, Schmier JK, Van Kerkhove MD, et al: Impact of long-term inhaled corticosteroid therapy on bone mineral density: results of a meta-analysis.
Ann Allergy Asthma Immunol. 2004;92:201-207. ♦♦

COMMENT: *For clinical allergists, allergenic proteins are the "coin of the realm." This very comprehensive review addresses the very important issues of "cross-reactivity" and "co-sensitization" with respect to eleven groups of allergens.*
E. J. B.
Ferreira F, Hawranek T, Gruber P, et al: Allergic cross-reactivity: from gene to the clinic.
Allergy. 2004;59:243-267. ♦♦

COMMENT: *This succinct review puts in perspective the increasing evidence that chronic airway inflammation typical of asthma results in increased oxidative stress of the airways. The effect of currently available anti-asthmatic drugs on oxidative stress has not been completely elucidated. The authors review the potential application of alternative antioxidant compounds in the treatment of asthma.*
E. J. B.
Caramori G, Pap A: Oxidants and asthma.
Thorax. 2004;59:270-273. ♦♦

COMMENT: *These authors conducted a review and meta-analysis of randomized, controlled trials of the effectiveness of leukotriene receptor antagonists (LRAs) in patients with allergic rhinitis. Of 196 citations, 11 studies were selected; 8 permitted evaluation of LRAs alone and the remainder in combination with other treatments. LRAs were modestly better than placebo, as effective as antihistamines, but less effective than nasal steroids in improving symptoms and quality of life in allergic rhinitis.*
E. J. B.
Wilson AM, O'Byrne PM, Parameswaran K: Leukotriene receptor antagonists for allergic rhinitis: a systemic review and meta-analysis.
Am J Med. 2004;116:338-344. ♦♦

COMMENT: *Claims of mold-induced health effects are often controversial. However, there is no controversy about the ability of* Alternaria *species to induce allergy and asthma. This case study presents an opportunity for the authors to review the pathobiology of* Alternaria, *which has been associated with mortality from asthma.*
R. J. M.
Bush RK, Prochnau JJ: Alternaria*-induced asthma.*
J Allergy Clin Immunol. 2004;113:227-234. ♦♦

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