

ALLERGYWATCH®

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

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Can Neonatal Emollients Prevent Atopic dermatitis?

ATOPIC dermatitis (AD) is rising in prevalence among children worldwide, with a major socioeconomic and quality-of-life impact. Although past efforts at prevention have met with limited success, recent studies suggest that skin barrier defects play an important role in the development of AD, and possibly in allergic sensitization. This trial evaluated the use of skin barrier enhancement using emollients for prevention of AD in newborn infants at risk.

The randomized US/UK trial included 124 newborns at high risk of AD, based on family history of atopic disease. In the intervention group, parents were instructed to apply emollient to the infant's entire body (except the scalp) at least once daily, starting within 3 months after birth and continuing until age 6 months.

Parents were offered their choice of an emollient oil, cream/gel, or ointment, chosen based on safety, tolerability, or barrier-protective qualities. Controls were asked to use no emollients.

As a primary feasibility outcome, 42% of eligible parents agreed to be randomized. All parents in the emollient group found the intervention acceptable. Two-thirds chose the cream/gel emollient.

At 6 months, cumulative incidence of AD was 22% in the emollient group versus 43% in the control group—a 50% reduction. The difference remained significant in sensitivity analyses. There was no difference in adverse events, and no emollient-related adverse events.

For newborns with a family history of atopic disease, daily application of emollient seems to be a safe and effective intervention to lower the risk of AD. Emollients may work by correcting subclinical skin barrier dysfunction and early inflammation, improv- ➤➤

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ing skin hydration and reducing skin permeability. Further studies are needed, including assessment of the effects on IgE sensitization.

SKIN barrier dysfunction is an important contributor to the development of atopic dermatitis (AD) in children, suggesting a possible preventive benefit of intensive emollient use in early life. This randomized trial evaluated the effects of daily emollient application on the development of AD, as well as allergic sensitization, in high-risk newborns.

The Japanese study included 118 newborns at high risk of AD; enrolled infants had a parent or sibling affected by AD. One group was assigned to daily application of an emulsion-type emollient for 32 weeks, starting in the first week of life. In the control group, parents were permitted to apply petroleum jelly, if they thought it necessary. The development of AD and eczema was compared between groups, assessed by a dermatologist using modified Hanifin and Rajka criteria. Allergic sensitization, based on serum allergen-specific IgE levels, was evaluated as a secondary outcome.

By age 32 weeks, AD/eczema had developed in about 32% of infants assigned to daily moisturizer use, compared to 47% in the control group. Thus the risk of AD/eczema was reduced by about one-third in the intervention group. The study was halted early because of the superior effectiveness of daily moisturizer application.

There was no significant difference in the level of egg white-specific IgE between groups. Risk of egg sensitization was significantly increased for infants who developed AD/eczema: odds ratio 2.86.

The results show a reduced rate of AD with daily moisturizer application in infants at high risk. The risk of allergic sensitization is unaffected by moisturizer use, but infants who develop AD are more likely to be sensitized to egg. The authors note that moisturizer application was also associated with increased hydration of the stratum corneum at 12 weeks.

COMMENT: *The ability to prevent disease with a safe intervention would be embraced by all families of infants predisposed to atopy. These two prospective pilot studies evaluated daily application of emollient for either 24 or 36 weeks in neonates at risk for atopy. In both studies, infants receiving the emollient treatment had a significantly lower incidence of AD. In fact, the Japanese study was stopped early after initial analysis showing a dramatic 32% reduction in AD. In the US/UK study, the risk reduction was 50% in the intervention group.*

The Japanese researchers could not show a statistically significant reduction in egg allergen sensitization with emollient treatment, although among infants who did develop AD, there was at least a threefold greater risk of egg allergy. Both studies were limited by small numbers; other confounders included the ability to use petroleum jelly in controls in the Japanese study and the use of various, albeit similar, emollients in the US/UK study. Nevertheless the potential to the development of AD in high-risk infants, with a simple, safe, inexpensive intervention is intriguing.

S.M.F.

Simpson E, Chalmers J, Hanifin JM, et al: Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention.

J Allergy Clin Immunol. 2014;134:818-823.

Horimukai K, Morita K, Narita M, et al: Application of moisturizer to neonates prevents development of atopic dermatitis.

J Allergy Clin Immunol. 2014;134:824-830. ♦♦

Epithelial IL-25 Is Key Mediator in Th2-High Asthma

TYPE 2 cytokine pathways play an important role in a subset of asthma cases. Patients with "Th2-high" asthma have increased levels of interleukin (IL-13), associated with differences in clinical and pathologic characteristics. Although epithelial cytokines can trigger type 2 responses, the role of specific cytokines in Th2-high asthma are unclear. This study evalu- ➤➤

ated the role of epithelial cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) in Th2-high asthma.

The investigators analyzed epithelial cytokine expression in 43 patients with asthma and 21 healthy controls. The asthma patients were studied during 8 weeks of treatment with inhaled budesonide. Expression of epithelial IL-25, IL-33, and TSLP was analyzed for association with Th2 responses and with clinical responsiveness to budesonide.

The results showed high expression of epithelial IL-25, but not IL-33 or TSLP, in about half of the asthma patients. High IL-25 expression was associated with increased airway hyperresponsiveness, increased airway and blood eosinophilia, higher serum IgE levels, greater subepithelial thickening, and increased Th2 signature gene expression. Asthma patients with high IL-25 showed improvements in FEV₁ and airway hyperresponsiveness, while the group with low IL-25 did not.

Plasma IL-25 levels were significantly correlated with epithelial IL-25 expression, as well as with airway eosinophil levels and clinical response to inhaled corticosteroid. Plasma IL-25 was significantly decreased after 4 weeks of inhaled budesonide, particularly in the subset with IL-25-high asthma.

Airway epithelial IL-25 expression can identify IL-25-high and IL-25-low subgroups of asthma patients. These groups have differing clinical and pathologic characteristics, including increased responsiveness to inhaled corticosteroid in the IL-25-high group. Plasma IL-25 measurement may be useful for identifying patients with Th2-high asthma, and in selecting appropriate treatments.

COMMENT: *This work extends the seminal observations made by Woodruff et al (Am J Respir Crit Care Med. 2009;180:388-395), previously reported in AllergyWatch. Interleukin-25 is an upstream mediator that drives IL-13 and IL-5 production. These data help better define the potential role of IL-25 as a driver of Th2-high corticosteroid-responsive asthma. The accompanying editorial by Byers (Am J Respir Crit Care Med. 2014;190:715-716) provides an outstanding and concise perspective on the likely roles of IL-25, IL-33, and TSLP in various asthma phenotypes.*

*B.E.C.
Cheng D, Xue Z, Yi L, et al: Epithelial interleukin-25 is a key mediator in Th2-high, corticosteroid-responsive asthma.*

Am J Respir Crit Care Med. 2014;190:639-648. ♦♦

Obesity Frequently Leads to COPD Misdiagnosis

IN many cases, chronic obstructive pulmonary disease (COPD) is diagnosed clinically, without spirometric confirmation of airflow obstruction. Dyspnea is common in patients with overweight and obesity, and may be falsely ascribed to airflow obstruction (AFO). This study evaluated the rate of incorrect COPD diagnosis and treatment among overweight and obese patients.

From three Veterans Administration Medical Centers in the Pacific Northwest, the researchers identi-

fied veterans who had been clinically diagnosed with COPD and subsequently underwent spirometry between 2003 and 2007. The relationship of overweight and obesity with AFO demonstrated on spirometry—defined as a postbronchodilator FEV₁/FVC below the lower limit of normal—was assessed. Rates of escalation or de-escalation of inhaled medications from 3 months before to 9 to 12 months after spirometry were assessed as well.

Among 5,493 patients with clinically diagnosed COPD, the rate of spirometrically confirmed AFO was 52%. On adjusted analysis, the proportion of veterans with AFO decreased from 0.64 for normal-weight patients, to 0.53 for those with overweight, 0.44 with class I obesity, 0.41 with class II obesity, and 0.37 with class III obesity.

One or more inhaled medications were prescribed to 53% of patients without AFO before spirometry and 41% after spirometry. At both times, inhaled treatments were more likely to be prescribed to veterans who were overweight or obese. De-escalation of inhaled medications was also less likely for overweight or obese patients, compared to normal-weight patients.

Overweight or obese patients appear more likely to receive an incorrect diagnosis of COPD, and less likely to have their inhaled medications reduced after spirometry showing no AFO. The results suggest a "dose-response" relationship between body mass index and COPD misdiagnosis. Physicians may be missing opportunities to identify and manage other causes of dyspnea in overweight and obese patients.

COMMENT: *Chronic obstructive pulmonary disease and obesity frequently coexist. Furthermore, many patients with obesity have dyspnea. This study from several VA hospitals evaluated patients diagnosed with COPD who subsequently had spirometry. The adjusted proportion of patients with AFO decreased as body mass index increased. Overweight or obese patients were also less likely to have their inhaled medications de-escalated after determining the lack of obstruction on spirometry. This study shows that the majority of obese patients diagnosed with COPD did not have AFO! In those with BMI of 40 or higher, only 29.9% had obstruction. Thus misdiagnosis of COPD appears to be common in overweight and obese patients, leading to inappropriate therapy and likely worse outcomes since the primary cause of their dyspnea is not being addressed.*

D.A.K.

Collins BF, Ramenofsky D, Au DH, et al: The association of weight with the detection of airflow obstruction and inhaled treatment among patients with a clinical diagnosis of COPD.

Chest. 2014;146:1513-1520. ♦♦

Is Sunbathing a Contraindication to Skin Prick Testing?

SKIN damage due to natural aging is a different process than skin changes due to photodamage. In older patients undergoing skin prick testing (SPT), histamine responses are often small or absent on the ►►

upper back and forearms but larger or present on the lower back. This study compared responses to SPT in areas of skin with photoaging versus natural aging.

The researchers performed histamine prick-puncture tests in sun-exposed and sun-protected areas in two groups of about 60 volunteers: a younger group, aged 20 to 50, and an older group, aged 60 to 87. Photoaging was assessed by physical examination, with coloration measured by a colorimeter.

Photoaging scores varied widely, but averaged higher in the older group (mean 1.59 versus 4.30). Fair skin had greater photoaging. The two age groups were not significantly different in terms of histamine wheals and flare. However, subjects with the greatest amount of photoaging showed smaller wheal and flare responses to histamine on the upper back, along with a trend toward smaller flares on the volar forearms and lower back. There was wide intraindividual variation in histamine responses, depending on the test site.

Photoaged skin shows small responses to histamine in sun-exposed areas, whereas there is no such association for age alone. Sun-protected areas should be chosen for SPT, avoiding areas of photodamage. If there is no appropriate sun-protected area, *in vitro* allergy testing may be preferable.

COMMENT: Skin prick test results are affected by a variety of factors. This is the first study to investigate the effects of photoaging on SPT histamine response. Interestingly, no differences were seen between younger versus older groups of patients, comparing the natural aging process. On the other hand, photoaging did affect the SPT response to histamine. This study challenges the allergist to examine the skin for sun damage prior to performing SPT, and consider *in vitro* testing for patients without sun-protected skin.

V.H.-T.

King MJ, Phillips SE, Lockey RF, et al: Effect of photoaging on skin test response to histamine independent of chronologic age.

Ann Allergy Asthma Immunol. 2014;113:647-651. ♦♦

Blood Eosinophils May Be a Useful Biomarker After All

UNCONTROLLED asthma associated with exacerbations is an important public health problem. Patients with uncontrolled asthma commonly have high blood eosinophil counts, but it is unknown whether measuring blood eosinophils can help in assessing exacerbation risk. This study evaluated high blood eosinophil count as a risk factor for future exacerbations in adults with persistent asthma.

Kaiser Permanente Southern California databases were used to identify adult patients (aged 18 to 64) with persistent asthma, based on Health Effectiveness Data and Information Set 2-year criteria. Eligible patients underwent blood eosinophil measurement in 2010. Eosinophil count was analyzed for association with asthma exacerbations, defined as asthma outpatient visits requiring systemic corticosteroids, or 5 asthma emergency department visits or hospitalizations.

Dispensing of seven or more canisters of short-acting β_2 -agonists (SABA) was evaluated as a secondary outcome. Associations were adjusted for demographic factors, comorbid conditions, and asthma burden.

In 2011, this group of persistent asthma patients had an asthma exacerbation rate of 0.41 events per person-year. Exacerbation risk was significantly increased for patients with a blood eosinophil count of 400/mm³ or greater in 2010: adjusted rate ratio 1.31. The same blood eosinophil level was associated with dispensing of seven or more SABA canisters: risk ratio 1.17. The association of blood eosinophil count with asthma exacerbations was similar in magnitude to that of other risk factors, including SABA use, female sex, black race, and obesity, but not as strong as previous history of asthma exacerbations.

Among adults with persistent asthma, high blood eosinophil count is associated with an increased risk of future asthma exacerbations and excessive SABA use. The associations remain significant after adjustment for other characteristics associated with uncontrolled asthma. Routine blood eosinophil measurement might be a useful addition to asthma care.

COMMENT: As we learn more about the inflammatory processes in asthma, there is increased effort to find objective measures to monitor control, particularly biomarkers. Using retrospective data from patients enrolled in a closed-panel managed care organization, the authors report that asthma patients with high peripheral blood eosinophils are at greater risk for future asthma exacerbations and increased use of SABA. The concept of using blood eosinophilia as a biomarker was suggested in the 1980s. With our improved understanding about the inflammatory process and the potential availability of new agents targeting eosinophilic inflammation, we may be seeing more reports suggesting a role for this simple laboratory study in monitoring asthma control.

S.M.F.

Zeiger R, Schatz M, Li Q, et al: High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma.

J Allergy Clin Immunol Pract. 2014;2:741-750. ♦♦

ICS Step-down Did Not Cause Exacerbations in COPD

IN patients with frequent exacerbations of chronic obstructive pulmonary disease (COPD), combination therapy with an inhaled steroid (ICS) plus a long-acting β -agonist (LABA) has been recommended to reduce the exacerbation rate. However, it is unclear whether ICS has any further benefit in patients already receiving two classes of long-acting bronchodilators. The effects of ICS withdrawal in COPD patients taking a long-acting antimuscarinic agent (LAMA) plus a LABA were examined in a multicenter trial.

The randomized "Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management" (WISDOM) trial included 2,485 patients with a history of COPD exacerbations, enrolled at 200 centers in 23▶▶

countries. All were receiving triple therapy with a LAMA, tiotropium 18 µg once daily; a LABA, salmeterol 50 µg twice daily; and an ICS, fluticasone propionate, 500 µg twice daily. One group underwent ICS withdrawal in three steps over 12 weeks, while the other continued on the three-drug combination. Rates of COPD exacerbations were compared between groups, with secondary outcomes including lung function, health status, and dyspnea.

Fluticasone withdrawal did not lead to any increase in COPD exacerbations—the hazard ratio of 1.06 was nonsignificant, compared to the specified noninferiority margin of 1.20. Time to first moderate to severe COPD exacerbation was also similar between groups. The ICS step-down group had a greater decline in lung function, with a 38 mL difference in adjusted mean trough FEV₁ at 18 weeks. Dyspnea was unchanged, while fluticasone showed only minor changes.

In contrast to current recommendations, ICS withdrawal in patients with severe COPD who are also taking a LABA and a LAMA does not reduce the risk of exacerbations. The results do suggest a significant reduction in lung function during the final fluticasone withdrawal step, however.

COMMENT: *This intriguing large-scale study explored the gradual withdrawal of ICS in patients with severe COPD who were clinically stable on triple therapy: LAMA, LABA, and ICS. No impact on exacerbations was seen over a 12-month period, although a decrease in lung function was observed. As noted in the accompanying editorial by Reilly (N Engl J Med. 2014;371:1340-1341), these data imply that the decision to continue ICS therapy in patients with COPD taking long-acting bronchodilators should, in the future, be driven by the health-status improvement attributable to ICS rather than to prevent exacerbations.*

C.D.

Magnussen H, Disse B, Rodriguez-Roisin R, et al: Withdrawal of inhaled glucocorticoids and exacerbations of COPD.

N Engl J Med. 2014;371:1285-1294. ◆◆

Asthma Benchmarks in a Hospital Setting

EVIDENCE-based guidelines have been developed for the leading causes of hospitalization in children: asthma, pneumonia, and bronchiolitis. The lack of accepted benchmarks poses a challenge to hospitals seeking to improve the quality of care for these conditions. Based on performance on clinical quality indicators at US children's hospitals, the researchers developed clinically achievable benchmarks of care (ABCs) for these three conditions.

The study used the Pediatric Health Information System database to assess clinical quality indicators for patients with asthma, bronchiolitis, and pneumonia at 42 children's hospitals. The analysis included 22,186 encounters for pediatric asthma (age range 2 to 18 years), 14,882 for bronchiolitis (2 months to 2 years), and 12,983 for asthma (age 2 months to 18 years). The

researchers used a published method for developing ABCs, with benchmarks calculated using the best-performing hospitals comprising at least 10% of the total patient population for each clinical quality indicator.

For asthma, the ABCs were 24.5% for use of chest x-rays, 6.6% for antibiotic treatment, and 0% for more than 2 days of treatment with ipratropium bromide. The ABCs for bronchiolitis included 32.4% for chest x-rays, 0.6% for viral testing, 18.5% for antibiotic administration, 11.4% for more than 2 days of bronchodilator use, and 6.4% for steroid use.

Pneumonia ABCs were 28.8% for complete blood cell count, 1.5% for viral testing, 60.7% for initial use of narrow-spectrum antibiotics, 3.5% for erythrocyte sedimentation rate, and 0.1% for C-reactive protein. With the exceptions of blood culture and narrow-spectrum antibiotics for pneumonia, ABCs were lower than reported medians for all clinical indicators.

The study provides ABCs for the top three admission diagnoses at pediatric hospitals, representing "measurable and attainable goals" for these conditions. Based on average utilization rates at high-performing hospitals, the benchmarks may provide a useful starting point for local quality improvement efforts.

COMMENT: *A study using data from 42 hospitals on children admitted with asthma, bronchiolitis, or pneumonia helped construct achievable benchmarks of care (ABCs). Asthma ABCs established were chest radiograph utilization, 24.5%; antibiotic administration, 6.6%; and ipratropium bromide use less than 2 days, 0%. These are below previously reported median values and may provide opportunities for local quality improvement initiatives at healthcare practices that are divergent from these benchmarks.*

C.D.

Parikh K, Hall M, Mittal V, et al: Establishing benchmarks for the hospitalized care of children with asthma, bronchiolitis, and pneumonia.

Pediatrics. 2013;134:555-562. ◆◆

Infrared Technology May Help Diagnosis of Atopic Dermatitis

WATER damage and other moisture problems in homes are known to be associated with respiratory symptoms. However, there are few data on the relationship between water damage and atopic dermatitis (AD) symptoms. Using an infrared camera to assess water damage, the researchers evaluated the association between moisture problems and AD severity in children.

The researchers made visits to the homes of 52 Korean children with AD, mean age 4 years. The presence of water damage was assessed with the use of an infrared camera to show variations in surface temperature, as well as by visual evidence of mold or water stains. Environmental analysis also included air samples from the living room and the child's bedroom. The relationship between home water damage and AD severity was assessed, with consideration of other aggravating factors.

Evidence of water damage was found in 59.6% of homes, with nearly three-fourths of these showing▶▶

water damage in the child's bedroom. Airborne mold levels were significantly higher in water-damaged homes, but did not differ for homes with versus without visible mold or water stains. The overall mean SCORAD score was 26.1 for children in water-damaged homes, compared to 15.8 for those in homes with no infrared evidence of water damage. On multivariate analysis, the adjusted odds ratio for moderate to severe AD in children living in water-damaged homes was 14.52.

The results suggest increased severity of pediatric AD for children living in water-damaged homes. Infrared cameras can detect water damage in many homes without visible mold or water stains. The authors call for further study to identify the mechanism by which moisture and/or molds aggravate skin inflammation in children with AD.

COMMENT: *This study investigated the use of an infrared camera to assess the presence of water damage in homes of children with AD. The infrared technology detected the presence of moisture behind walls, even when water stains were not visible. Patients in homes with water damage were 15 times more likely to have severe AD symptoms. This new technology may aid our diagnosis of patients with severe AD.*

V.H.-T.

Seo S, Han Y, Kim J, et al: *Infrared camera-proven water-damaged homes are associated with the severity of atopic dermatitis in children.*

Ann Allergy Asthma Immunol. 2014;113:549-555. ◆◆

Exhaled NO as Inflammatory Marker in Occupational Asthma

ACCURATE diagnosis of occupational asthma (OA) is important, but can be difficult to achieve. Exhaled nitric oxide measurement may be a useful, non-invasive tool for assessing airway inflammation, although its added value for investigation of OA is open to debate. This study assessed exhaled NO responses to specific inhalation challenge (SIC) in patients being evaluated for possible OA.

The prospective study included 178 patients undergoing investigation SIC for suspected OA at a tertiary center between 2006 and 2012. At baseline and 24 hours after SIC, the patients underwent assessment of exhaled NO and sputum eosinophil count. A two-step cluster analysis was performed to identify phenotypes of patients with OA who shared common clinical characteristics. Variables associated with increases in exhaled NO after SIC were identified by multivariate logistic regression analysis.

The results of SIC were positive in 98 patients. Cluster analysis of this subgroup identified three clusters. Subjects in cluster 3, who were only exposed to low-molecular-weight agents, had no increase in exhaled NO, despite positive responses to SIC. The molecular weight of the agent was the only factor associated with an increase in exhaled NO in patients with a positive SIC: odds ratio 4.2 with high- versus low-molecular-weight agents. Increases in exhaled NO in response to these two types of agents were 28.8 versus 9.5 ppb, respectively.

In patients undergoing evaluation for possible OA, an increase in exhaled NO occurs more consistently in those with OA caused by high-molecular-weight agents, compared to low-molecular-weight agents. Further research is needed to evaluate possible mechanisms of these differing patterns of SIC responses.

COMMENT: *It is often difficult to document immunologically triggered OA. This study analyzed the responses of patients after specific inhalation challenge (SIC). The interesting finding was that exhaled NO was increased in those patients with OA after exposure to high-molecular-weight agents, but not after SIC to low-molecular-weight agents. Sputum eosinophils increased after both, but could not be measured in 37% of patients because of technical difficulties. It would be helpful if exhaled NO could be used as a diagnostic tool, particularly in asthmatic patients with difficult-to-document OA. However, its usefulness still needs further study.*

S.M.F.

Lemiere C, Nguyen S, Sava F, et al: *Occupational asthma phenotypes identified by increased fractional exhaled nitric oxide after exposure to causal agents.*

J Allergy Clin Immunol. 2014;134:1063-1067. ◆◆

Food Elimination in EoE: Four May Be Better Than Six

Asix-food group elimination diet yields clinical remission in most patients with eosinophilic esophagitis (EoE). On gradual reintroduction of foods, 65% to 85% of patients are found to have one or two food triggers, suggesting that some of the dietary restrictions in this group of patients may be avoidable. This study evaluated a four-food group elimination diet in adult patients with EoE.

The prospective study included 52 adults with EoE, enrolled at four Spanish hospitals. Twelve patients had failed previous treatment with topical steroids. All were managed on a four-food group elimination diet: dairy, wheat, egg, and legumes. Clinical and histologic responses, based on a peak eosinophil count of less than 15 per hpf, were assessed.

After response, the four food groups were individually introduced over 6 weeks, followed by endoscopy and esophageal biopsy. Patients who did not respond were offered a six-food group elimination diet.

In 54% of patients, clinical and histologic remission was achieved with the four-food group elimination diet. Of the 19 nonresponders, 31% responded to the six-food group elimination diet. Individual foods were reintroduced in 22 of the 28 responders to the four-food group elimination diet. In this group, milk was the most common EoE trigger, identified in 50% of patients. Egg was implicated in 36% of patients, wheat in 31%, and legumes in 18%. All patients had only one or two EoE triggers, with milk being the only trigger in 27%.

Most adult patients with EoE achieve clinical and pathologic remission on a four-food group elimination diet. Nearly one-third of nonresponders achieve remission with a rescue six food-group elimination diet, for a combined success rate of 72%. This multistage ➤➤

approach may offer several important advantages in clinical management of EoE.

COMMENT: *The interesting point about this report is that half the patients had improvement eliminating just four food groups: dairy, wheat, eggs, and legumes. Of those who did not respond, eliminating just two more foods--fish and nuts--resulted in improvement in 72%. This is similar to the figure seen in other reports of the six-food elimination diet in EoE. Although this study was prospective, it included a small number of patients with no control group and no allergy skin tests. The authors point out that eliminating only four foods was less onerous for the patients, who enjoyed a Spanish diet typically including fish and nuts. The reduced frequency of endoscopy was an added benefit.*
S.M.F.

J Molina-Infante, Arias A, Barrio J, et al: Four-food group elimination diet for adult eosinophilic esophagitis: a prospective multicenter study.

J Allergy Clin Immunol. 2014;134:1093-1099. ♦♦

Nonpharmacologic Management of Asthma: Slowing Respiratory Rate Works!

HYPERVENTILATION or overbreathing is associated with increased symptoms and decreased quality of life in asthma. New hypoventilation retraining techniques, including feedback on end-tidal CO₂ (PCO₂) and respiratory rate (RR), were evaluated in patients with asthma.

The randomized trial included 120 adults with asthma of varying severity. One group received capnometry-assisted respiratory training (CART), which provided continuous feedback on PCO₂ and RR to maintain a target PCO₂ of 40 to 42 mm Hg. The other group received slow breathing and awareness training (SLOW), which provided feedback on RR only. Both groups received five sessions of biofeedback-guided therapy. Asthma control, PCO₂, and diurnal peak flow variability were compared at up to 6 months' follow-up, along with secondary outcomes.

The two approaches yielded similar improvements in asthma control and diurnal peak flow variability. However, PCO₂ improved only with CART--an improvement of 2.7 was apparent at 1 month and sustained at 6 months. The two groups had similar reductions in daily bronchodilator doses, but CART was associated with larger improvements in weekly asthma symptoms and exacerbation symptoms. Both CART and SLOW were associated with improved airway hyperreactivity and reduced RR.

These biofeedback-guided approaches yield significant and sustained improvements in asthma control and other outcomes in adult patients with asthma of differing severity and pathophysiology. Improvements in PCO₂ and peak flow variability are seen only with the CART approach, but both CART and SLOW are associated with slowing of the RR. These techniques may provide useful nonpharmacologic adjunct approaches to improve asthma control.

COMMENT: *This study evaluated a novel approach to asthma self-management. It compared two approaches to hypoventilation training, one using continuous PCO₂ feedback (capnometry-assisted). Both groups had improvement in asthma symptoms, bronchodilator use, lung function, and methacholine responsiveness. The group using capnometry-assisted training showed better outcomes in a few areas, but the results were modest. Although a "sham" control group would have been helpful, these results suggest that a five-session biofeedback approach to slowing respiratory rate seems helpful in improving asthma.*

D.A.K.

Ritz T, Rosenfield D, Steele AM, et al: Controlling asthma by training of capnometry-assisted hypoventilation (CATCH) vs slow breathing.

Chest. 2014;146:1237-1247. ♦♦

Have Allergists Improved Pediatricians' Perceptions of Our Specialty?

PREVIOUS survey studies have found continued deficiencies in pediatricians' understanding of the specialty of allergy/immunology. With the increasing rates of allergic diseases and improved understanding of immunodeficiency disorders, it is critical for primary care pediatricians to understand the scope of disorders managed by allergists/immunologists. An updated survey of pediatricians' attitudes and practice toward allergy/immunology is reported.

A questionnaire was sent to 293 St Louis-area pediatricians, with a response rate of 46%. The most common reasons for allergist/immunologist referral were allergy skin testing, food allergy, anaphylaxis, and asthma or allergic rhinitis not improving on conventional therapy. Compared to a survey performed in the late 1990s, referrals for chronic urticaria had increased while referrals for asthma and atopic dermatitis had decreased. The main factor affecting attitudes was personal experience with allergy/immunology referrals. Exposure to the specialty during medical training showed little effect on pediatricians' attitudes.

Allergy/immunology continues to be an underused specialty by primary care pediatricians. The authors discuss the implications for efforts to improve physicians' attitudes and address barriers to allergy/immunology referrals.

COMMENT: *Past surveys have indicated that pediatricians don't understand our specialty well. This follow-up survey reveals the continued need for education and improved communication with primary care physicians. The results are a call for us to further increase education of our referring physicians, and ultimately to improve the care of patients with allergy and immunologic diseases. With the many changes in health care, the survey reminds us that an opportunity exists to increase the numbers of referrals for allergic patients--particularly those with atopic dermatitis and asthma. Further studies including a nationwide cohort of physicians would be helpful, as this one focused on a limited area.* ➤➤

V.H.-T.

Convers KD, Slavin RG, et al: Attitudes toward allergy: what do the pediatricians think?

Ann Allergy Asthma Immunol. 2014;113:544-548. ♦♦

Pollutant Exposure Linked to Increased Wheezing Incidence in Adults

A GROWING body of evidence suggests that ambient air pollution is involved in the development of childhood asthma, but there are limited data on relationship between pollutant exposure and asthma in adults. This study evaluated the association between traffic-related air pollutants—specifically, nitrogen dioxide and particulate matter less than 2.5 µm in diameter (PM_{2.5})—among women.

The researchers analyzed data from The Sister Study, a nationwide US cohort study of nearly 51,000 sisters of women with breast cancer, enrolled between 2003 and 2009. Annual average exposure to ambient NO₂ and PM_{2.5} was estimated using 2006 data on pollutant concentrations at the participants' home address. Outcomes assessed at follow-up in 2008-12 included incident self-reported wheezing, chronic cough, and physician-diagnosed asthma in women with and without these symptoms at baseline.

Outcome analysis included 254 cases of asthma, 1,023 cases of wheezing, and 1,559 cases of chronic cough. Higher estimated exposure to PM_{2.5} was associated with an increased risk of incident asthma and wheezing: for an interquartile range (IQR) difference of 3.6 µg/m³, adjusted odds ratio (OR) was 1.20 for asthma and 1.14 for wheezing.

Higher NO₂ exposure was also associated with an increased risk of incident wheezing: OR 1.08 per IQR of 5.8 ppb. Risk of chronic cough was unrelated to either pollutant.

The findings support an association between exposure to ambient NO₂ and PM_{2.5} and incident asthma symptoms in US adults. The researchers call for further studies to evaluate the surrogates for unmeasured pollutants. Further research is needed to evaluate the relationship between "complex multipollutant mixtures" and adult-onset asthma.

COMMENT: The risk of developing asthma in children has been associated with traffic related air pollution. The risk of incident adult asthma, especially in women, has been clarified by this study. In addition to NO₂ and PM_{2.5} exposure, smoking, BMI, healthcare coverage, dietary fiber, and indoor exposures must be considered. The findings in this large nationwide cohort suggest that these exposures may be involved, either directly or indirectly, in the development of wheeze and asthma in women.

B.E.C.

Young MT, Sandler DP, DeRoo LA, et al: Ambient air pollution exposure and incident adult asthma in a nationwide cohort of US women.

Am J Respir Crit Care Med. 2014;190:914 ♦♦

Can Mediators Identify HAE Severity?

H EREDITARY angioedema due to C1-inhibitor deficiency (HAE-C1-INH) varies widely in symptom frequency, even within individual patients. Some objective indicator of disease severity could be of great value for clinical decision-making in this challenging condition. This study evaluated possible laboratory indicators of disease severity in HAE-C1-INH.

The study included two groups of patients with HAE-C1-INH—162 with disease of varying severity studied during remission and 31 studied during HAE-C1-INH attacks—along with 81 healthy controls. Various laboratory markers were analyzed as potential indicators of HAE severity, including complement parameters, spontaneous plasma kallikrein activity, the capacity of plasma to inhibit exogenous kallikrein activity, and cleavage of high-molecular-weight kininogen (HK). A subgroup of 65 patients were screened for C1-INH gene mutations.

The patients with HAE-C1-INH had reduced plasma C1-INH levels and activity and low C4 levels, compared to controls. Patients in remission had higher spontaneous plasma kallikrein activity than controls. During acute attacks, spontaneous plasma kallikrein activity was significantly increased. In contrast, the capacity of inhibiting kallikrein activity was lower in HAE-C1-INH patients in remission compared to controls, and even lower during attacks.

Patients with HAE-C1-INH in remission had increased levels of cleaved HK compared to controls, with further increases during acute attacks. Among the HAE-C1-INH patients, cleaved HK levels were higher among those with high symptoms severity, compared to those with less-frequent attacks. Genetic analysis identified 35 difference C1-INH gene mutations, with equal distribution in patients with different attack frequencies.

Plasma levels of cleaved HK levels are a potentially useful laboratory marker of disease severity in patients with HAE-C1-INH. However, sensitivity would need to be increased before this and other biochemical markers could be used to guide therapeutic decision-making in HAE-C1-INH.

COMMENT: It is well recognized that HAE patients within a family can vary widely in disease severity. Finding a laboratory marker to assess disease severity in HAE has been elusive. Cicardi and colleagues from Milan have evaluated several mediators, including cleavage of high-molecular-weight kininogen (HK), in patients with HAE. Although cleaved HK was higher in more-symptomatic than less-symptomatic HAE patients, there was considerable overlap, indicating that this marker is not suitable for clinical decision-making. Interestingly, the investigators also showed that C1q decreased during acute attacks in HAE, implying that this could cause confusion in discriminating HAE from acquired C1-INH deficiency.

D.A.K.

Suffritti C, Zanichelli A, Maggioni L, et al: High-molecular-weight kininogen cleavage correlates with disease states in the bradykinin-mediated angioedema due to hereditary C1-inhibitor deficiency.

Clin Exp Allergy. 2014;44:1503-1514.j9 ♦♦

Will Component Testing Help in Diagnosing Wheat Allergy?

WHEAT is an important food allergen, particularly among children with multiple food allergens. Although wheat-specific IgE measurement may raise suspicion of wheat allergy, little is known about the relationship between specific wheat proteins and clinical allergy phenotypes. This study evaluated 12 known wheat allergen components for diagnosis of wheat allergy.

The researchers performed open or double-blind, placebo-controlled wheat oral challenges in 108 children with suspected wheat allergy. The patients' median age was 1.5 years. Skin-prick testing and serum IgE measurement were performed to evaluate responses to different wheat allergen components.

In response to wheat challenge, 28% of children had immediate and 25% had delayed symptoms. Ninety-three percent of children with immediate reactions had positive IgE responses to at least one of the 12 wheat allergen components tested, compared to 41% of children with delayed symptoms and 43% with no reaction.

The presence of positive IgE responses to five or more different wheat allergen components improved diagnostic accuracy for wheat allergy, with a positive likelihood ratio (LR+) of 5.10. Allergen components of particular value in distinguishing children with immediate symptoms to wheat challenge (compared to no reaction) were alpha-amylase inhibitors (AAI), especially dimeric AAI 0.19, LR+ 6.12; alpha-, beta-, and gamma-gliadins, with (LR+ values ranging from 3.57 to 4.53; and high-molecular-weight (HMW) glutenin subunits, LR+ 4.37.

The findings suggest that measuring IgE responses to different allergen components may improve the accuracy of wheat allergy diagnosis. Dimeric AAI 0.19 may be especially useful in identifying children with clinical reactions. However, the investigators conclude, "[W]heat allergy diagnostics is difficult, even using sophisticated component methods."

COMMENT: *Food-specific IgE has been helpful in determining the likelihood of challenge-confirmed food allergy for a number of foods, but not wheat. These authors looked at 12 known wheat components measured by microarray in children with challenge-proven wheat allergy. Alpha-amylase inhibitor 0.19 had the highest likelihood ratio (6.1) for immediate wheat reactions, but still had only modest positive and negative predictive values. Thus even with component testing, laboratory diagnosis of true wheat allergy remains difficult, and challenges are still required.*

D.A.K.

Mäkelä MJ, Eriksson C, Kotaniemi-Syrjänen A, et al: *Wheat allergy in children—new tools for diagnostics.* *Clin Exp Allergy.* 2014; 44:1420-1430. ◆◆

In Patients with Persistent Milk Allergy, BMD Increases after Oral Immunotherapy

DAILY milk consumption has an important impact on bone strength and density from childhood to

young adulthood. This study evaluated bone mineral density (BMD) in young adults with persistent cow's milk allergy (CMA), including the potential benefits of desensitization using oral immunotherapy (OIT).

The researchers performed bone densitometry in 33 postpubertal patients with IgE-mediated CMA, mean age 19.7 years, as well as in a matched control group of controls without CMA. The results showed significant reductions in BMD at the hip, femoral neck, and lumbar spine of the patients with CMA. Twenty-seven percent of the milk-allergic subjects had a *T*-score less than -2.5 standard deviations, consistent with a risk of osteoporosis. The young patients with CMA severely reduced calcium intake, compared to controls: 335 versus 768 mg.

In addition, densitometry was performed in a group of 12 patients with a history of IgE-mediated CMA who underwent OIT. These patients, who consumed milk for 12 to 39 months after desensitization, had BMD levels higher than those in the patients with persistent CMA, and similar to those in controls.

The study confirms a significant rate of low BMD among young adults with persistent CMA. The osteopenia appears to be reversible after successful OIT permitting milk consumption. The findings highlight the need for effective approaches to achieving adequate calcium intake in patients following a nondairy diet.

COMMENT: *Cow's milk provides a high concentration of bioavailable calcium. Therefore BMD in our patients with CMA is a concern. These Israeli researchers found that BMD was, in fact, reduced in CMA patients. After undergoing an oral immunotherapy/desensitization protocol and 1 to 3 years' of milk ingestion, young patients had BMD comparable to the normal control group. Fortunately, most infants lose their milk allergy. But for those older children with persistent milk allergy, desensitization protocols can not only expand their diet, but positively impact their bone density as well. We anxiously await approval of these types of food allergy treatment protocols.*

S.M.F.

Nachshon L, Goldberg M, Schwartz N, et al: *Decreased bone mineral density in young adult IgE-mediated cow's milk-allergic patients.*

J Allergy Clin Immunol. 2014;134:1108-1113. ◆◆

Can Herbs Suppress IgE Production In Patients with Food Allergy?

NEW treatments for food allergy are needed; approaches to suppress IgE production might be a useful new strategy. Studies in a mouse model of peanut allergy have reported prevention of anaphylaxis and lowering of peanut-specific IgE with Food Allergy Herbal Formula 2 (FAHF-2), a combination of 9 Chinese herb extracts. A series of in vitro studies was performed to identify the FAHF-2 components active in suppressing IgE production.

Both FAHF-2 and the butanol-purified product B-FAHF-2 significantly inhibited IgE production in the human B-cell line U266. Suppression was nine times higher with B-FAHF-2, with maximal inhibition of ►►

92% at a concentration of 120 µg/mL. Two significant inhibitors of IgE production were isolated from bark of *Philodendron chinensis*: berberine and limonin.

Berberine was the more potent of the two, showing 80% inhibition of IgE production at a concentration of 0.62 µg/mL in peripheral blood mononuclear cells from patients with peanut allergy. It also inhibited ε-germline transcript expression and suppressed phosphorylated IκBα level. In addition, berberine increased mRNA expression of T-box transcription factor TBX21 and signal transducer and activator of transcription-3.

The results show significant suppression of IgE production by two components of FAHF-2: limonin and berberine. The study also lends insights into the possible mechanism of effect of berberine, which has the larger IgE-inhibiting effect. Further studies are needed to clarify the immune-modulatory effects of FAHF-2 and B-FAHF-2.

COMMENT: *Studies of food allergy in the murine model have shown benefit of herbal supplements in peanut anaphylaxis. This thought-provoking study investigated the use of FAHF-2 and B-FAHF-2 in human peripheral blood mononuclear cells from patients with food allergy. IgE production was suppressed by berberine, found in some plants, and limonin, which is found in citrus fruits. Further studies are needed to determine if these compounds will be beneficial for the treatment of food allergies.*

V.H.-T.

Yang N, Wang J, Liu C, et al: Berberine and limonin suppress IgE production by human B cells and peripheral blood mononuclear cells from food-allergic patients.

Ann Allergy Asthma Immunol. 2014;113:556-564. ♦♦

Does Asthma Differ in the Elderly?

THE prevalence and impact of asthma in the elderly are high and increasing. There have been few comprehensive studies of how asthma may differ in older adults compared to younger patients. The authors performed a detailed study of asthma pathophysiology in the elderly.

The retrospective study included 45 elderly asthma patients, older than 65, and a comparison group of 67 younger patients. The findings of spirometry, CT scans, and impulse oscillation analyses were analyzed to compare the characteristics of the two groups.

Asthma patients older than 65 had a median FEV₁ of 81.2%, compared to 88.8% in the younger group. The elderly group also had lower values for mid-forced expiratory flow, 50.9 vs 78.6 percentage production; and FEV₁/FVC ratio, 0.72 vs 0.78. The CT scans show increased airway wall thickening and air trapping in older vs younger patients. On impulse oscillation studies, the elderly patients had greater resistance at 5 Hz, reflecting increased total airway resistance. The older group also showed differences consistent with possible small airway disease, including a greater decrease in resistance from 5 to 20 Hz, a higher ratio of decrease in resistance from 5 to 20 Hz to resistance at 5 Hz, a high-

er integrated area between 5 Hz and frequency of resonance, greater frequency of resonance, and lower reactivity at a frequency of 5 Hz.

Differential cell counts in blood and sputum, exhaled nitric oxide levels, and methacholine airway responsiveness were similar between age groups. The elderly asthma patients had lower total serum IgE levels and were less likely to test positive for specific IgE antibodies against several allergens.

The study suggests some pathophysiologic differences in elderly patients with asthma, particularly increased involvement of small and large airways. Patients over age 65 also appear to have less atopy than younger patients. Disease duration appears to have little effect on the differences between age groups.

COMMENT: *This study shows greater large- and small-airway involvement in elderly patients with asthma. The findings may affect therapy, particularly through enhanced use of HFA inhaled steroids with small particle size.*

C.C.R.

Inoue H, Niimi A, Takeda T, et al: Pathophysiological characteristics of asthma in the elderly: a comprehensive study.

Ann Allergy Asthma Immunol. 2014;113:527-533. ♦♦

Can Mouse Exposure Decrease Allergic Rhinitis Risk in Children?

SOME previous studies have linked exposure to mouse urinary protein, Mus m 1, to mouse sensitization and asthma control/severity. This study evaluated the relationship between mouse allergen exposure and the risk of allergic rhinitis (AR) in children.

The study included a random household sample of 511 children, aged 6 to 14 years, living in San Juan, Puerto Rico. Rhinitis symptoms were assessed by a questionnaire; mouse allergen exposure was assessed using household dust samples. Children who had current rhinitis symptoms and at least one positive skin test result were considered to have AR. The authors hypothesized that mouse allergen exposure would be associated with a lower prevalence of AR.

Nearly half (48.3%) of children met the study definition of AR. On multivariate analysis higher exposure to mouse allergen was associated with a lower prevalence of AR: odds ratio 0.75 per log₁₀ increment in Mus m 1 level. The associations mainly reflected a lower risk of AR among children not sensitized to mouse.

Exposure to endotoxin and mouse allergen were significantly correlated with each other. However, the inverse association between Mus m 1 and AR was not explained by exposure to endotoxin or other markers of microbial or fungal exposure.

Puerto Rican children with higher exposure to mouse allergen show a lower prevalence of AR. The findings suggest possible induction of tolerance with early-life exposure to mouse allergen.

COMMENT: *Recent studies have reported exposure to mouse urine is associated with asthma severity. ►►*

This study investigated levels of mouse allergen and risk of rhinitis in school-aged children. Levels of house dust endotoxin or microbial exposure did not explain the decreased odds of AR in children. Further studies investigating reasons for the decreased odds of AR in a larger cohort of children are needed.

V.H.-T.

Jacobs TS, Forno E, Brehm JM, et al: Mouse allergen exposure and decreased risk of allergic rhinitis in school-aged children.

Ann Allergy Asthma Immunol. 2014;113:614-618. ♦♦

Asthmatics Who Smoke Need Evidence-Based Smoking Cessation Programs

THERE is evidence of a bidirectional association between asthma and smoking, with asthmatic patients smoking at least as much as nonasthmatics. Smoking by people with asthma may be a "distinct disease entity." An interview study was performed to assess the healthcare needs and preferences of asthma patients who smoke.

The researchers performed qualitative, semi-structured telephone interviews with 24 adult Australian asthma patients who smoked. Topics included smoking topography and initiation, perceptions of the interrelationship between asthma and smoking, motivation and readiness to quit, and proposed smoking cessation techniques.

Most interview subjects perceived that smoking was associated with worsening of their asthma, including increased symptom frequency and severity. Interest in quitting smoking was largely driven by fears of asthma exacerbations and poor self-control. Most patients reported high motivation to quit smoking, and believed that quitting "cold turkey" would be the best approach for them. They believed that healthcare professionals can provide helpful advice, but that such advice is more valuable if coupled with the individual's will power and determination to quit. The patients reported that professionals were not proactive in asking about smoking and providing an action plan for quitting.

The study lends insights into the unique needs of asthmatic smokers. Although these patients know they need to quit smoking, they may find it difficult to do so without support. The authors call for evidence-based smoking cessation programs, tailored to the needs of patients with asthma.

COMMENT: *Most asthma patients who smoke are motivated to quit because of apprehension of asthma exacerbations and loss of disease control. They need public, social, professional, and pharmaceutical intervention to accomplish and maintain smoking cessation. The authors demonstrate a clear need for an evidence-based smoking cessation program suited to the needs of smokers with asthma.*

C.C.R.

Saba M, Dan E, Bittoun R, Saini B: Asthma and smoking—healthcare needs and preferences of adults with asthma who smoke.

J Asthma. 2014;51:934-942. ♦♦

Respiratory Disorders Don't Increase Risk of Anxiety or Depression Over Time

PREVIOUS cross-sectional studies have reported increased rates of mood and anxiety disorders among adult patients with respiratory diseases. However, there are few data on the nature of these associations over time or the possible role of confounders. This 10-year follow-up study examined the incidence of depression and anxiety associated with respiratory disease.

The study included adults enrolled in nationally representative Midlife Development in the United States survey. A total of 2,101 participants were interviewed at wave 1 in 1994 and wave 2 in 2005. The incidence and persistence of depression or anxiety disorders at wave 2 associated with respiratory disorders at wave 1 were analyzed. Potential mediators of these associations were analyzed as well.

At both times, respiratory disorders were cross-sectionally associated with increased odds of depression and anxiety disorders. However, the presence of respiratory disorders at wave 1 was not associated with an increased incidence of depression and anxiety disorders at wave 2. Among participants with depression or anxiety disorders at wave 1, the presence of respiratory disorders at wave 1 was associated with a greater likelihood of persistent anxiety/depression at wave 2. The associations were not explained by demographic characteristics, secondhand smoke exposure, or history of childhood maltreatment.

The study confirms that patients with respiratory disease are more likely to have depression or anxiety disorders, as well as an increased rate of persistent anxiety/depression. However, the presence of respiratory disease at baseline isn't associated with an increased incidence of depression or anxiety disorders at 10 years' follow-up. Further studies of this issue should address additional contributing factors, such as obesity and family history of mood disorders.

COMMENT: *This longitudinal study showed that, although adult patients with respiratory disease are more likely to have depression and/or anxiety disorders, they are not at increased risk of developing anxiety or depression over time.*

C.C.R.

Goodwin RD, Scheckner B, Pena L, et al: A 10-year prospective study of respiratory disease and depression and anxiety in adulthood.

Ann Allergy Asthma Immunol. 2014;113:565-570. ♦♦

Is Atopy Patch Testing a Useful Test for EoE in Children and Adults?

PREVIOUS studies have suggested an important role of atopy in eosinophilic esophagitis (EoE). The symptoms of EoE differ between children and adults; it is unclear whether there is a similar age difference in terms of atopy. ➤➤

This retrospective study compared atopic features and allergic sensitization in 50 children and 50 adults with biopsy-confirmed EoE, diagnosed at an allergy clinic. Most patients in both groups were white males. Patient characteristics, atopic disease history, and findings of allergy tests were compared between groups.

Fifty-two percent of children with EoE had a history of asthma, compared to 24% of adults. The two age groups were similar in terms of history of allergic rhinitis, atopic dermatitis, IgE mediated food allergy, and family history of atopy. Nor was there any difference in immediate-type sensitization to foods and aeroallergens.

Children were also twice as likely to have a positive reaction to one or more foods on patch testing: 62%, compared to 31 percent of adults. Both age groups had high rates of comorbid atopic disease and sensitization to foods and environmental allergens was seen in both children and adults.

Among patients with diagnosed EoE, history of asthma and positive reactions to foods on patch testing are more common in children than adults. The study draws attention to the high rates of other atopic disorders among both children and adults with EoE.

COMMENT: *Diagnosis and treatment of patients with EoE can be challenging. Studies have shown varying results regarding the use of atopy patch tests (APTs) for diagnosis of food allergy. This study compared children and adults with EoE. More children had a history of asthma. More children had positive APT to foods than adults. In children, positive APTs were seen most commonly to vegetables, meats, milk and soy, as compared to vegetables, potato and milk in adults. Across all patients, allergic disease was common, with almost two-thirds of patients having allergic rhinitis. As the authors point out, a benefit to this study was the comparison of a group of children and adults from the same area. This study reminds us about the likelihood of other forms of atopic disease in these patients.*

V.H.-T.

Vernon N, Sapna S, Lehman E, Ghaffari G: Comparison of atopic features between children and adults with eosinophilic esophagitis.

Allergy Asthma Proc. 2014;35:409-414. ◆◆

— PRACTICE PARAMETER —

GUIDELINE UPDATE

Yellow Zone' Parameter Fills Gaps in Current Recommendations

COMMENT: *The ground-breaking "Management of Acute Loss of Asthma Control in the Yellow Zone" practice parameter is a critical review of pharmacologic interventions for management of home exacerbations of asthma. The 'Yellow Zone' (YZ) is the zone of dynamic intervention where prompt recognition and treatment of acute loss of control may help prevent adverse outcomes. Currently recommended interventions include increasing administration of inhaled short-acting β_2 agonist*

(SABA), followed by a short course of systemic corticosteroids, if needed. Unfortunately, symptom relief in the form of SABA therapy does not have the potential to reverse the loss of asthma control. Studies have shown that patients often spontaneously escalate their asthma medications—both relievers and controllers—in response to sporadic worsening of symptoms. Empowering them to manage home exacerbations by escalating anti-inflammatory therapy aligns with the keystone concepts of step-based asthma management and patient-provider partnership.

The new practice parameter document defines criteria for identifying the YZ and details the evidence behind various therapeutic strategies, based on individual patient profile, response and preference. Options may include increasing total daily inhaled corticosteroid dose by fourfold or higher or using inhaled steroids on a symptom-driven basis. Adjustable maintenance dosing strategies have been widely studied and adopted in Europe and Canada, but remain "off-label" in the United States. Further research on these and other interventions is needed. Meanwhile, it is hoped that routine use of effective YZ interventions as part of written or electronic asthma action plans will result in mitigated morbidity and enhanced quality of life for individuals with asthma. The full practice parameter is available for free download at <http://allergyparameters.org>

C.D.

Dinakar CD, Oppenheimer J, Portnoy J, et al: Management of acute loss of asthma control in the yellow zone: a practice parameter.

Ann Allergy Asthma Immunol. 2014;113:143-159. ◆◆

REVIEWS OF NOTE

COMMENT: *This position statement helps us better understand the potential harmful effects of nicotine exposure, which may be the introduction to long term cigarette smoking addiction. The review highlights the uncertain safety of e-cigarettes.*

B.E.C.

Schraufnagel DE, Blasi F, Drummond MB, et al: Electronic cigarettes: a position statement of the Forum of International Respiratory Societies.

Am J Resp Crit Care Med. 2014;190:611-618. ◆◆

COMMENT: *This systematic review of 12 articles from the literature reveals that up to 2.7% of patients develop eosinophilic esophagitis after oral immunotherapy for food allergy. This is important for allergists to discuss as a possible outcome in patients undergoing oral immunotherapy. As always, risk-benefit discussions are essential in educating our patients during the informed consent process.*

V.H.-T.

Lucendo AJ, Arias Á, Tenias JM: Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis.

Ann Allergy Asthma Immunol. 2014;113:624-629. ◆◆