AllergyWatch®

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

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

Volume 16, Number 1 January - February 2014

Are Nasal Steroids Safe Enough for OTC?

ALLERGIC rhinitis is a common problem in children, with a significant impact on school performance and other areas of life. Beclomethasone dipropionate (BDP) nasal aerosol is safe and effective for treatment of allergic rhinitis in adolescents and adults; a formulation for children younger than 12 is under development. This study evaluated the safety and efficacy of BDP nasal aerosol for allergic rhinitis in children.

The randomized multicenter trial included 713 children at 60 U.S. centers, aged 6 to 11 years, with seasonal allergic rhinitis. Children were assigned to once-daily treatment with BDP nasal aerosol, 80 or 160 µg, or placebo nasal aerosol. Treatment continued for 2 weeks. Change in average morning and evening reflective total nasal symptom score were compared among groups.

The 2 BDP nasal aerosol groups had better symptom responses than the placebo group. Differences in average morning and evening reflective total nasal symptom score were -0.71 µg with the 80 µg dose and -0.76 with the 160 µg dose. Differences in average morning and evening instantaneous total nasal symptom score were -0.63 and -0.73, respectively. There was no significant increase in adverse events with BDP, compared to placebo.

The results support the use of BPS nasal aerosol for treatment of seasonal allergic rhinitis in children aged 6 to 11 years. At the 80 µg/d dose, BDP nasal aerosol is likely to be an effective and well-tolerated treatment for moderate to severe allergic rhinitis in children. Further evaluation of safety is needed.

COMMENT: *Topical nasal triamcinolone is now approved for over-the-counter use. This study is accompanied by a pro/con debate highlighting concerns over the potential adverse effects of making inhaled steroids available OTC. (For the pro/con editorials, see Ann Allergy Asthma Immunol. 2013;316-318 and 319-322.) The risks include minimal growth effects in chil-*➤➤

CONTENTS

1 Are Nasal Steroids Safe Enough for OTC?
2 Exercise-Induced Laryngomalacia and VCD--Is There a Clinical Difference?
3 Predictors of Response to Add-On Tiotropium
3 Trial Supports Safety of Tiotropium Respimat Inhaler
4 Exhaled NO and Blood Eosinophils Predict Asthma in the Population
4 In Baltimore, Mouse Affects Asthma More than Cockroach
4 Risk Factors and Mediators for Severe Anaphylaxis: Prospective Study
5 Dampness and Mold Linked to Rhinitis Outcomes
5 Specialties Differ in Managing AD in Young Children
6 Genes and SHS Show Synergistic Effect on Adult Asthma Risk
6 Eosinophil Inflammatory Markers Vary by Body Weight in Severe Asthma
7 Outdoor Allergens Linked to Seasonal Variations in Asthma
7 More on Palivizumab and Prevention of Recurrent Wheezing in Premature Infants
8 Judge Not the Vitamin D Status by the Color of the Skin
8 Once-Daily ICS/LABA Combination for Asthma: Simple and Effective
9 Airway Eosinophilia Is Related to Some Features of Remodeling--But Not All
9 CLINICAL TIDBITS
9 Nasal ST2 and IL-16 Increase with Allergen Challenge
9 Hairdressers May Be More Likely to React to NMBAs
10 Is Immunotherapy an Option for Atopic Dermatitis?
10 Can We Predict Which PPI to Use in Patients with PPI Hypersensitivity Reactions?
11 Does Maternal Infertility Increase a Child's Risk for Nut Sensitization?
11 Premedication May Reduce Systemic Reactions to Fire Ant Rush Immunotherapy
11 Influenza-Related Deaths in Children: Patient Characteristics
12 Bronchial Thermoplasty for Refractory Asthma: Safety and Effectiveness
12 REVIEWS OF NOTE

The American College of Allergy, Asthma & Immunology expresses its appreciation to MERCK for its grant in support of the publication of *AllergyWatch*®.

The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

"*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 Anthony Montanaro, MD., Editor, The Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, PV 320, Portland, Oregon 97201-3098. Telephone (503) 494-8531. ISSN 1521-2440.

dren, especially with concomitant inhaled steroids for asthma; and failure to seek specialty evaluation and treatment for allergic rhinitis. The study authors conclude that a 2-week trial of BDP nasal aerosol is safe and efficacious in children with moderate to severe allergic rhinitis. However, long-term use should be monitored.
C.C.R.
Storms WW, Segall N, Mansfield LE, et al: Efficacy and safety of beclomethasone dipropionate nasal aerosol in pediatric patients with seasonal allergic rhinitis.
Ann Allergy Asthma Immunol. 2013;111:408-414. ♦♦

Exercise-Induced Laryngomalacia and VCD--Is There a Clinical Difference?

An incorrect diagnosis of asthma may be made in patients with exercise-induced respiratory symptoms and paradoxical laryngeal motion. Previous reports have described exercise-induced vocal cord dysfunction (VCD) and exercise-induced laryngomalacia. Hypothesizing that exercise-induced VCD and laryngomalacia represent the same clinical syndrome, the authors performed a systematic comparison of patients receiving these diagnoses.

The retrospective analysis included patients with confirmed diagnoses of exercise-induced VCD and exercise-induced laryngomalacia at the authors' practice. All patients had symptoms provoked by a free running exercise challenge, with documented paradoxical motion of the vocal cords (VCD, 83 patients) or paradoxical arytenoid motion without abnormal vocal cord motion (laryngomalacia, 60 patients).

Patients with exercise-induced VCD were somewhat older, had a higher body mass index, and had a higher grade point average (GPA), compared to those with laryngomalacia. However, the two groups were similar in terms of previously reported "hallmark features" of these disorders, including sex distribution, presenting symptoms, other aggravating factors, atopy, confirmed bronchospasm, number of asthma controller medications, history of psychiatric disorders, and lung function. Few patients fit the profile of an "elite" athlete with anxiety or depression.

The analysis finds "remarkably few differences" between patients receiving a diagnosis of exercise-induced VCD versus laryngomalacia. The authors call for prospective studies to clarify whether these conditions are truly distinct syndromes. They also suggest that the possibility of paradoxical laryngeal motion be considered in adolescents with apparent exercise-induced asthma who do not have an adequate response to treatment.

COMMENT: *Current guidelines recommend consideration of VCD in elite athletes with exercise-related dyspnea unresponsive to asthma therapy. This study debunks the stereotyped VCD profile of an elite athlete with high GPA and anxiety or depression, noting little difference between individuals with confirmed exercise-induced VCD and exercise induced laryngomalacia. Although patients with VCD were older, with higher BMI and GPA, there were otherwise no differences in demographics, pulmonary function, or symptomatic presentation. The study was limited by its retrospective nature and lack of continuous laryngeal visualization during peak exercise. The two entities may be indistinguishable as part of a spectrum of laryngeal obstruction or vulnerable laryngeal syndrome in the differential diagnosis of exercise-induced bronchoconstriction.*
C.C.R.
Tilles SA, Ayars AG, Picciano JF, Altman K: Exercise-induced vocal cord dysfunction and exercise-induced laryngomalacia in children and adolescents: The same clinical syndrome?
Ann Allergy Asthma Immunol. 2013;111:342-346. ♦♦

Predictors of Response to Add-On Tiotropium

RECENT studies have indentified predictors of response to various asthma medications. However, there are few data on factors affecting the response to long-acting bronchodilators, including patients treated with both long-acting β-agonists and long-acting muscarinic agonists. This study evaluated predictors of response in asthma patients receiving add-on therapy with salmeterol or tiotropium.

The randomized trial included 210 patients with inadequate control of asthma symptoms on low-dose inhaled corticosteroid (ICS). Patients were assigned to double the dose of ICS alone or single-dose ICS plus salmeterol or tiotropium. Patients received each treatment for 2 weeks, with 1-week washout periods. Individual patient responses and differential responses to salmeterol versus tiotropium were assessed, along with predictors of clinical response.

For FEV_1, 104 patients showed a differential response to tiotropium while 62 showed a differential response to salmeterol. In contrast, similar numbers of patients had differential responses for the outcomes of morning peak flow (PEF) and asthma control days.

On analysis of predictors, patients with an acute response to a short-acting bronchodilator, especially albuterol, were more likely to have positive responses to tiotropium for FEV_1 and morning PEF: odds ratio 4.08 and 2.12, respectively. Patients with a lower FEV1/FVC ratio also had a better FEV_1 response to tiotropium: each 1% decrease in FEV_1/FVC was associated with a 0.39% increase in FEV_1. Higher cholinergic tone also predicted a better response to tiotropium. Sex, ethnicity, atopy, IgE level, sputum eosinophil count, exhaled nitric oxide, duration of asthma, and body mass index were not significant predictors.

The study identifies factors associated with a better response to add-on tiotropium in patients who do not have adequate symptom control with ICS alone. Patients with evidence of airway obstruction--reduced FEV_1/FVC and/or acute response to albuterol--may be good candidates for add-on tiotropium. Further study is needed to determine the best use of this strategy.

COMMENT: *Recent efforts to manage persistent asthma have focused on targeted therapy and personalized treatment approaches. This study from the Asthma Clinical Research Network reports results from a blinded, three-way crossover trial that used add-on therapy for asthmatic adults whose asthma was not controlled with ICS alone. Several factors seemed to predict the response to tiotropium, including acute reversibility of FEV_1 after albuterol, reduced FEV_1/FVC ratio, and increased cholinergic tone. Surprisingly, acute response to ipratropium and various markers of airway inflammation did not predict the response to add-on tiotropium. The authors suggest that asthma patients with reduced FEV_1/FVC and/or a positive response to albuterol may be good candidates for add-on tiotropium, although confirmatory studies are necessary before we change our clinical practice.*
S.M.F.

Peters SP, Bleecker ER, Kunselman SJ, et al: Predictors of response to tiotropium versus salmeterol in asthmatic adults.
J Allergy Clin Immunol. 2013;132:1068-1074. ♦♦

Trial Supports Safety of Tiotropium Respimat Inhaler

TIOTROPIUM aqueous solution, at a dose of 5 μg via Respimat inhaler, has shown efficacy similar to that of an 18 μg dose of tiotropium dry-powder formulation delivered via HandiHaler. However, placebo-controlled trials suggest higher mortality with tiotropium Respimat, compared to tiotropium HandiHaler. This trial compared mortality with tiotropium Respimat versus HandiHaler in patients with chronic obstructive pulmonary disease (COPD).

In the randomized trial, 17,135 COPD patients were assigned to once-daily treatment with tiotropium Respimat, 2.5 or 5.0 μg, or tiotropium HandiHaler, 18.0 μg. The analysis included a noninferiority study with a primary endpoint of death and a superiority study with an endpoint of first COPD exacerbation. Cardiovascular safety was assessed in patients with stable cardiac disease.

At a mean follow-up of 2.3 years, mortality was similar across treatment groups: 7.7% with tiotropium Respimat 2.5 μg, 7.4% with tiotropium Respimat 5.0 μg, and 7.7% with tiotropium HandiHaler 18.0 μg. Exacerbation rates were 49.4%, 47.9%, and 48.9%, respectively. Causes of death and rates of major adverse cardiovascular events were similar as well.

Tiotropium Respimat has safety and efficacy similar to that of tiotropium HandiHaler in patients with COPD. The large randomized trial shows no significant difference in serious adverse events or in fatal or nonfatal cardiovascular events. The findings contrast with the safety concerns raised by previous meta-analyses.

COMMENT: *Recent reports have raised concerns about the safety of tiotropium with the Respimat inhaler, in contrast to the experience with tiotropium via HandiHaler. Those concerns prompted a large-scale, prospective evaluation of the safety and efficacy of tiotropium Respimat, including more than 34,000 patient-years of exposure. In this study of 17,135 patients with COPD (including 1,825 with cardiac arrhythmia and 3,152 with ischemic heart disease, coronary artery disease, or heart failure), tiotropium Respimat had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler. Notably, there was no placebo arm and patients with unstable cardiovascular conditions were excluded from the study.*
C.D.
Wise RA, Anzueto A, Cotton D, et al: Tiotropium Respimat inhaler and the risk of death in COPD.
N Engl J Med. 2013;369:1491-1501. ♦♦

Exhaled NO and Blood Eosinophils Predict Asthma in the Population

ASTHMA is associated with elevated exhaled nitric oxide (eNO) and blood eosinophil count (B-Eos), reflecting local and systemic inflammation, respectively. There are few data on associations of these markers with asthma in the general population. Associations of eNO and B-Eos, alone and together, with asthma outcomes and wheezing were evaluated in a National Health and Nutrition Examination Survey (NHANES) sample.

The analysis included 12,408 children and adults participating in NHANES 2007-2008 and 2009-2010. Measurements of eNO and B-Eos were evaluated for association with current wheezing, diagnosed asthma, and asthma events within the preceding 12 months.

Participants with intermediate or high values of eNO or B-Eos had higher rates of asthma, wheezing, and asthma attacks. Asthma-related emergency department (ED) visits were associated with intermediate and high B-Eos, but not eNO. For the combination of high eNO (50 ppb or higher) and high B-Eos (500 cells/mm_3 or higher), adjusted odds ratios were 4.5 for wheezing, 5.1 for asthma, 5.4 for asthma attacks, and 2.9 for asthma-related ED visits. The association with wheezing was significant even after exclusion of current asthma.

Elevated levels of eNO and B-Eos are independently associated with wheezing, asthma diagnosis, and asthma events in a large general population sample. The results suggest that local and systemic Th2 cytokine-driven processes contribute to the development of respiratory symptoms and clinical asthma. While further study is needed, measurement of both eNO and B-Eos may aid in identifying patients with wheezing or asthma who are at risk of asthma exacerbations.

COMMENT: *Recently there has been an effort to identify various asthma phenotypes with the hope that this will guide us in targeting therapies to help achieve symptom control. Using NHANES data, these authors demonstrate that although both B-Eos and eNO independently identified asthmatics at risk for wheezing and exacerbations, the combination of the two was associated with a fivefold increase in asthma risk. Interestingly, each marker seemed to identify a different phenotype for eosinophilic inflammation, suggesting that the B-Eos reflects the IL-5 pathway while eNO is associated with IL-4/IL-13 triggers. The authors suggest that this could represent a "double-hit" for the development of eosinophilic inflammation in asthma.*
S.M.F.

Malinovschi A, Fonseca JA, Jacinto T, et al: Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects.
J Allergy Clin Immunol. 2013;132:821-827. ♦♦

In Baltimore, Mouse Affects Asthma More than Cockroach

COCKROACH and mouse allergens are thought to be major contributors to asthma morbidity in urban minority children. The importance of these two allergens in specific inner-city communities remains unclear, as does the role of sensitization and exposure to multiple allergens. This study sought to identify the allergens with the greatest impact on pediatric asthma morbidity in Baltimore.

The researchers identified 144 children with persistent asthma in Baltimore City. The children ranged from 5 to 17 years of age; more than 90% were African American. Each subject underwent skin prick testing at baseline with clinical follow-up for 12 months. Dust from the children's homes was tested for indoor allergens. Sensitization and exposure status for each allergen were analyzed, adjusted for age, sex, and serum total IgE.

Based on samples of bedroom dust, 41% of children were sensitized and exposed to mouse and the same percentage to cockroach. For both allergens, sensitization and exposure were associated with acute care visits for asthma as well as bronchodilator reversibility. In addition, mouse sensitization and exposure were associated with decreased FEV_1/FVC percentage values and exhaled nitric oxide. Mouse-specific IgE was associated with greater health impact of asthma for a wide range of outcomes, compared to cockroach-specific IgE.

The associations with mouse allergen were independent of cockroach allergen. Although children sensitized and exposed to both mouse and cockroach generally had poorer asthma outcomes, this mainly reflected the contribution of mouse allergen.

For asthmatic children in Baltimore, mouse allergen appears to be a stronger contributor to poor asthma outcomes than cockroach allergen. This is so even in a population with high levels of exposure to both allergens. The authors discuss the importance of identifying the allergen most relevant to public health in each specific community.

COMMENT: *In this study, both mouse and cockroach allergens were present at significant levels in the homes of urban children with asthma. However, mouse allergen levels and sensitization were associated with greater asthma morbidity. The small sample was a weakness of the study, but strengths include the prospective design with careful repeated allergen measurements and clinical follow-up. The authors suggest that relevant allergen identification in a community is critical to focus intervention efforts for asthma control. Since mouse allergen is also found in suburban homes, this study has implications for all, and highlights the need to properly identify relevant triggers for our asthmatic patients.*
S.M.F.

Ahluwalia SK, Peng RD, Breyesse PN, et al: Mouse allergen is the major allergen of public health relevance in Baltimore City.
J Allergy Clin Immunol. 2013;132:830-835 ♦♦

Risk Factors and Mediators for Severe Anaphylaxis: Prospective Study

MANY different mediators have been implicated in anaphylaxis. However the correlations between mediators and their effects on reaction severity ➤➤

remain unclear. This study prospectively analyzed the clinical and biochemical findings in a large sample of patients seen in the emergency department (ED) for anaphylaxis.

The study included 402 patients seen at eight Australian EDs for a total of 412 apparent anaphylactic reactions between 2006 and 2009. Biochemical mediators--including mast cell tryptase, histamine, anaphylatoxins, cytokines, soluble tumor necrosis factor receptor I, and platelet activating factor acetyl hydrolase--were measured in serial blood samples. Mediator patterns were assessed by principal component analysis. Logistic regression was performed to identify mediator patterns and other risk factors for severe and delayed anaphylactic reactions.

Three hundred fifteen reactions met National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria for anaphylaxis. Ninety-seven reactions were severe, a rate of 31%. Of these, 46% were hypotensive, 24% were hypoxemic, and 30% were mixed reactions. One patient died.

There was a 9.2% rate of delayed deterioration after treatment with epinephrine; this was more common after hypotensive reactions and in patients with preexisting lung disease. Three-fourths of delayed deteriorations occurred within 4 hours after epinephrine administration. Two of the remaining seven delayed deteriorations were severe, occurring within 10 hours after initially severe reactions.

All biochemical mediators investigated were associated with severity. Delayed deterioration was linked to a mediator pattern of mast cell tryptase, histamine, interleukin-6 and -10, and tumor necrosis factor receptor I. Severe reactions were associated with low platelet activating factor acetyl hydrolase activity.

Prospective analysis of a large series of anaphylactic events identifies factors associated with severe reactions. Severe anaphylaxis appears to be driven by multiple inflammatory pathways. Delayed deterioration occurs in about 9% of patients; in these cases, initial epinephrine treatment may mask a protracted inflammatory process.

COMMENT: *This unique report prospectively studies mediator release in patients with anaphylaxis. Analyzing data collected over 2½ years in eight Australian EDs, the authors concluded that more severe patterns of clinical anaphylaxis were associated with older age, lung disease and reactions triggered by medications. Interestingly, delayed or biphasic reactions occurred in 9.2% of cases, with 76% of these patients presenting within 4 hours after initial treatment with epinephrine. Low levels of platelet activating factor were associated with more severe clinical presentations. Although this inverse association has been previously reported, the involvement of multiple inflammatory markers is of interest--particularly since the data suggest that we should be monitoring patients who present with anaphylaxis for at least 4 hours.*
S.M.F.

Brown SGA, Stone SF, Fatovich DM, et al: Anaphylaxis: clinical patterns, mediator release, and severity.
J Allergy Clin Immunol. 2013:132:1141-1149. ♦♦

Dampness and Mold Linked to Rhinitis Outcomes

EXPOSURES related to indoor dampness are common worldwide, especially in warm climates. The relationship of indoor dampness with molds and rhinitis remains unclear. This article presents the first systematic review and meta-analysis of the literature on this topic.

The systematic review identified 31 studies of the association between indoor dampness and mold and the outcomes of rhinitis, allergic rhinitis, or rhinoconjunctivitis. On meta-analysis, the factor most strongly related to health outcomes was mold odor: effect estimate (EE) 2.18 for rhinitis and 1.87 for allergic rhinitis. Significant associations were also noted for visible mold: EE 1.82 for rhinitis, 1.51 for allergic rhinitis, and 1.66 for rhinoconjunctivitis. Associations with dampness were also significant, and similar to those for visible mold. Water damage was not associated with any of the rhinitis outcomes.

Analysis of available evidence supports the association between indoor dampness and molds with rhinitis outcomes. The strong link to mold odor suggests that microbial causes are important. Interventions to prevent or eliminate indoor dampness and mold are likely to alleviate problems with rhinitis.

COMMENT: *Indoor allergens and odors are important contributors to respiratory illness. This meta-analysis included 31 studies examining indoor dampness and mold on the risk of developing rhinitis. It was not just dampness or the presence of mold in the home that was associated with rhinitis--rather, mold odor itself was the strongest determinant for rhinitis. The importance of fragrances and irritants as triggers for rhinitis and respiratory illness is well known. Perhaps we should be asking our patients, "How does your house smell?"*
S.M.F.

Jaakkola MS, Quansah R, Hugg TT, et al: Association of indoor dampness and molds with rhinitis risk: A systematic review and meta-analysis.
J Allergy Clin Immunol. 2013;132:1099-1110. ♦♦

Specialties Differ in Managing AD in Young Children

ATOPIC dermatitis (AD) is a common condition in children, most often beginning in infancy. Treatment focuses on reducing symptoms and preventing flares; dietary recommendations vary. This study compared the management of AD in infants and children under age 3 by U.S. pediatricians, dermatologists, and allergists.

The survey study included a nationally representative sample of 101 pediatricians, 26 dermatologists, and 26 allergists. Management of AD in children aged 36 months or younger was compared among the three groups of specialists, including referrals, laboratory tests, and dietary and/or pharmacologic management. ➤➤

Pediatricians were more likely to refer infants and children with AD to dermatologists than to allergists: 52.4% versus 32.0% in mild cases and 60.6% versus 38.1% in moderate to severe cases. For dermatologists, referral to allergists increased from 9.1% in mild cases to 40.7% in moderate to severe cases.

Dietary management--ie, a change in infant formula, with or without emollients--was reported in at least some patients by 59.0% of pediatricians and 61.5% of allergists, compared to 26.9% of dermatologists. Soy-based formulas were commonly recommended. Initial pharmacologic therapy for mild AD usually consisted of topical emollients, topical corticosteroids, and barrier repair topical therapy/medical devices.

A combined dietary and pharmacologic approach was reported by more than 80% of physicians. However, dermatologists were more likely to use pharmacologic treatments only. For a similar proportion of physicians, treatment was influenced by the location of AD lesions.

Pediatricians, dermatologists, and allergists differ in their management of AD in infants and toddlers. In general, pediatricians and allergists are more likely to follow dietary strategies while dermatologists use pharmacologic approaches. The findings underscore the need for a standardized, evidence-based approach to clinical management of AD in infants and young children.

COMMENT: *Allergists and dermatologists commonly see children with refractory AD. This study reviews differences in treatment between pediatricians and specialists. Allergists tend to investigate etiologies as well as treating children with topical medications. Dermatologists tend to rely on topical medicaments only. Reliance on practice parameters is helpful to our management of these difficult cases.*
S.F.W.

Saavedra JM, Boguniewicz M, Chamlin S, et al: Patterns of clinical management of atopic dermatitis in infants and toddlers: A survey of three physician specialties in the United States.
J Pediatr. 2013;163:1747-1753. ♦♦

Genes and SHS Show Synergistic Effect on Adult Asthma Risk

BASED on a growing body of evidence, secondhand smoke (SHS) may be an independent risk factor for asthma in adults as well as children. Identifying susceptible populations would help in targeting preventive actions and interventions. This study evaluated the relationship between asthmatic heredity and the effects of SHS on the risk of adult-onset asthma.

The population-based study included 226 Finnish adults (aged 21 to 63 years) with adult-onset asthma, matched to 450 asthma-free controls from the same geographic area. Current and former smokers were excluded from both the case and control groups. Exposure to SHS and family history of asthma were assessed by questionnaires. The researchers assessed the independent and joint effects of different categories of asthma heredity and SHS exposure on the risk of adult-onset asthma.

There was a synergistic effect of parental history of asthma and recent SHS exposure on the risk of new-onset asthma. Adjusted odds ratios were 1.97 for SHS, 2.94 for parental asthma, and 9.08 for the joint effect of both risk factors. There was evidence of a dose-dependent synergistic effect for both recent and cumulative SHS exposure: relative excess risk of 6.17 for adults with parental asthma and SHS exposure of more than 100 cigarette-years. There was also a combined effect of SHS and history of asthma in siblings.

Family history of asthma and exposure to SHS have a synergistic effect on the risk of developing adult-onset asthma. The joint effect appears stronger at higher levels of exposure. Individuals with asthmatic heredity could be targeted for avoidance of SHS exposure to reduce their risk of adult-onset asthma.

COMMENT: *This study supports the gene and environment interaction with SHS in a genetically predisposed population. This appears to be a dose-dependent phenomenon, with cumulative exposure dramatically increasing the relative risk of asthma. These data are very important and useful in counseling families regarding SHS exposure.*
B.E.C.

Lajunen TK, Jaakkola JJK, Jaakkola MS: The synergistic effect of heredity and exposure to second-hand smoke on adult-onset asthma.
Am J Respir Crit Care Med. 2013;188:776-782. ♦♦

Eosinophil Inflammatory Markers Vary by Body Weight in Severe Asthma

RECENT studies suggest that obesity may be associated with a distinct phenotype of severe asthma. However, there is debate over the association between airway inflammation and obesity in severe asthma. Sputum mediator profiles and eosinophilic inflammation were compared in normal-weight, overweight, and obese patients with severe asthma.

Based on body mass index, 131 patients with severe asthma were classified as lean, overweight, and obese: 28, 48, and 55 patients, respectively. Sputum interleukin-5 (IL-5) was significantly correlated with body mass index: geometric mean values were 1.8 pg/mL in obese, 1.1 pg/mL in overweight, and 0.9 pg/mL in normal weight patients. Sputum cell count and other sputum mediators did not differ among groups.

An independent group of 45 patients with severe asthma and 19 healthy controls, also stratified by body weight, underwent bronchoscopy. Median eosinophil count in the bronchial submucosa was 19.4 cells/mm^2 in the obese group versus 8.8 cells/mm^2 in the lean group and 4.6 cells/mm^2 in healthy controls. Blood and sputum eosinophil counts were unrelated to body mass index.

In severe asthma, obesity is related to elevated sputum IL-5 and submucosal eosinophil levels, but not to sputum eosinophil count. It remains to be seen whether obese patients with severe asthma can benefit from specific antieosinophil therapies, and whether diet and lifestyle interventions have anti-inflammatory effects in these patients. ➤➤

COMMENT: *This article continues to expand our knowledge base regarding identification of subjects who may benefit from adjunctive therapy with disease-modifying agents. The understanding that sputum eosinophilia is not an appropriate marker in obese patients complicates evaluation and assessment for additional treatment. Clearly, more work is needed to define the appropriate patient population who may benefit from anti-IL-5 therapy.*
B.E.C.

Desai D, Newby C, Symon FA, et al: Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma.
Am J Respir Crit Care Med. 2013;188:657-663. ♦♦

Outdoor Allergens Linked to Seasonal Variations in Asthma

SEASONAL fluctuations in asthma exacerbations are attributed to variations in ambient allergens, respiratory infections, and weather. Small studies suggest that asthma severity may be greater in summer among patients sensitized to grass, and greater in winter for those sensitized to house dust mite. This study evaluated seasonal variations in asthma in a population of patients with known sensitization status.

The study included 2,637 young adult asthma patients participating in the European Community Respiratory Health Survey. Sensitization was assessed by pinprick testing; months of the year in which patients experienced asthma attacks were assessed by questionnaire. Seasonal variations in asthma were assessed by sensitization status.

Most patients reported more-frequent asthma attacks during certain times of the year, ranging from 47% in Sweden to 86% in Spain. These seasonal variations were unrelated to sensitization to house dust mite or cat. With some differences by region, sensitization to grass, birch, and *Alternaria* were associated with seasonal variations in asthma.

Southern European patients with grass sensitization were more likely to report asthma attacks in spring or summer versus winter: odds ratio (OR) 2.60 in March/April versus 4.43 in May/June. In contrast, for Northern European patients, the peaks were smaller and appeared later in the year: OR 1.25 in May/June and 1.66 in July/August. Asthma patients with self-reported hay fever but without grass sensitization did not have seasonal variations.

The findings confirm seasonal variations in asthma attacks among young asthmatic adults. Patterns of variation are affected by sensitization to outdoor allergens, but not indoor allergens. Seasonal allergens are an important trigger for asthma attacks in sensitized patients.

COMMENT: *This appears to be the largest database study confirming what we in the allergy community have known for decades. It is interesting to note that indoor allergen exposure to house dust mite or cat did not modify the seasonal variation associated with pollens. (Also see the accompanying editorial by Cecchi: Eur Respir J. 2013;42:898-900.)*
B.E.C.

Canova C, Heinrich J, Anto JM, et al: The influence of sensitisation to pollens and moulds on seasonal variations in asthma attacks.
Eur Respir J. 2013;42:935-945. ♦♦

More on Palivizumab and Prevention of Recurrent Wheezing in Premature Infants

EARLY infection with respiratory syncytial virus (RSV) is a risk factor for childhood asthma and wheezing. In preterm infants, monthly treatment with the humanized anti-RSV antibody palivizumab reduces hospitalization for RSV infection, and may reduce the incidence of current wheezing. This "real world" study assessed the impact of prophylactic RSV on the development of recurrent wheezing in preterm infants.

The prospective, observational study included 444 preterm infants enrolled at 52 Japanese hospitals. As part of standard medical practice during the 2007-08 RSV season, 349 infants received palivizumab during the first 6 months of life. The remaining 95 infants were not treated. At follow-up to age 3, rates of physician-diagnosed recurrent wheezing were compared between groups. The study achieved 98% follow-up using a mobile phone-based reporting system incorporating a QR code reader.

The incidence of recurrent wheezing through age 3 was 6.4% in preterm infants receiving palivizumab versus 18.9% in untreated infants: relative risk 0.34. The protective effect remained significant after adjustment for known risk factors. Prophylactic palivizumab was also associated with a trend toward reduction in atopic asthma, but not in hospitalizations for respiratory-related diseases.

This Japanese experience suggests that treating preterm infants with palivizumab reduces the risk of recurrent wheezing up to age 3. The authors plan a future report extending follow-up through age 6.

COMMENT: *This industry-sponsored observational study from Japan supports previous reports suggesting that avoiding early RSV infection in preterm infants with the use of palivizumab decreases the incidence of wheezing in the first few years of life. However, as discussed in a thoughtful accompanying editorial (Pediatrics. 2013;132;915-916), the bigger question is whether this intervention is cost-effective. The benefit of RSV prophylaxis is a small reduction in episodes of recurrent wheezing above the approximately 5% absolute reduction in RSV hospitalization rates. However, the cost of prophylaxis (acquisition cost, $202, 635) far exceeds the savings from reduced hospitalization rates ($8,530) in the United States, making it challenging to justify.*
C.D.

Yoshihara S, Kusuda S, Mochizuki H, et al: Effect of palivizumab prophylaxis on subsequent recurrent wheezing in preterm infants.
Pediatrics. 2013;132:811-818. ♦♦

Judge Not the Vitamin D Status by the Color of the Skin

BLACK Americans have lower total 25-hydroxyvitamin D levels compared to their white counterparts. Racial differences in the vitamin D-binding protein gene have been reported, with possible implications for vitamin D deficiency. This study compared vitamin D-binding gene and protein levels in black versus white Americans.

The study included data on 2,085 black and white adults from a U.S. population-based study. In addition to measurement of total 25-hydroxyvitamin D, vitamin D-binding protein, parathyroid hormone, and bone mineral density (BMD), subjects underwent genotyping for the common rs7041 and rs4588 polymorphisms. In those identified as homoxygotes, bioavailable 25-hydroxyvitamin D was measured.

Mean total 25-hydroxyvitamin D level was 15.6 ng/mL in black versus 25.8 ng/mL in white participants. Black subjects also had lower levels of vitamin D-binding protein: 168 versus 337 μg/mL, respectively. After adjustment for other factors, the rs7041 and rs4588 polymorphisms explained nearly 80% of the variation in vitamin D-binding protein levels, as well as 10% of the variation in total 25-hydroxyvitamin D.

Once genotype was taken into account, race explained less than 0.1% of the variation in vitamin D-binding protein. Despite their lower vitamin D levels, black subjects had higher mean BMD. Within each parathyroid hormone category, total 25-hydroxyvitamin D was lower in black subjects. On analysis of the homozygous subgroup, bioavailable 25-hydroxyvitamin D levels were similar by race and within categories of parathyroid hormone level.

Racial differences in vitamin D-binding protein help to explain differences in vitamin D levels and clinical vitamin D deficiency in black versus white patients. Black patients have lower total 25-hydroxyvitamin D, but also have lower levels of vitamin D-binding protein; thus, levels of bioavailable 25-hydroxyvitamin D levels are similar between racial groups. Measurement of vitamin D-binding protein could have important implications for assessing racial/ethnic differences in vitamin D levels.

COMMENT: *Low levels of total 25-hydroxyvitamin D are common among black Americans, frequently resulting in a diagnosis of vitamin D deficiency. However, blacks have higher BMD and a lower risk of fragility fracture. This novel study shows that racial differences in the prevalence of common genetic polymorphisms result in lower levels of vitamin D-binding protein in black Americans, but similar concentrations of estimated bioavailable 25-hydroxyvitamin D similar to those in white Americans. At the least, this study should trigger the development of assays that directly measure bioavailable 25-hydroxyvitamin D as an indicator of vitamin D status. An accompanying editorial (N Engl J Med. 2013; 369:2047-2048) speculates on the evolutionary implications of these differences.*
C.D.

Powe CE, Evans MK, Wenger J, et al: Vitamin D-binding protein and vitamin D status of black Americans and white Americans.
N Engl J Med. 2013;369:1991-2000. ♦♦

Once-Daily ICS/LABA Combination for Asthma: Simple and Effective

ADD-ON therapy with a long-acting inhaled β_2-agonist (LABA) may be used for asthma that is uncontrolled by inhaled corticosteroid (ICS) therapy. A combination of fluticasone furoate (FF) with the novel LABA vilanterol (VI) is under development as a once-daily treatment for asthma and COPD. This trial compared FF/VI with fluticasone propionate/salmeterol (FP/SAL) for persistent asthma.

The randomized, double-blind trial included 806 patients with persistent asthma that remained uncontrolled on medium doses of ICS. Patients were assigned to receive FF/VI 100/25 μg once daily in the evening, delivered via the Ellipta dry-powder inhaler; or FF/SAL 250/50 μg twice daily via Diskus/Accuhaler. Serial weighted mean FEV_1 from 0 to 24 hours was compared after 24 weeks of treatment, along with secondary outcomes.

The two combinations led to similar and significant improvements in 0- to 24-hour weighted mean FEV_1: 341 mL with FF/VI and 377 mL with FP/SAL. Serial weighted mean FEV_1 from 0 to 4 hours and trough FEV_1 were similar as well. Important clinical outcomes, including asthma control, quality of life, and exacerbation rates, were also similar with FF/VI and FP/SAL. The two combinations were well-tolerated, had no significant effects on urinary cortisol excretion or vital signs, and caused no serious adverse events.

The once-daily FF/VI combination shows evidence of benefit in patients with persistent asthma despite medium-dose ICS. Improvements in lung function, asthma control, and quality of life are similar to those with twice-daily FP/SAL. Future studies should evaluate the long-term benefits of once-daily FF/VI in "real world" settings.

COMMENT: *Asthma therapies have evolved over the last several decades from four-times-daily β-agonists to twice-daily ICS and LABA combination therapies. This Glaxo-sponsored trial evaluated the efficacy and safety of a new once a day ICS/LABA combination FF/VI, compared to FP/SAL twice daily, in patients whose asthma was not controlled on medium ICS monotherapy. Once-daily FF/VI brought similar improvement in baseline FEV_1 and all secondary outcomes, compared to FP/SAL. Exacerbation rates were quite low in both groups. A once-daily combination therapy is clearly appealing; a "real-world" effectiveness trial would be interesting to see if there really is an advantage to this dosing regimen. This once-daily therapy certainly adheres to the "KISS" principle: keep it simple stupid.*
D.A.K.

Woodcock A, Bleecker ER, Lotvall J, et al: Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial.
Chest. 2013;144:1222-1229. ♦♦

Airway Eosinophilia Is Related to Some Features of Remodeling--But Not All

AIRWAY eosinophilia and remodeling are key characteristics of asthma. Eosinophilia is linked to submucosal matrix deposition, but its interrelationships with other aspects of remodeling are unclear. This study evaluated associations of airway eosinophilia with epithelial damage and other characteristics of airway remodeling.

The researchers analyzed bronchial biopsy specimens from patients with mild to moderate asthma: 20 each with low (0 to 0.45 mm^{-2}) and high (23.43 to 46.28 mm^{-2}) submucosal eosinophil counts. Epithelial damage was compared between groups, including epidermal growth factor receptor staining to differentiate in vivo damage from that caused by sampling or biopsy processing. The study also assessed other features of remodeling, including mucin expression, airway smooth muscle (ASM) hypertrophy, and inflammatory cells within ASM.

Specimens from patients with high submucosal eosinophil counts showed 27.37% in vivo damaged epithelium, compared to 4.14% in the low-eosinophil group. There was no significant difference in mucin expression or goblet cell numbers, although the high-eosinophil group had higher MUC-2 expression. Both asthma groups had increased percentage of submucosa occupied by ASM, compared to nonasthmatic controls. Within the ASM, high-eosinophil specimens showed higher eosinophil and T-lymphocyte numbers, compared to the low-eosinophil and control groups. Mast cell numbers were increased in the high-eosinophil group compared to controls.

The results show a significant and possibly causative association between submucosal eosinophilia and epithelial damage in bronchial biopsies from patients with mild to moderate asthma. High submucosal eosinophil counts are also associated with ASM infiltration of eosinophils and T lymphocytes, but not with mucus metaplasia or smooth muscle hypertrophy. More research on the contributions of eosinophils to airway remodeling in asthma is needed.

COMMENT: *Airway eosinophilia is considered a hallmark of asthma, but its relationship to features of remodeling is not entirely clear. Epithelial damage previously attributed to eosinophils may be due to damage during sampling or processing. This study of patients with mild to moderate asthma confirms that increased submucosal eosinophilia is associated with a lower amount of intact epithelium, which is not due to sampling or processing. In contrast, airway smooth muscle is higher in asthmatic patients versus controls--but this is irrespective of elevated airway eosinophils, suggesting a different mechanism. The study helps confirm the role of eosinophils in epithelial damage but implies that other therapeutic targets may be necessary to affect the increased airway smooth muscle in asthma patients.*
D.A.K.
Wilson SJ, Rigden HM, Ward JA: The relationship between eosinophilia and airway remodeling in mild asthma.
Clin Exp Allergy. 2013;43:1342-1350. ♦♦

CLINICAL TIDBITS

Nasal ST2 and IL-16 Increase with Allergen Challenge

THE newly discovered cytokine interleukin-33 (IL-33) and its decoy receptor ST2, along with IL-16, are elevated in the serum of patients with allergic rhinitis. Animal models suggest that IL-16, soluble ST2, or anti-IL-33 may reduce type 2 cytokines in allergic asthma or allergic rhinitis. Release of these and other cytokines in response to allergen were studied in patients with allergic rhinitis.

Seasonal allergen exposure led to increased nasal levels of IL-5, IL-16, and soluble ST2 in allergic rhinitis patients, although IL-33 remained undetectable. Nasal IL-16 showed a weak inverse correlation with nasal symptoms; soluble ST2 was inversely correlated with nasal symptoms and positively correlated with IL-16.

Nasal allergen challenge led to increases in nasal IL-5, IL-16, and ST2 but not IL-33. At 24 hours, there was a trend toward inverse correlation between local ST2 and IL-5. Most subjects showed increased serum levels of IL-5, IL-16, and soluble ST at 5 or 24 hours after allergen challenge.

Both natural and experimental allergen exposure are associated with upregulation of soluble ST2 and IL-16. Further study is needed to clarify how these cytokines may contribute to the inflammatory process in allergic rhinitis.

COMMENT: *Interleukin-33 is a recently discovered epithelial cytokine that is felt to have potential relevance as a biomarker and therapeutic target in asthma. These researchers evaluated pollen allergy with nasal allergen challenge and during natural seasonal exposure to evaluate IL-33 and its soluble receptor ST2. They found ST2 to be upregulated and speculate that it has an important regulatory role in the allergic inflammatory reaction. Stay tuned for therapeutic trials targeting this pathway.*
S.A.T.
Baumann R, Rabaszowski M, Stenin I, et al: Nasal levels of soluble IL-33R ST2 and IL-16 in allergic rhinitis: inverse correlation trends with disease severity.
Clin Exp Allergy. 2013;43:1134-1143. ♦♦

Hairdressers May Be More Likely to React to NMBAs

IMMEDIATE hypersensitivity reactions to neuromuscular blocking agents (NMBAs) used for anesthesia can occur in patients with no previous exposures, suggesting an environmental exposure source. Specific IgE to quaternary ammonium ions was assessed in 2 occupational groups.

The study included 128 hairdressers and 108 bakers/pastry makers with occupational exposure to quaternary ammonium ions, along with 379 controls. Positive IgE against quaternary ammonium ions ➤➤

was 4.6 times more frequent in hairdressers, compared to bakers or controls. Hairdressers also had significantly higher competitive inhibition of quaternary ammonium in the presence of succinylcholine. Competitive inhibition assays implicated benzalkonium chloride and polyquaternium-10, two compounds widely used by hairdressers. On multivariate analysis, working as a hairdresser and total IgE level greater than 100 kU/L were the two independent predictors of IgE sensitization against quaternary ammonium ions.

The increased prevalence of IgE sensitization to quaternary ammonium compounds among hairdressers may place them at increased risk of reactions to NMBAs. The authors note that this association is significant despite the absence of reported exposure to pholcodine and anesthetics.

COMMENT: *Following up structural studies suggesting that quaternary and tertiary ammonium ions may be important antigens, these authors sought to show that prior occupational contact exposure in hairdressers may result in IgE sensitization that cross-reacts with NMBAs. The results showed that the frequency of IgE to NMBAs was indeed higher among hairdressers, compared to bakers or normal controls.*
S.A.T.

Dong S, Acouetey DS, Gueant-Rodriguez R-M, et al: Prevalence of IgE against neuromuscular blocking agents in hairdressers and bakers.
Clin Exp Allergy. 2013;43:1256-1262. ♦♦

Is Immunotherapy an Option for Atopic Dermatitis?

THERE is debate over the use of specific allergen immunotherapy (SIT) for atopic dermatitis (AD) associated with aeroallergen sensitivity. The evidence regarding the use of immunotherapy for AD was analyzed in a systematic review.

A literature search identified seven randomized, double-blind trials of SIT for patients with AD. Five studies used dust mite allergen alone, and five used subcutaneous immunotherapy. All trials reported improvement in AD clinical symptoms; some studies found greater improvement in patients with mild AD and others in those with severe AD. Study quality was rated moderate to low, with limitations including high dropout rates, problems with randomization and blinding, and lack of intention-to-treat analysis.

Available trials provide only weak evidence supporting the use of SIT for AD. Until higher-quality data are available, the decision to use immunotherapy for AD "should be approached carefully from an individualized standpoint."

COMMENT: *Atopic dermatitis is a chronic condition, and treatment is often multifaceted. The authors performed a literature review of randomized controlled trials of SIT in patients with AD. All studies reported improvement in AD; however, sample sizes were small and many patients did not complete the studies. The authors conclude that evidence for SIT in AD is weak at this time. Further double-blind, randomized controlled trials are needed to determine if immunotherapy is a treatment modality that should be routinely considered for AD.*
V.H.-T.

Gendelman SR, Lang DM: Specific immunotherapy in the treatment of atopic dermatitis: a systematic review using the GRADE system.
Ann Allergy Asthma Immunol. 2013;111:555-561. ♦♦

Can We Predict Which PPI to Use in Patients with PPI Hypersensitivity Reactions?

PROTON pump inhibitors (PPIs) are usually well tolerated, but hypersensitivity reactions can occur. Based on a review of the literature, the authors outline an evidence-based approach to patients with hypersensitivity reactions to PPIs.

The literature review identified 39 reports describing 118 cases of immune-mediated hypersensitivity reactions to PPIs. Most of the reactions were IgE-mediated; omeprazole was the most commonly involved drug. Cutaneous reactions were the most frequent manifestation, although other types of reactions did occur. Skin testing showed variable patterns of cross-reactivity between PPIs. There was one case report of successful PPI desensitization.

The findings suggest formal investigation of patients with hypersensitivity reactions to PPIs, especially those for whom there is no reasonable alternative treatment. The authors outline an approach to skin testing for patients with immune-mediated reactions to PPIs, along with a suggested desensitization protocol.

COMMENT: *Gastrointestinal diseases, such as gastroesophageal reflux, are common. While avoidance is recommended for most patients with hypersensitivity reactions to medications, some will require treatment with a medication from the same class. This extensive review of the literature investigated the frequency of hypersensitivity reactions to PPIs. The most commonly reported reaction was cutaneous, although anaphylaxis has been reported. The authors report specific concentrations of drug that are non-irritating for skin testing. Since some patients may require use of a PPI, one article reported successful PPI desensitization. The authors suggest an algorithm for the diagnosis and management of these patients, which can aid the allergist in finding a medication for the patient who may need treatment with a PPI despite history of reaction.*
V.H.-T.

Bose S, Guyer A, Long A, Banerji A, et al: Evaluation and management of hypersensitivity to proton pump inhibitors.
Ann Allergy Asthma Immunol. 2013;111:452-457. ♦♦

Does Maternal Infertility Increase a Child's Risk for Nut Sensitization?

RISING rates of childhood allergy to peanut (PN) and tree nuts (TN) could be partly related to maternal diet or medications. Peanut or sesame seed oil are used in progesterone formulations used for assisted reproduction. Treatment for infertility and other maternal or dietary factors were evaluated as risk factors for childhood PN, TN, or sesame seed (SS) allergy.

The study included questionnaire data from the parents of 1,272 children evaluated by allergists. Maternal history of infertility, in vitro fertilization, or use of progesterone in oil was unrelated to PN, TN, or SS sensitization in the children.

However, maternal consumption of TN during the first two trimesters was associated with increased risk of PN, TN, or SS sensitization in the child: odds ratio 1.60. A similar association was noted for maternal SS consumption. The associations were twice as strong in children with asthma or environmental allergies.

Although history of infertility is not a significant factor, maternal ingestion of TN or SS during pregnancy may increase the risk of childhood PN, TN, or SS allergy. The results suggest the possibility of studies evaluating the effects of maternal avoidance of antigenic foods during pregnancy.

COMMENT: *Since allergy to both PN and TN is increasing, this interesting study looked at the possibility of drugs used during infertility treatment as contributors to sensitization. Questionnaires were completed by the parents of children with food allergy seen at academic allergy practices in Boston. No increase in sensitization to PN, TN, or SS was seen in children whose mothers had infertility, underwent in vitro fertilization, or used progesterone (in peanut or sesame oil). However, maternal ingestion of TN or SS during the first two trimesters resulted in increased odds of sensitization. Patients with allergy were also twice as likely as controls to have a history of atopy. Prior ingestion of PN was reported more frequently in patients sensitized to PN, TN, or SS.*
V.H.-T.

Hsu JT, Missmer SA, Young MC, et al: Prenatal food allergen exposures and odds of childhood peanut, tree nut, or sesame food sensitization.
Ann Allergy Asthma Immunol. 2013;111:391-396. ♦♦

Premedication May Reduce Systemic Reactions to Fire Ant Rush Immunotherapy

IMPORTED fire ants (IFAs) have become an important cause of hypersensitivity reactions in endemic areas of the southern United States. Rush immunotherapy (RIT) protocols are associated with high rates of systemic reactions. This study evaluated a premedication regimen for patients undergoing RIT for IFA.

The analysis included 80 patients undergoing a 1-day RIT protocol using IFA whole-body extract: 10 injections every 30 to 60 minutes to achieve a 0.3 mL 1:100 (wt/vol) dose. In an initial experience without premedication, the systemic reaction rate was 24.3%.

Subsequent patients received a 3-day course of premedication, starting 2 days before 1-day RIT: oral prednisone 20 mg twice daily, ranitidine 150 mg; and loratadine 10 mg. On days 8 and 15, patients received a 0.5 mL 1:100 (wt/vol) maintenance injection. With premedication, the systemic reaction rate decreased to 9.5%; the most severe reaction consisted of dizziness, angioedema, and urticaria. Just 1 mild reaction occurred in 53 patients undergoing follow-up sting challenges.

The results support the efficacy of a 1-day RIT protocol for IFA hypersensitivity. The premedication regimen described may reduce the systemic reaction rate, although confirmatory studies are needed.

COMMENT: *Since patients with venom allergy are not always able to avoid exposure, RIT is an option that can protect patients who live in endemic areas. Imported fire ants, in particular, have high annual sting rates. Anaphylaxis is well reported, and thus immunotherapy to whole-body extract is both safe and effective. Rush immunotherapy protocols can lead to adverse reactions. This study investigated whether premedication would decrease the risk of adverse reactions during single-day fire ant RIT. The authors reported more systemic reactions in patients who were not premedicated. All patients responded to RIT. Larger studies are needed to further investigate the use of premedication for patients undergoing RIT for IFA hypersensitivity.*
V.H.-T.

Arseneau AM, Nesselroad TD, Dietrich JJ, et al: A 1-day imported fire ant rush immunotherapy schedule with and without premedication.
Ann Allergy Asthma Immunol. 2013;111:562-566. ♦♦

Influenza-Related Deaths in Children: Patient Characteristics

ALTHOUGH influenza is usually a self-limited illness, children with influenza die each year in the United States. Reports submitted to the Centers for Disease Control and Prevention were analyzed to examine the characteristics of deaths related to influenza in U.S. children.

From the 2004-05 through the 2011-12 influenza seasons, 830 influenza-associated deaths in patients younger than 18 years were reported. The number of pediatric deaths ranged from 282 in the 2009-10 season to 35 in the 2011-12 season. Fifty-three percent of the children who died were male; the median age was 7 years. Thirty-five percent of patients died before hospital admission.

Of children whose medical history was known, 43% had no high-risk medical conditions, 33% had neurologic disorders, and 12% had genetic or chromosomal disorders. Children without high-risk conditions were more likely to die before hospital admission and within 3 days after initial symptoms: relative risk 1.9 and 1.6, respectively. Many deaths were associated with bacterial co-infections and pneumonia. ➤➤

The findings lend insights into the characteristics of influenza-associated deaths occurring in American children. Severe outcomes are possible even in children without high-risk medical conditions. The report underscores the importance of recommended influenza vaccination and early empirical antiviral therapy.

COMMENT: *A national surveillance review of the pediatric influenza-associated deaths from 2004 to 2012 showed that 78% of the children had influenza A and 20% had influenza B virus infections. Of 794 children with a known medical history, 26% had a pulmonary disorder, including 16% with asthma. Bacterial coinfections and pneumonia were commonly reported among children who died. These findings underscore the importance of annual influenza vaccination and early institution of antiviral therapy in high-risk children or those with more severe illness.*
C.D.
Wong KK, Jain S, Blanton L, et al: Influenza-associated pediatric deaths in the United States.
Pediatrics. 2013;132:796-804. ♦♦

Bronchial Thermoplasty for Refractory Asthma: Safety and Effectiveness

BRONCHIAL thermoplasty, a procedure to reduce excess airway smooth muscle, has shown good 1-year outcomes in patients with severe refractory asthma. The authors report 5-year follow-up data on patients from a previous trial of bronchial thermoplasty.

The trial included 15 adults with severe asthma requiring high-dose inhaled corticosteroids and long-acting β_2 agonists, with or without other treatments. Five-year follow-up data were available in 14 patients. From year 2 through 5 after bronchial thermoplasty, rates of respiratory adverse events were 1.4, 2.4, 1.7, and 2.4 per patient per year. Reductions in hospitalizations and ED visits were maintained through 5 years, as were improvements in pulmonary function measures.

In this clinical trial sample, the good outcomes of bronchial thermoplasty for severe refractory asthma persist through 5 years' follow-up. The authors note that maintenance medication requirements did not increase during follow-up.

COMMENT: *Bronchial thermoplasty is a newly approved treatment option for severe asthma, which has demonstrated safety and efficacy in three randomized trials with 1- year follow-up. In this study 14 of 15 patients who had bronchial thermoplasty in a previous study were followed out to 5 years. The data showed decreased ED visits and hospitalizations with maintenance of pulmonary function. The authors conclude that bronchial thermoplasty for severe refractory asthma is safe and effective for at least 5 years after treatment.*
C.C.R.
Pavord ID, Thomson NC, Niven RM, et al: Safety of bronchial thermoplasty in patients with severe refractory asthma.
Ann Allergy Asthma Immunol. 2013;111:402-407. ♦♦

REVIEWS OF NOTE

COMMENT: *This is a well-done position paper regarding classification of idiopathic interstitial pneumonia.*
B.E.C.
Travis WD, Costabel U, Hansell DM, et al: An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias.
Am J Respir Crit Care Med. 2013;188:733-748. ♦♦

COMMENT: *Aspergillus colonization causing allergic bronchopulmonary aspergillosis can occur in patients with severe asthma. This provocative review discusses the finding that some of the pathologic asthma-like changes in response to the inhalation of an aspergillus protease depend on Toll-like receptor 4 and the presence of a coagulation factor--a fibrinogen cleavage product--akin to the way Toll is activated by Spätzle in fruit flies. While additional research is required, this opens the door to the exciting possibility that antithrombotic medications could become part of the asthma armamentarium.*
C.D.
Lambrecht BN, Hammad H: Asthma and coagulation.
N Engl J Med. 2013:369:1964-1966. ♦♦

COMMENT: This very brief overview of asthma summarizes genetics, phenotyping, natural course, and current and future trends in treatment.
S.F.W.
Martinez FD, Vercelli D: Asthma.
Lancet. 2013;382:1360-1372. ♦♦