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 15, Number 2 March - April 2013

Trials Show Promising Results with SLIT for Peanut Allergy

AVOIDANCE and epinephrine are currently the only treatments with patients with peanut allergy. Sublingual immunotherapy (SLIT) has shown efficacy in the treatment of asthma and allergic rhinitis, and has been used for treatment of several types of food allergies--including peanut allergy. This study presents the results of the first multicenter, randomized, placebo-controlled trial of SLIT for patients with peanut allergy.

The Consortium of Food Allergy Research trial included 40 children and adults (median age 15 years) with peanut allergy, enrolled at five centers. At baseline, all performed an oral food challenge (OFC) consisting of up to 2 g of peanut powder, approximately half of which was protein; the median successfully consumed dose (SCD) was 46 mg. Patients were then randomly assigned to double-blind treatment with daily peanut or placebo SLIT.

After 44 weeks, patients performed a 5 g peanut OFC. Treatment was then unblinded and placebo patients were crossed-over to higher-dose peanut SLIT, with another 5 g OFC after 44 weeks. The results of the pre- and post-treatment OFCs were compared. Patients who successfully completed the 5 g challenge or consumed ten times more peanut powder than at baseline were considered treatment responders.

By this definition, 70% of patients assigned to peanut SLIT were treatment responders, compared to 15% of the placebo group. For SLIT responders, the median SCD increased from 3.5 mg at baseline to 496 mg at 44 weeks, with a further increase to 996 mg after 68 weeks. At the week 44 crossover OFC, median SCD was 603 mg, compared to 71 mg at baseline. The response rate in the crossover group (who received a higher dose of peanut SLIT) was 44%; median SCD increased from 21 to 496 mg in responders.

Of nearly 11,000 peanut SLIT doses through 44 weeks, 63.1% were symptom-free. Excluding oral-pharygneal symptoms, 95.2% of doses were symptom-free. ➤➤

CONTENTS

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.

Most patients with peanut allergy achieve a "modest level of desensitization" in response to peanut SLIT, as used in this trial. Longer treatment durations are associated with greater increases in SCD. More research will be needed to determine the therapeutic role of SLIT for food allergies.

COMMENT: *This multicenter, randomized trial of peanut SLIT shows promise for patients with peanut allergy. After 44 weeks of peanut SLIT, allergic patients had a dramatic improvement in their "successfully consumed dose" of peanut, compared to the placebo SLIT group. The study excluded patients who had severe anaphylaxis. In addition, 40% of the time patients receiving active peanut SLIT reported oral-pharyngeal pruritus compared to none receiving placebo, which makes true blinding problematic. Patients at risk for life-threatening anaphylaxis would be relieved if this type of therapy could eventually result in even some reasonable protection from accidental exposure.*
S.M.F.

Fleischer DM, Burks AW, Vickery BP, et al: Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial.
J Allergy Clin Immunol. 2013;131:119-127. ♦♦

FOCUS ON FOOD ALLERGY

We lead off this issue of *AllergyWatch* with reviews of several timely new papers on food allergy.

Oral Immunotherapy to Milk: Too Dangerous for the Patients Who Need It Most?

THERE is great interest in oral immunotherapy (OIT) as an alternative to strict dietary avoidance for children with cow's milk allergy. A previous study of a Spanish OIT protocol for milk allergy reported complete desensitization in 77.2% of patients. The current analysis evaluated the safety of this OIT protocol, including clinical and immunologic predictors of adverse events.

The prospective study included 81 children, aged 5 to 18 years, undergoing OIT for cow's milk allergy, without premedication. All reactions to OIT doses were recorded and analyzed, including their resolution over time and clinical and immunologic factors associated with persistent reactions. Patients were followed up for a mean of 25 months.

Ninety-five percent of patients had some type of reaction to OIT doses, with 91% of reactions affecting a single organ. Seventy-five percent of children had occasional symptoms that resolved with time. Complete desensitization, defined as tolerance of a 200 mL dose of cow's milk, was achieved in 86% of this group.

However, 25% of children had frequent, more severe, and unpredictable reactions that persisted over follow-up. Six patients had persistent reactions leading to treatment withdrawal. On Kaplan-Meier analysis of all patients, the estimated cumulative probability of resolution was 25% at 3 months and 50% at 8 months.

Three independent predictors of persistent reactions were identified: cow's milk specific IgE level greater than 50 kU/L^{-1}, skin prick test size 9 mm or larger, and Sampson's severity grade 2 to 4 at baseline food challenge. Hazard ratio for persistent reactions was 2.26 for children with two risk factors and 6.06 for those with all three factors.

The cow's milk OIT protocol evaluated in this study is "insufficiently safe" for one-fourth of milk-allergic children. The clinical and immunologic risk factors identified may be useful in identifying highly reactive patients before the start of OIT. Children in this group might benefit from individualized dose schedules and premedication. ➤➤

COMMENT: *Oral immunotherapy strategies are being studied for a variety of food allergens. This study used a commonly employed desensitization protocol to specifically evaluate the safety of OIT in 80 children with milk allergy. Nearly all subjects experienced adverse allergic reactions, which were typically quite mild--although 1 out of 4 subjects experienced much more concerning symptoms. Patients who did not tolerate the treatment tended to have a higher specific IgE level, skin test wheal diameter, clinical reaction grade during their qualifying oral challenge. These results remind us that OIT for food allergy involves adverse allergic reactions, that these reactions are prohibitive in a significant subset of patients, and that this treatment is still experimental.*
S.A.T.
Vázquez-Ortiz M, Álvaro-Lozano M, Alsina L, et al: Safety and predictors of adverse events during oral immunotherapy for milk allergy: severity of reaction at oral challenge, specific IgE and prick test.
Clin Exp Allergy. 2012;43:92-102. ♦♦

Is Egg-Based Flu Vaccine Safe in Severe Egg Allergy?

THERE is a long history of concern over the safety of administering egg-containing seasonal trivalent influenza vaccine (TIV) to children with egg allergy. Recent reports have suggested that the risk of reactions is very low, and that vaccination can be safely given without either skin testing or split-dosing. This multicenter study evaluated the safety of TIV administration for children with severe egg allergy.

The first phase of the study included 31 egg-allergic children, all with a history of severe reactions to egg, treated at seven study sites. One group received a split dose, with 0.1 mL of influenza vaccine followed by the rest of the age-appropriate dose if there was no reaction during a 30-minute observation period. The other group received initial injection of normal saline, followed by the full age-appropriate dose.

The second phase of the study was a retrospective analysis of 112 egg-allergic children receiving influenza vaccine: 87 received a single dose and 25 a split dose. About 45% of children in the first phase and 78% in the second phase had a history of anaphylaxis after egg ingestion.

None of the children in either phase experienced an allergic reaction to TIV. The experience in these combined 143 cases was consistent with previous reports of 241 children with severe egg allergy receiving TIV, published between 1998 and 2012.

The findings, including new prospective data, support the safety of seasonal TIV administration even for children with a history of severe egg allergy. A full age-appropriate dose was well-tolerated in all cases, obviating the need for a split-dose regimen.

COMMENT: *Is egg-based injectable seasonal TIV safe for patients with severe egg allergy? In nine retrospective and prospective studies, including this study, a total of 384 severely egg-allergic patients tolerated the standard dose of injectable influenza vaccine, without reaction. Prospective placebo-controlled and retrospective trials comparing single dose versus split dose indicate that a full single dose is safely tolerated. The take-home message for practicing allergists is that the injectable influenza vaccine is tolerated by all egg-allergic patients. They may receive their vaccines from their primary care provider, with only a 30-minute observation period.*
C.C.R.
Greenhawt MJ, Spergel JM, Rank MA, et al: Safe administration of the seasonal trivalent influenza vaccine to children with severe egg allergy.
Ann Allergy Asthma Immunol. 2012;109:426-430. ♦♦

Could Food Processing Methods Explain the Rise in Food Allergy?

RECENT years have seen a rapid increase in the prevalence of childhood peanut allergy in Western countries. Peanut allergy is less frequent and severe in Korea and other Asian countries, suggesting a possible influence of differences in cooking methods. This study assessed responses to major peanut allergens in Korean children with peanut allergy, including assessment of how different cooking methods affect peanut proteins.

The study included 42 Korean children with suspected peanut allergy, with a peanut-specific IgE level of 15 kUA/L or higher. Serum samples were used for immunolabeling of raw peanut protein extracts to detect specific binding to the major peanut allergens Ara h 1, Ara h 2, and Ara h 3. Pooled serum samples from 7 patients were used to examine how the allergenicity of peanuts was affected by different cooking methods: boiling, roasting, frying, and pickling.

In this Korean sample, 76.2% of serum samples reacted with Ara h1 and 78.6% with Ara h 3 from raw peanuts. In contrast, just 53.0% of patients had specific IgE against Ara h 2. Patients with severe reactions to peanut had a higher prevalence of IgE binding to Ara h 2, compared to those with milder reactions: 90% versus 30%.

As reported in previous studies, roasting of peanuts was associated with increased allergenicity of Ara h 2. In contrast, Ara h 2 allergenicity was unaffected or even decreased by the other cooking methods tested.

The findings suggest that the major peanut allergen Ara h 2 is an important predictor of severe clinical symptoms in children with peanut allergy. In addition, reactivity to Ara h 2 appears less prevalent among Korean children compared to children in Western countries. The findings may at least partly reflect regional differences in cooking methods. The authors note that young children in Korea do not often eat roasted peanuts, which may be associated with increased Ara h 2 allergenicity.

COMMENTS: *This interesting study from Korea explored the possibility of differences in the allergenicity of peanuts based on processing. The authors* ➤➤

describe increased allergenicity of Ara h 2 by roasting. Patients with more severe reactions to peanuts had more binding of IgE to Ara h 2. One limitation of the study was the lack of oral challenge to peanuts. As practicing allergists, we are frequently asked by patients about the reasons for the increasing prevalence of peanut allergy. This study gives us some "food for thought" and reminds us of the need for further studies on this topic.
V.H.-T.
Kim J, Lee JY, Han Y, Ahn K: Significance of Ara h 2 in clinical reactivity and effect of cooking methods on allergenicity.
Ann Allergy Asthma Immunol. 2013;110: 34-38. ♦♦

Fusion Protein Could Lead to New Approach to Peanut Immunotherapy

SOME type of allergen-specific immunotherapy for peanut allergy is needed. The authors describe the development and initial evaluation of a new peanut-human fusion protein to block peanut-induced allergic reactions.

Genetic techniques were used to design and express a fusion protein consisting of the major peanut allergen Ara h 2 and human Fcγ1. The function of this novel "AHG2" fusion protein was tested in vitro in purified human basophils. In vivo studies were performed in transgenic mice expressing human FcεRIα as well as in a mouse model of peanut allergy.

In basophils from peanut-allergic patients, AHG2 inhibited histamine release in response to whole peanut extract (WPE). In contrast, the fusion protein itself did not induce mediator release. In passively sensitized hFcεRIα transgenic mice, AHG2 blocked WPE-induced, IgE-mediated cutaneous anaphylaxis. It also inhibited acute anaphylactic reactivity, including the characteristic drop in body temperature resulting from peanut challenge in WPE-sensitized mice.

Histologic evidence of peanut-induced airway inflammation was reduced by AHG2, which did not itself produce an airway inflammatory effect in peanut-sensitized animals. In mice without FcγRII, AHG2 had no effect in blocking peanut allergy.

The new AHG2 fusion protein appears to inhibit peanut-specific IgE-mediated allergic reactions in vitro and in vivo. These experiments suggest a potential role of linking peanut-specific allergen to Fcγ in developing effective new approaches to immunotherapy for peanut allergy.

COMMENT: *There is currently no safe, approved treatment for patients with the frightening and life-threatening condition of peanut protein allergy. This study evaluated a novel fusion protein prepared by combining Ara h 2 with human IgG1 Fcγ. There was modest but impressive blocking of anaphylaxis when the fusion protein was administered to passively sensitized peanut-allergic mice challenged with whole peanut protein. It is interesting that the fusion protein was effective against whole peanut challenge, even though it was made using only one peanut component protein, Ara h2. The potential therapeutic benefit is yet to be determined, particularly since there was no sustained effect.*
S.M.F.
Liu Y, Sun Y, Chang L-J, et al: Blockade of peanut allergy with a novel Ara h2-Fcγ fusion protein in mice.
J Allergy Clin Immunol. 2013;131:213-221. ♦♦

Understanding Ara h 2: The Key to Accurate Diagnosis and Effective Immunotherapy?

MOST patients who test positive for peanut sensitization using current diagnostic approaches do not develop clinical peanut allergy. Some clinical test is needed to accurately identify patients who will develop allergic reactions and/or anaphylaxis to peanut. The ImmunoCAP ISAC, a new component-resolved diagnostic tool, was used to differentiate asymptomatic peanut sensitization from peanut allergy.

From a larger study of food allergy, the researchers identified 58 children with asymptomatic peanut sensitization, 55 with nonanaphylactic peanut allergy, 53 with anaphylactic reactions to peanut, and 20 nonatopic controls. Component-resolved diagnostic tests were used to compare IgE and IgG4 to 103 allergens, including four peanut allergens, among these groups. Each allergen's ability to predict clinical peanut allergy and/or anaphylaxis was assessed.

Patients with clinical peanut allergy, with or without anaphylaxis, had increased IgE reactivity to the peanut allergens Ara h 1-3, compared to children with asymptomatic sensitization. The peanut allergy groups also had increased IgE reactivity to the soy allergens Gly m 5-6. A similar but smaller association was noted for IgG4 to Ara h 2.

The result most useful in distinguishing patients with peanut allergy from those with asymptomatic sensitization was IgE to Ara h 2. At a cutoff point of 0.65 ISU-E, this parameter was 99.1% sensitive in predicting clinical peanut allergy, with specificity of 98.3% and a misclassification rate of just 1.2%. IgE to Ara h 2 had higher discriminative accuracy than IgE to whole peanut; none of the other IgE and IgG4 allergen tests were able to make this differentiation.

Component-resolved diagnostic testing for IgE to Ara h 2 may offer an efficient new approach to identifying patients with clinical peanut allergy versus those with asymptomatic peanut sensitization. Offering a wider sensitization profile for each patient, the ImmunoCAP ISAC test could be an important advance in allergy risk assessment and individualized advice on allergen avoidance.

COMMENT: *Using component-resolved diagnostic testing, these authors found that more than 99% of peanut allergic children tested positive for Ara h 2 specific IgE. For levels above 0.65 ISU-E, testing was also 98% sensitive. With further validation, these methods could prove extremely valuable by reducing the number of "sensitized but not allergic" patients who abound in our practices.*
S.A.T. ➤➤

Hong X, Caruso D, Kumar R, et al: IgE, but not IgG4, antibodies to Ara h 2 distinguish peanut allergy from asymptomatic peanut sensitization.
Allergy. 2012;67:1538-1546. ♦♦

CONVENTIONAL immunotherapy for peanut allergy is effective, but carries a high risk of anaphylaxis. Immunotherapy directed at targeted T cell epitopes may be a useful alternative; in recent years, computer simulations have been used to develop predictive algorithms for identifying T cell epitopes. This "in silico" approach was evaluated for use in identifying candidate peptides for an Ara h 2 peptide-based immunotherapy vaccine for peanut allergy.

The in vitro study used peripheral blood mononuclear cells (PBMCs) from 80 patients with confirmed peanut allergy. After stimulation with overlapping 20-mer Ara h 2 peptides, two previously described algorithms--NetMHCIIpan-2.0 and NetMHCII-2.2--were used to predict major histocompatibility complex (MHC) class II-binding peptides. Multiplex assays were used to evaluate cell supernatant profiles, and HLA-DRB1* and HLA-DQB1 typing studies were performed.

Proliferation of PBMCs with a Th2 pattern of cytokine production was induced by four regions of overlapping sequences. Thirty different DRB1* allele specificities and 8 DQ serologic specificities were identified on HLA genotyping studies. Similar regions were found on in silico analysis, which predicted a similar or identical set of core 9-mer epitopes. A peptide vaccine incorporating the 15 peptides identified on in vitro analysis and the 9 core epitopes identified on in silico analysis was predicted to cover all patients in the study cohort.

This in vitro study identifies four dominant regions of Ara h 2 containing candidate sequences for peptide-based peanut immunotherapy. In silico analysis is a promising tool for predicting significant MHC-binding peptides from large major allergens, and thus for selecting candidate peptides for use in immunotherapy vaccines.

COMMENT: *The absence of an effective treatment for food allergies is arguably the most glaring unmet need facing our specialty. Although using whole peanut extract to administer subcutaneous, oral, sublingual, or transcutaneous immunotherapy appears efficacious, these strategies all result in frequent allergic reactions. Using in silico analysis, these authors identified four immunodominant Ara h 2 T cell epitopes. They propose that this map be used to develop a peptide vaccine that would be much safer than traditional immunotherapy. Stay tuned!*
S.A.T.
Pascal M, Konstantinou GN, Masilamani M, et al: In silico *prediction of Ara h 2 cell epitopes in peanut-allergic children.*
Clin Exp Allergy. 2012;43:116-127. ♦♦

Oral CRTH2 Antagonist Shows Promise for Allergic Rhinoconjunctivitis

THE CRTH2 pathway plays an important role in mediating activation of Th2 cells, eosinophils, and basophils in response to prostaglandin D_2. OC00459, an oral CRTH2 antagonist, has shown beneficial effects on airway inflammation and lung function in moderate persistent asthma. This randomized trial evaluated the symptomatic effects of OC00459 in patients with grass pollen allergic rhinoconjunctivitis.

The placebo-controlled crossover study included 35 healthy men with confirmed grass pollen allergy. Out of pollen season, participants were studied during 8 days on treatment with OC00459, 200 mg bid, and 8 days on placebo. On days 2 and 8 of each treatment, the subjects were exposed to grass pollen, 1,400 grains/m^3 or higher, for 6 hours. Nasal and ocular symptom responses were compared between OC00459 and placebo, with a 3-week washout period between treatments.

During the first treatment period, OC00459 was associated with significant reduction in both nasal and ocular symptoms in response to grass pollen challenge. The symptomatic effect was apparent by day 2, increasing further by day 8. There was an apparent carryover effect, with the benefits of OC00459 persisting through the washout period. Safety outcomes were similar between the two treatments.

The oral CRTH2 OC00459 antagonist reduces nasal and ocular symptoms in response to grass pollen challenge in grass-allergic patients. Treatment with OC00459 is safe and well tolerated. Further studies are needed to confirm its benefits in clinically relevant settings and to examine the duration and mechanisms of the persistent effects on allergic symptoms.

COMMENT: *The CRTH2/prostaglandin D_2 pathway is known to play an important role in mast cell-dependent activation of Th2 cells and eosinophils. Multiple products that target this pathway are being developed as treatments for asthma or rhinitis. This crossover study used an inhalational challenge procedure to demonstrate efficacy and safety of an oral CRTH2 antagonist in grass-allergic subjects, compared to placebo. Although the data do not suggest an effect magnitude greater than intranasal corticosteroids, the drug effect appears to have persisted throughout the 3-week washout period. If validated, this unexpected finding could prove important in justifying the drug's further development.*
S.A.T.
Horak F, Zieglmayer P, Zieglmayer R, et al: The CRTH2 antagonist OC000459 reduces nasal and ocular symptoms in allergic subjects exposed to grass pollen, a randomised, placebo-controlled, double-blind trial.
Allergy. 2012;67:1572 -1579. ♦♦

Can SABA Use Predict Asthma Exacerbations?

DISPENSING of short-acting beta agonists (SABAs) is commonly used in identifying adult asthma patients at high risk of adverse outcomes. Relatively few studies have evaluated SABA use as a predictor of asthma events in children. This study assessed the levels of SABA use most strongly associated with asthma exacerbation risk in adult and pediatric patients.

Claims databases were used to identify two groups of adults and children with asthma: approximately 34,000 Medicaid patients and 101,000 commercially insured patients. Use of SABAs was measured in terms of canisters used during 3-, 6-, and 12-month periods after the date of first claim for asthma medications. The analysis focused on the number of SABA canisters that best predicted the risk of exacerbations and the optimal time during which SABA use should be measured.

For children in both the Medicaid and commercially insured groups, use of three or more SABA canisters over a 12-month period was the best predictor for future risk of asthma exacerbations. For exacerbations resulting in hospitalization or ED visits, odds ratios were 1.80 for children in the Medicaid group and 2.23 for those in the commercial insurance group.

For adults, the optimal predictor was two or more canisters over a 3- to 6-month period. For each additional SABA canister used, exacerbation risk increased by 8% to 14% in children and by 14% to 18% in adults.

In children as in adults with asthma, SABA use can predict the risk of future asthma exacerbation. The study provides "critical values" of SABA canisters used over specific time periods. Exacerbation risk increases with each additional SABA canister used.

COMMENT: *Short-acting beta-agonist use has been traditionally utilized to monitor asthma control and need for controller therapy in adults. The authors demonstrate in Medicaid and privately insured pediatric populations that the use of three or more SABA canisters over 12 months predicted a twofold enhanced risk for asthma exacerbation with hospitalization or ER visit in the subsequent year. In adults, use of two or more canisters in periods of 3 and 6 months was similarly predictive of subsequent-year exacerbations. Practicing allergists should be cognizant that high use of SABAs predicts asthma exacerbations. A limited SABA prescription and careful monitoring to ensure concomitant controller therapy are needed to provide for optimal control of asthma.*
C.C.R.

Stanford RH, Shah MB, O'Souza AO, et al: Short-acting β-agonist use and its ability to predict future asthma-related outcomes.
Ann Allergy Asthma Immunol. 2012;109:403-407. ♦♦

Can Hymenoptera Immunotherapy Be Given Every 3 to 4 Months?

STANDARD Hymenoptera venom immunotherapy (VIT) includes extended maintenance doses given every 4 to 6 weeks. Longer treatment intervals have been suggested to help manage long-term adherence problems. A 3- to 4-month extended maintenance dose schedule was evaluated.

In the prospective study, patients receiving single-venom immunotherapy were offered extended maintenance-dose (EMD) therapy, every 3 to 4 months. The patients were then followed up for field re-stings involving the specific insect for which they were receiving VIT. Outcomes were compared with those of a comparable group of patients receiving the conventional maintenance dose (CMD), every 4 to 6 weeks.

The analysis included 76 patients--60 male and 16 female, mean age 48 years--receiving EMD for honeybee or yellow jacket. During a mean 73 months' follow-up, patients were re-stung by the insect for which they were receiving immunotherapy on 247 occasions. The CMD group consisted of 110 patients, who were re-stung on 167 occasions over a mean follow-up of 22 months.

The rate of re-sting without reaction was 93.5% for patients in the EMD group--significantly higher than the 81.5% rate in the CMD group. On logistic regression analysis, age was a significant predictor of systemic reactions to re-stings, but the maintenance dose regimen was not.

For patients receiving VIT, an extended maintenance regimen with dosing every 3 to 4 months is "at least as effective and safe" as conventional 4- to 6-week dosing. On the basis of convenience and cost, EMD appears to be preferred over CMD.

COMMENT: *Due to the need for long-term treatment and concern for patient compliance, the authors studied patients with Hymenoptera allergy who were re-stung during therapy. This article addresses the possibility of using VIT every 3 to 4 months during maintenance dosing, instead of the conventional dosing protocol of every 4 to 6 weeks. Less-frequent dosing appears to be a promising option for the treatment of patients with Hymenoptera allergy to a single venom. Since VIT requires long-term treatment, this may be an opportunity to make it easier for patients while continuing to provide high-quality allergy care.*
V.H.-T.

Simioni L, Vianello A, Bonadonna P, et al: Efficacy of venom immunotherapy given every 3 or 4 months: a prospective comparison with the conventional regimen.
Ann Allergy Asthma Immunol. 2012;110:51-54. ♦♦

Is It Really Safe to Perform Drug Challenge in Patients with Drug Allergy?

ALLERGISTS commonly use drug challenges when diagnostic tests don't have good predictive value in patients with a questionable history of drug allergy. Many patients report subjective reactions to placebo challenge. The authors review their 6-year experience with placebo-controlled drug challenges, including factors associated with subjective symptoms in response to placebo.

From 2006 to 2012, the authors' department per- ➤➤

formed a total of 123 clinically indicated drug challenges in 114 patients. The analysis excluded patients with a history of certain types of severe life-threatening drug reactions, local anesthetic challenges, and those with aspirin-exacerbated respiratory disease (AERD) undergoing aspirin challenge.

Three-fourths of patients were female; the median number of recorded drug allergies was three. About two-thirds of challenges were to antibiotics. Challenge results were considered negative in patients with subjective symptoms not consistent with an allergic reaction--eg, headache or isolated tongue itching. Factors associated with subjective symptomatic reactions were analyzed.

One patient had a true positive result on drug challenge: a pruritic rash in response to cefuroxime. Another 20 challenges produced subjective symptoms classified as negative results. Most often, these patients had symptoms in response to placebo or only during the early steps of graded challenge. Factors associated with subjective symptoms included female sex, higher number of recorded allergies, and history of primarily subjective reactions.

Drug challenges are safe in properly selected patients, with a low rate of true positive results. A significant proportion of patients report subjective symptoms that are not consistent with true allergic reactions. The study identifies risk factors for such purely subjective reactions, which may be useful in selecting patients for placebo-controlled challenges.

COMMENT: *The selection of patients who should undergo drug challenge is important in our everyday practice. The authors report on challenges in patients with different types of reactions to medications, excluding those with life-threatening reactions and certain other groups. This retrospective review of 124 drug challenges reports only one positive challenge, which was not severe. As allergists are aware, patients may report subjective symptoms that do not result in severe allergic reactions during the drug challenge. For this reason, the authors remind us that placebo-controlled challenge may be beneficial in some female patients or in those with previous reports of subjective symptoms. This study reassures the practicing allergist that the majority of patients, selected according to the authors' exclusion criteria, are able to tolerate drug challenge.*
V.H.-T.

Kao K, Rajan J, Roy L, et al: Adverse reactions during drug challenges: a single US institution's experience.
Ann Allergy Asthma Immunol. 2013;110:86-91. ♦♦

Fish: Friend or Foe? It Depends on the Timing

SOME evidence suggests that fish consumption during pregnancy or later childhood may be associated with a lower risk of asthma in children. However, the optimal time to introduce fish into the diet is unclear; since fish can be highly allergenic, the question is an important one. Information from a population-based Dutch study was analyzed to assess the effects of timing of fish introduction on the risk of asthma-like symptoms in preschoolers.

Data were drawn from a prospective birth cohort study of children in Rotterdam. When the children were 12 to 14 months old, parents were asked when fish was first introduced into the child's diet and the amount of fish consumed. When the children were 36 to 48 months old, parents were asked about the occurrence of asthma-like symptoms in the preceding year.

Children in whom fish was introduced between age 6 and 12 months were less likely to have wheezing at 48 months: odds ratio (OR) 0.64. Compared to this group, wheezing risk at age 4 was significantly higher when fish was not introduced in the first year, OR 1.57; and when it was introduced between 0 and 6 months, OR 1.53. The amount of fish consumption at age 14 months was unrelated to the risk of wheezing or other asthma-like symptoms.

Introducing fish into the infant diet between 6 and 12 months is associated with a lower rate of wheezing by preschool age. The amount of fish consumed does not appear to affect the risk of asthma-like symptoms in young children. Considering that wheezing risk is higher when fish is introduced at 0 to 6 months or after 1 year, 6 to 12 months may be a "window of exposure" in which introducing fish can reduce the risk of asthma.

COMMENT: *Studies have shown protective effects of fish and fish fatty acids during pregnancy against the development of asthma in children. In this Dutch study, introduction of fish between 6 and 12 months--but not later fish consumption--was associated with a lower risk of wheezing. No introduction of fish or introduction between 0 and 6 months of life increased the risk of wheezing. Limitations of the study include the subjectivity in recall, lack of quantification of fish intake, and challenges of identifying "asthma-like" symptoms. Nevertheless it reinforces the tantalizing concept of the "window of opportunity" for interventions resulting in development of protective immune tolerance.*
C.D.

Kiefte-de Jong JC, de Vries JH, Franco OH, et al: Fish consumption in infancy and asthma-life symptoms at preschool age.
Pediatrics. 2012;130:1060-1068. ♦♦

Smoking Spares Neither Sex; Timely Quitting May Turn Back the Clock

DURING the twentieth century, increases in smoking at younger ages--first in men, then in women--led to rising rates of smoking-related deaths. Recent years have seen significant changes in smoking in the U.S. population. This study examined recent trends in smoking related deaths, particularly in women compared to men.

The researchers assessed temporal trends in smoking-related mortality during three periods: 1959-65, 1982-88, and 2000-10. Data were drawn from two historical cohort studies and five pooled contemporary cohort studies. ➤➤

The relative risk of death from lung cancer for women who currently smoked (compared to never-smokers) increased sharply over time: 2.73 in the 1960s, 12.65 in the 1980s, and 25.66 in the 2000s. The relative risk for lung cancer death for men who smoked increased from 12.22 in the 1960s to 23.81 in the 1980s, but plateaued at 24.97 in the 2000s. In most recent decade, relative risks of death from other smoking-related diseases were about the same in women and men: 22.35 and 25.61 for chronic obstructive pulmonary disease (COPD), 2.86 and 2.50 for ischemic heart disease, and 2.10 and 1.92 for stroke, respectively.

Relative risk of death from all causes combined was 2.76 for women and 2.80 for men. In recent years, the risk of death from COPD continued to increase in all groups of men who smoked. All-cause mortality for current smokers was at least three times higher at age 55 to 74 years in men and 60 to 74 years in women, compared to never-smokers. Mortality dropped significantly after smoking cessation, in all age groups.

Risks of smoking-related death in women have continued to increase since the 1960s, and are now similar to the risks in men. For men, the risk of death from most smoking-related causes has leveled off since the 1980s. The exception is COPD, which shows a continued, unexplained increase in deaths among male smokers.

AVAILABLE estimates of U.S. deaths attributable to smoking are extrapolated from studies performed in the 1980s. Contemporary data on the hazards of smoking and the benefits of smoking cessation at various ages are needed.

This updated analysis used data on 113,752 women and 88,496 men from the U.S. National Health Interview Survey. Participants provided data on smoking and smoking cessation at initial interviews between 1997 and 2004 and at follow-up through 2006. Associations between current smoking and mortality were assessed, with adjustment for age, education, body fat, and alcohol consumption.

Among adults aged 25 to 79, all-cause mortality was about three times higher for current smokers versus never-smokers. Hazard ratios were 3.0 for women and 2.8 for men, with neoplastic, vascular, respiratory, and other smoking-related diseases accounting for most of the excess mortality. The chances of survival from age 25 to 79 were 38% for women and 26% for men who smoked versus 70% and 61% for never-smokers, respectively.

Life expectancy was reduced by about 10 years for current smokers compared to never-smokers. Increases in life expectancy after smoking cessation were 10 years for people who quit smoking at age 25 to 34 years, 9 years at age 35 to 44 years, and 6 years at age 45 to 54 years.

The updated data suggest that risk of death is approximately tripled for current smokers. Smoking reduces live expectancy by 10 years or more, but this risk is largely offset by smoking cessation, especially before age 40.

COMMENT: *The large U.S. cohort study by Thun et al starkly shows that the risks of death for women (from lung cancer, COPD, ischemic heart disease, stroke, or all causes combined) have continued to increase and now equal those for men. The authors speculate that design changes in cigarettes result in deeper inhalation of more dilute smoke, increasing exposure of the lung parenchyma and thereby causing injury and COPD.*

The companion article by Jha et al reveals that smokers lose at least one decade of life expectancy, compared to those who have never smoked. The silver lining is the uplifting finding that quitting smoking at any age dramatically lowers mortality from all major smoking-related diseases. In fact, cessation before age 40 reduces the risk of death by about 90%, compared to continued smoking. Of note, quitting smoking was much more effective than reducing the number of cigarettes smoked. We therefore need to continue to educate and counsel our patients and families regarding smoking cessation.

C.D.

Thun MJ, Carter BD, Feskanich D, et al: 50-year trends in smoking-related mortality in the United States. **N Engl J Med**. 2013;368:351-364*; Jha P, Ramasundarahettige C, Landsman C, et al: 21st century hazards of smoking and benefits of cessation in the United States.* **N Engl J Med**. 2013;368:341-350.

Five-Grass Pollen Tablet Is Effective for SLIT in U.S. Adults

SUBLINGUAL immunotherapy (SLIT) is an appealing option for the treatment of allergic rhinoconjunctivitis (ARC). A five-grass pollen sublingual tablet has proven effective in the treatment of grass pollen-induced ARC in adults and children. This study evaluated the safety and efficacy of this SLIT tablet in U.S. patients with grass pollen allergy.

The randomized trial included 473 adults with grass pollen allergy and a Rhinoconjunctivitis Total Symptom score of 12 or higher during the previous pollen season. One group received SLIT using the 300 index of reactivity (IR) five-grass pollen sublingual tablet, starting 4 months before and continuing throughout pollen season. The other group received placebo SLIT. The main outcome measure was the 0-to-3 daily Combined Score (CS), which assesses both symptoms and medication use.

In pollen season, the mean daily CS was significantly lower for patients receiving the 300IR grass pollen tablet: least-squares mean difference &#150-0.13, for a relative reduction of 28%. In the placebo group, the daily CS least-squares mean was 0.32 in patients with timothy grass-specific IgE levels less than 0.1 kU/L, compared to 0.46 for those with higher levels.

Common adverse events including oral pruritus, throat irritation, and nasopharyngitis. There were no cases of anaphylaxis and no events requiring epinephrine treatment.

The 300IR five-pollen SLIT tablet shows clinical safety and efficacy in U.S. adults with grass pollen-induced ARC. This treatment is most effective in patients ➤➤

with measurable levels of timothy grass-specific IgE. The authors suggest that future studies should require a measurable level of allergen-specific serum IgE for inclusion.

COMMENT: *This well-designed study demonstrates clinical and immunologic improvement in U.S. patients with grass pollen allergy using a five-grass sublingual tablet. Besides showing that this tablet was efficacious, the study also reinforces the critical importance of patient selection in analyzing therapeutic value of immunotherapy. Despite the fact that 11% of the patients did not have significant levels of specific IgE to timothy grass, there was still a therapeutic effect in the overall population. Analysis of this subgroup clearly shows that immunotherapy is really only clinically helpful in patients who are truly sensitized to the antigens.*
S.M.F.

Cox LS, Casale T, Nayak AS, et al: Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE.
J Allergy Clin Immunol. 2012;130:1327-1334. ♦♦

Maternal Probiotic Supplements Reduce Infant Eczema Risk

EARLY-life probiotic supplementation is a promising approach to reducing the risk of eczema in infants. However, because of variability in previous studies, the optimal probiotic regimen remains undefined. This study evaluated a maternal probiotic supplementation approach for prevention of eczema in infants at high risk.

The randomized controlled trial included 241 mother-infant pairs in which the mothers had allergic disease and atopic sensitization. Mothers were randomly assigned to receive probiotic supplements or placebo, starting 2 months before delivery and continuing through the first 2 months of breast-feeding. Two probiotic supplements were tested: *Lactobacillus rhamnosus* LPR plus *Bifidobacterium longum* BL999 (LPR+BL999) and *Lactobacillus paracasei* ST11 and *B. longum* BL999 (ST11+BL999). Eczema and atopic disease were evaluated in the infants at age 24 months.

Complete follow-up was available for 205 infants. Both probiotic groups were at lower risk of developing eczema in the first 2 years of life: odds ratio 0.17 for LPR+BL999 and 0.16 for ST11+BL999. Odds ratios for chronically persistent eczema were 0.30 and 0.17, respectively. Skin prick testing found no reduction in atopic sensitization with probiotics.

Maternal probiotic supplementation before delivery and during breast-feeding may reduce the risk of eczema among infants at high risk. Maternal supplementation is a safe, inexpensive, and easy intervention that avoids the need to give probiotics to the infants themselves.

COMMENT: *The use of probiotics in infants to prevent allergic diseases is controversial, with particular concern over exposing the developing gut and immune system to live bacteria. These Finnish researchers found that giving probiotics to the mothers, 2 months before delivery and for the first 2 months of nursing, reduced the risk of eczema in high-risk infants. Both combinations of probiotics studied had an impact, so it is not clear that any one specific probiotic is the best. What has been considered alternative medicine is becoming more mainstream.*
S.M.F.

Rautava S, Kainonen E, Salminen S, Isolauri E: Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant.
J Allergy Clin Immunol. 2012;130:1355-1360. ♦♦

Is There an 'Obese Phenotype' in Children with Asthma?

PREVIOUS studies have described an obesity-related, non-Th2 asthma "phenotype" in adults. There are questions as to the existence of a similar childhood asthma phenotype in children, as well as regarding the contribution of obesity to asthma control in children. The study assessed asthma control and related outcomes in obese children, including influence of Th1 or Th2 polarization.

The researchers performed a post hoc analysis of data from 269 children, aged 6 to 17 years, from the National Heart Lung and Blood Institute Severe Asthma Research Program. The analysis included questionnaire responses, spirometry and plethysmography results, exhaled nitric oxide levels, and blood Th1/Th2 cytokine levels. Asthma control was defined using criteria from national guidelines.

Of the children studied, 22% were overweight (body mass index [BMI] between the 85th and 95th percentile) and 25% were obese (BMI above the 95th percentile). Asthma was "very poorly controlled" in 66% of children overall. Overall asthma control was no worse in obese children, although they had higher rates of nonspecific symptoms such as dyspnea and nighttime awakenings. Obese patients had lower disease-specific quality of life and increased health care utilization; these differences were associated with decreased functional residual capacity rather than airflow limitation. There was no obesity-related "phenotype" of Th1 or Th2 polarization.

The findings raise the possibility that poor asthma control may be overestimated in obese children. Obesity may be associated with increased reports of dyspnea and other nonspecific symptoms related to altered mechanical properties of the chest wall. The researchers emphasize the need to evaluate physiologic parameters as well as symptoms in obese children with respiratory symptoms. Weight loss may be necessary to reduce symptoms and improve quality of life in this group of patients.

COMMENT: *This well-done post hoc analysis shows that although overweight and obese children with asthma used more corticosteroids, had more emergency department visits and had more nonspecific asthma symptoms, there were no significant differences in FEV_1 values or inflammatory cytokine levels. Children with higher BMI did have lower functional residual capacity and tended to have higher IgE levels and higher* ➤➤

exhaled NO values. The authors conclude that since the overweight children had enhanced perception of dyspnea, they tended to overestimate their symptoms. This is a problem we're seeing with increasing frequency as the "obesity epidemic" escalates.
S.M.F.
Sah PK, Teague WG, Demuth KA, et al: Poor asthma control in obese children may be overestimated because of enhanced perception of dyspnea.
J Allergy Clin Immunol Pract. 2013;1:39-45. ♦♦

Platelet Activating Factor Reflects Anaphylaxis Severity

THE proinflammatory phosphoplid platelet activating factor (PAF) is an important mediator of anaphylaxis. It is unclear how well PAF is correlated with the severity of anaphylaxis, especially relative to other mediators such as histamine and tryptase. This question was addressed in a series of patients seen in the emergency department for acute allergic reactions.

The study included 41 patients with acute allergic reactions, rated for severity from grade 1 to 3. Levels of blood PAF, histamine, and tryptase were measured and evaluated for correlation with severity of the reaction. Twenty-three healthy controls were studied for comparison.

The percentage of patients with elevated PAF levels increased with severity: 20% for patients with grade 1 reactions, 66.7% with grade 2, and 100% with grade 3. Proportions with elevated histamine levels were not significantly different across severity groups: 40%, 57%, and 70%, respectively. Tryptase was elevated for none of the patients with grade 1 reactions, 4.8% of patients with grade 2, and 60% with grade 3. In patients with acute allergic reactions, PAF levels increase along with the severity of reactions. All patients with severe anaphylaxis have elevated PAF, but don't necessarily have elevated histamine and tryptase. The results suggest that PAF plays a "pivotal role" as a mediator of anaphylaxis.

COMMENT: *A virtual panoply of chemical mediators are rapidly released during anaphylaxis. This well-done study analyzed major mediator levels in patients presenting to the ED for anaphylaxis. There was a clear-cut correlation of increasing levels of PAF with increasing clinical severity of anaphylaxis. This was not the case for tryptase or histamine; neither was well correlated with severity scores. Platelet-activating factor has a critical role in anaphylaxis; it would be nice if there were medications that could directly block PAF to improve our treatment of these patients.*
S.M.F.
Vadas P, Perelman B, Liss G: Platelet-activating factor, histamine, and tryptase levels in human anaphylaxis.
J Allergy Clin Immunol. 2013;131:144-149. ♦♦

***Editor's Note**: This issue we're pleased to welcome a new Associate Editor: David A. Khan, M.D., of the University of Texas Southwestern Medical Center in Dallas.*
A.M.

Obesity-Associated Asthma: A New Phenotype?

OBESITY is now thought to be an important risk factor for asthma, and one which may also affect asthma control and airway inflammation. The association between obesity and severe asthma is unclear; some studies have reported steroid resistance in obese patients. The association between body mass index (BMI) and severe asthma was evaluated in large group of patients with refractory asthma.

The study included data on 666 patients with severe asthma, drawn from the British Thoracic Society Difficult Asthma Registry. Demographic factors, asthma characteristics, and health care utilization were compared for normal-weight, overweight, and obese patients, based on standard BMI categories.

The median BMI was 29.8, with 48.3% of patients were classified as obese. Nearly half (48.9%) of obese patients with difficult asthma were taking maintenance oral steroids, compared to 40.4% of the overweight group and 34.5% of the normal-weight group. Obese patients had higher use of steroid burst therapy and short-acting β_2-agonists. They also had a higher rate of gastroesophageal reflux disease: 53.9%, compared to 48.1% of overweight and 39.7% of normal-weight patients.

Obese patients had higher bone density scores. On pulmonary function tests, obesity was associated with lower forced vital capacity and higher carbon monoxide transfer coefficient. As BMI increased, serum IgE levels decreased. The obese group had a higher rate of eczema but a lower rate of nasal polyps.

Among patients with refractory asthma, different BMI groups show a pattern of distinct clinical characteristics. The results add to the evidence that obesity-related severe asthma may be a distinct clinical phenotype. Further studies of the mechanisms of this association are needed to improve treatment.

COMMENT: *A growing body of evidence (no pun intended) has demonstrated a link between obesity and asthma. This study examines a large British cohort of severe asthma patients stratified by BMI. Obese patients had greater asthma medication requirements (including oral steroids), more frequent gastroesophageal reflux disease, and higher rates of eczema but lower rates of nasal polyps. It is unclear whether oral steroids cause obesity or obesity-related changes result in worsening control, necessitating higher steroids. Although imperfect, BMI may be another variable useful in classifying asthma patients.*
D.A.K.
Gibeon D, Batuwita K, Osmond M, et al: Obesity associated severe asthma represents a distinct clinical ➤➤

phenotype: analysis of the British Thoracic Society Difficult Asthma Registry patient cohort according to body mass index.
Chest. 2013;143:406-414. ♦♦

Omalizumab Benefits Severe Asthma in the 'Real World'

PREVIOUS studies have reported that omalizumab reduces hospitalizations and emergency department (ED) visits for patients with severe, uncontrolled asthma. French postmarketing data were evaluated to evaluate how omazlimab was used under "real-world" conditions and whether it reduced the risk of severe asthma exacerbations.

The study included 767 adult patients with severe asthma that was uncontrolled despite optimal treatment with inhaled and oral corticosteroids and a long-acting β_2 agonist. Of these patients, recruited by 163 pulmonologists, 374 took omalizumab at least once. The effects of add-on omalizumab therapy on the risk of hospitalization or ED visits were assessed. Associations were adjusted for age and sex, smoking, BMI, gastroesophageal reflex, allergic status, allergic rhinitis, treatment, and asthma hospitalizations and ED visits in the preceding 2 months.

A total of 445 severe exacerbations occurred during follow-up. Omalizumab was associated with a reduced rate of asthma hospitalizations and ED visits: adjusted relative risk 0.57. Among patients receiving omalizumab, risk was lower during periods taking omalizumab, compared to times off treatment: relative risk 0.40. Times of omalizumab use were also associated with a lower rate of oral corticosteroid treatment: 49.2 versus 73.8 courses per 100 patient-years.

Omalizumab, added to standard therapy, appears to reduce the risk of severe asthma exacerbations in patients with uncontrolled severe asthma. These posmarketing data support studies showing a decreased risk of hospitalization or ED visits with omalizumab. The response to omalizumab may not be as good in patients taking oral corticosteroids at baseline.

COMMENT: *A number of controlled studies have shown various benefits of omalizumab in asthma. This large observational study from France provides a "real-world" experience with omalizumab as add-on therapy for severe poorly controlled asthma. A reduction of 60% in severe exacerbations (hospitalizations or ED visits) was observed in the omalizumab group. A surprisingly low rate of nonresponse (16%) and a potential placebo effect may have amplified the response seen in this observational study.*
D.A.K.
Grimaldi-Bensouda L, Zuriek M, Aubier M, et al: Does omalizumab make a difference to the real-life treatment of asthma exacerbations? Results from a large cohort of patients with severe uncontrolled asthma.
Chest. 2013;143: 398-405. ♦♦

CLINICAL TIDBITS

Imatinib Mesylate for Diffuse Cutaneous Mastocytosis

DIFFUSE cutaneous mastocytosis (DCM) is a rare, potentially life-threatening variant of childhood mastocytosis. It appears to be caused by activating KIT mutations. The authors report the successful use of the KIT inhibitor imatinib mesylate in the treatment of 2 children with DCM.

Both patients were both girls, aged 11 months and 3 years, respectively. Both had an itchy generalized skin eruption diagnosed as DCM, associated with an activating KIT mutation in exon 8. The children had rapid responses to imatinib mesylate, starting dose 100 mg/d, with complete resolution of skin lesions. Dosage was gradually tapered over several months. Both patients remained free of relapse at follow-up of 6 months to 2 years.

Imatinib mesylate provides an effective treatment in selected cases of DCM associated with activating KIT mutations. The authors call for further studies, including the dosage, optimal treatment duration, and possible long-term adverse effects.

COMMENT: *Diffuse cutaneous mastocytosis is a rare variant of childhood mastocytosis that presents as diffuse infiltrative yellow-orange xanthogranuloma-like subcutaneous nodules or as a widespread urticarial eruption with bullae and redness. It is generally self-limiting. Imatinib is a tyrosine kinase inhibitor approved for treatment of systemic mastocytosis. These two cases of children responding to this drug with tolerable side effects are suggestive of a treatment that can decrease manifestations of diffuse cutaneous mastocytosis in patients who have c-KIT mutations.*
S.F.W.
Morren, M-A, Hoppé A, Renard M, et al: Imatinib mesylate in the treatment of diffuse cutaneous mastocytosis.
J Pediatr. 2013;162:205-207. ♦♦

More Data Linking Cleaning Sprays to Asthma

PREVIOUS studies have suggested that use of cleaning sprays may be associated with an increased incidence of asthma. Data from a large study of asthma risk factors were used to explore the association between household use of cleaning sprays and asthma among women.

The study included 683 women from the Epidemiological Study on the Genetics and Environment of Asthma. In addition to precise information on asthma phenotype, the study included detailed questionnaire responses on domestic tasks.

Using at least two types of cleaning sprays weekly was associated with a high asthma symptom score: adjusted odds ratio (OR) 2.50. Associations were significant ➤➤

for both current asthma, OR 1.67; and poorly controlled asthma, OR 2.05, compared to women without asthma. For current asthma, the association was significant only among women who did not report avoidance of polluted places: OR 2.12.

The study adds further evidence for the association between use of household cleaning sprays and asthma. Given the high exposure to domestic cleaning products the findings could have important public health implications.

COMMENT: *This study is an extension of work previously reviewed in* AllergyWatch *(Zock JP, Plana E, Jarvis D, et al: Am J Respir Crit Care Med 2007;176:735-741). The results show that even once-weekly use of aerosol cleaning preparations leads to high asthma symptoms, recurrent asthma, and poorly controlled asthma. This is a very important and often overlooked domestic and occupational source of increased asthma activity.*
B.E.C.
Le Moual N, Varraso R, Siroux V, et al: Domestic use of cleaning sprays and asthma activity in females.
Eur Respir J. 2012;40:1381-1389. ♦♦

Early Exposure to Traffic Pollution Linked to Decreased FEV_1

CHILDREN with higher long-term exposure to ambient air pollution have reduced lung function. Long-term follow-up data from a birth cohort study were used to clarify the effects of the timing of air pollution exposure.

The analysis included repeated questionnaires and spirometry results from birth to age 8 in more than 1,900 Swedish children, along with dispersion modeling of exposure to road traffic-generated outdoor particulate matter of aerodynamic diameter less than 10 μm (PM_{10}). Exposure to PM_{10} in various time windows was analyzed for association with FEV_1 at 8 years.

For children in the 95th percentile of time-weight average PM_{10} exposure in the first year of life, FEV_1 was reduced by -59.3 mL, compared to those in the 5th percentile. The difference in FEV_1 was even greater, -136.9 mL, for highly exposed children who were also sensitized to common inhalant or food allergens. Exposure to PM_{10} after age 1 appeared to have less effect on FEV_1 at age 8.

Higher exposure to traffic-related air pollution in the first year of life is associated with reduced lung function at age 8, especially in children sensitized to common allergens. The results "provide further support that early life exposure has long-lasting impact on lung function development."

COMMENT: *This study shows a significant association with traffic-generated air pollution exposure during infancy and decreased lung function in children at 8 years of age. The results were particularly notable in children sensitized to both inhalant and food allergens. The effects of air pollution associated with fossil fuel combustible engines are significant. This is a public health area that must be addressed.*
B.E.C.
Schultz ES, Gruzieva O, Bellander T, et al: Traffic-related air pollution and lung function in children at 8 years of age.
Am J Respir Crit Care Med. 2012;186:1286-1291. ♦♦

REVIEWS OF NOTE

COMMENT: *Since data are limited with regard to mosquito allergy, the authors performed a MEDLINE review on the topic. While the majority of reports describe local reactions, some patients have been reported to have anaphylaxis. At-risk groups include immunodeficient patients, people who work outdoors, young children, and immigrants. Routine diagnostic testing is difficult due to limited specificity and sensitivity and the lack of standardized extract. The authors do not recommend routine testing of patients with local reactions. Treatment includes avoidance, barriers, and auto-injectable epinephrine in the case of anaphylaxis. The authors remind us that randomized placebo-controlled trials are needed, particularly among patients with systemic reactions.*
V.H.-T.
Crisp HC, Johnson KS: Mosquito allergy.
Ann Allergy Asthma Immunol. 2012;110:65-69. ♦♦

COMMENT: *This is an excellent review that focuses on how to recognize when a patient with urticaria should have a workup for an autoinflammatory condition. It's important to clinically distinguish run-of-the-mill chronic idiopathic urticaria from potentially dangerous syndromes, especially as practice parameters and performance measures encourage minimizing work-ups for patients with likely idiopathic urticaria.*
S.A.T.
Krause K, Grattan CE, Bindslev-Jensen C, et al: How not to miss autoinflammatory diseases masquerading as urticaria.
Allergy. 2012;67:1465-1474. ♦♦

COMMENT: *This is an excellent review of bronchodilator therapy in patients with COPD and the benefits of long-acting bronchodilators (LABAs) and long-acting antimuscarinic agents (LAMAs).*
B.E.C.
Wedzicha JA, Decramer M, Seemungal TAR: The role of bronchodilator treatment in the prevention of exacerbations of COPD.
Eur Respir J. 2012;40:1545-1554. ♦♦