

FEATURE ARTICLES

New Generation of Anti-IL-5 Asthma Biologics Nearing FDA Approval

High blood eosinophil count increases the risk of asthma exacerbations, suggesting that anti-interleukin 5 (IL-5) therapies might be beneficial. Reslizumab, an investigational anti-IL-5 monoclonal antibody, has shown short-term clinical efficacy in asthma patients with sputum eosinophilia. This paper reports two phase 3 clinical trials of reslizumab for patients with inadequately controlled asthma and high blood eosinophil counts.

The two identical studies enrolled patients with moderate to severe asthma that was uncontrolled despite medium- to high-dose inhaled corticosteroids, with at least one exacerbation in the previous year, and a blood eosinophil count of 400 cells/ μ L or higher. Patients were randomly assigned to

treatment with intravenous reslizumab, 3.0 mg/kg, or placebo, given every 4 weeks for 1 year. The main outcome of interest was annual rate of clinical asthma exacerbations. Outcomes were analyzed in masked fashion.

A total of 477 patients were assigned to reslizumab and 476 to placebo. In both studies, the exacerbation rate was significantly lower with reslizumab, compared to placebo: rate ratio 0.50 in study 1 and 0.41 in study 2. Reslizumab was also associated with improvement in FEV₁ and in asthma symptom, control, and quality of life scores.

The two groups had similar rates of adverse events, most commonly worsening asthma symptoms, upper respiratory tract infections, and nasopharyngitis. There were two cases of anaphylaxis in the reslizumab group, both of which responded to standard treatment. Eosinophil count decreased during reslizumab treatment and rose again after the end of treatment.

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Reslizumab reduces exacerbation rate in patients with inadequately controlled asthma and high blood eosinophil counts. Other measures of asthma control are improved as well, while most adverse events are similar to placebo. The authors believe that anti-IL-5 therapy with reslizumab might be a useful option before oral corticosteroid in this group of patients.

COMMENT: Will any new immunomodulators be added to our asthma armamentarium? This publication reports phase 3, large-scale, worldwide replication studies examining the utility of adding the IL-5 monoclonal antibody reslizumab in patients with elevated blood eosinophils whose asthma is not controlled on medium- to high-dose inhaled corticosteroids. Beyond demonstrating improvement in asthma quality of life measures and FEV₁, the study shows a significant reduction in asthma exacerbations. These benefits are achieved with a side effect profile similar to placebo, although two patients did develop anaphylaxis. This spring, an FDA Advisory Committee supported approval of another anti-IL-5 monoclonal antibody (mepolizumab). I am certain more is to come—meanwhile, it is tantalizing to think that we may have some new options for our patients with uncontrolled asthma.

J.J.O.

Castro M, Zangrilli H, Wechsler ME, et al: Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials.

Lancet Respir Med. 2015;3:355-366. ●

Sputum Periostin Predicts Eosinophilic Phenotype in Severe Asthma

Identifying patients with the "Th2-high" inflammatory phenotype may have implications for management of severe uncontrolled asthma. Periostin is a potentially useful biomarker of eosinophilic airway inflammation. This study evaluated periostin's utility for evaluation of severe asthma phenotypes.

The researchers analyzed induced sputum specimens from 62 patients with severe asthma seen at a specialized severe asthma unit. Phenotyping studies included various clinical, inflammatory, functional, and molecular indicators. Sputum periostin levels were compared for the different phenotype groups.

Phenotyping suggested that 80% of patients had late-onset asthma, 50% had fixed airway obstruction, and 66% had a Th2-high phenotype. The inflammatory phenotype was eosinophilic in 71% of patients and mixed granulocytic in 25%; the rest had a neutrophilic or paucigranulocytic phenotype.

The periostin level in sputum supernatant was 69.76 pg/mL in patients with fixed airflow limitation versus 43.84 pg/mL in those with variable airflow limitation. Periostin level was also higher for those with the eosinophilic versus mixed granulocytic phenotype: 61.58 versus 43.84 pg/mL, respectively.

Periostin level was inversely correlated with postbronchodilator FEV₁/FVC. There was no difference in periostin for obese versus nonobese, Th2-high versus Th2-low, and early- versus late-onset patients.

In severely asthmatic patients with persistent sputum eosinophilia, sputum periostin levels are associated with persistent airflow ● ● ●

limitation. The results support the potential value of periostin in phenotyping severe asthma.

COMMENT: As we explore more scientific approaches in the care of our asthmatic patients, it is hoped that an approach linking clinical features with molecular mechanisms will aid in better stratifying asthma phenotypes, with the ultimate goal of improving therapeutic choice. At present, our greatest hope revolves around the use of biomarkers to achieve this goal. One such marker is periostin—a structural homologue to the adhesion molecule fasciclin I. Elevated periostin has demonstrated association with a Th2 inflammatory response, including airway eosinophilia. Via the use of this measure, Corren et al (N Engl J Med. 2011;365:1088-1098) were able to better determine which asthmatic patients would respond to the anti-IL-13 monoclonal antibody lebrikizumab.

Bobolea and colleagues further our understanding by examining severe asthmatics with elevated periostin levels. Such patients are not only more likely to have an eosinophilic phenotype, but also to have fixed obstructive patterns, with a reduction in postbronchodilator FEV₁/FVC. Stay tuned, as much more is likely to come regarding better ratification asthmatic patients via this and other markers.

J.J.O.

Bobolea I, Barranco P, Del Pozo V, et al: Sputum periostin in patients with different severe asthma phenotypes.

Allergy. 2015;70:540-546. ●

Gateway to a New Era? GATA3 Blockade in Allergic Asthma

About half of asthma patients have a Th2 molecular endotype with eosinophil-dominated inflammation. Treatments directed at the zinc finger transcription factor GATA3—the "master transcription factor" of the Th2 pathway—might be useful. This study evaluated the GATA3-specific DNA enzyme SB010 in patients with allergic asthma.

The phase 2a randomized trial included 40 patients with allergic asthma and sputum eosinophilia, all with biphasic early and late asthmatic responses to allergen. Patients received 28 days of once-daily inhaled treatment with SB010, 10 mg, or placebo. The main outcome of interest was late asthmatic response to repeat allergen challenge, assessed as change in area under the curve, for FEV₁.

In posttreatment challenges, the mean late asthmatic response was reduced by 34% from baseline for patients receiving SB010, compared to a 1% increase in the placebo group. Treatment with SB010 was also associated with an 11% reduction in the early asthmatic response and a 22% improvement in the maximum decline in FEV₁.

The SB010 group had significant reductions in allergen-induced eosinophilia, sputum tryptase levels, and plasma interleukin-5 levels. There was no significant difference in exhaled nitric oxide after allergen challenge or in airway hyperresponsiveness to methacholine.

The study provides proof of concept that SB010 can reduce early- and late-phase responses to allergen in asthma patients with sputum eosinophilia. The clinical responses are associated with attenuation of Th2 inflammatory responses. Further study is needed to evaluate the clinical benefits of GATA3-directed treatment for asthma with a predominant Th2 phenotype.

COMMENT: Many of the biologic therapies we have been reading about recently relate to blockade of the individual Th2 cytokine culprits that cause inflammation in asthma, either by binding to the cytokines or targeting their cell surface receptors. Krug et al take a wider strike at preventing production of all Th2 cytokines by blocking GATA3, using the "DNAzyme" SB010, which binds to and cleaves GATA3 messenger RNA. In a proof-of-concept, phase 2a trial, they show that once-daily administration of SB010 in patients with mild allergic asthma with sputum eosinophilia mitigates both the early- and late-phase bronchoconstriction response after allergen bronchoprovocation. They also report a modest impact on eosinophils and markers of mast cell activation, but no effects on other parameters such as biomarkers and bronchial hyperreactivity. Although it is rare and encouraging to have a medication that blocks both the early- and late-phase response, the clinical effects appear to be less than with current available non-biologic asthma therapies. Further studies will help better delineate the role of new Th2 cytokine-targeted therapies in the care of patients with uncontrolled asthma.

C.D.

Krug N, Hohlfield JM, Kirsten A-M, et al: Allergen-induced asthmatic responses modified by a GATA3-specific DNAzyme.

N Engl J Med. 2015;372:1987-1995. ●

Which Biomarkers Predict Corticosteroid Response in Asthma?

Variable responses to inhaled corticosteroids (ICS) in asthma are associated with differences in underlying airway inflammation. Biomarkers of airway inflammation and steroid responsiveness might have important implications for treatment. This study evaluated three inflammatory biomarkers as predictors of response to ICS in asthma.

The researchers performed a secondary analysis of data from a previous study of 40 patients with stable persistent asthma. After an initial steroid-naïve phase, patients received open-label treatment with inhaled fluticasone, 500 µg twice daily. Three inflammatory biomarkers—exhaled nitric oxide, sputum eosinophil count, and urinary bromotyrosine (BrTyr)—were evaluated as predictors of clinical response to ICS.

Levels of all three biomarkers were higher in asthma patients compared to controls, before and after fluticasone. After 28 days on ICS, exhaled NO was decreased in 82% of patients, sputum eosinophil count in 60%, and urinary BrTyr in 58%. Levels of all three biomarkers during the ●●●

steroid-naïve phase were predictors of ICS responsiveness.

The strongest predictor of response to ICS was the combination of high exhaled NO and high urinary BrTyr: odds ratio 13.3 for two and 7.2 for three clinical outcomes. Decreases in biomarkers during ICS therapy did not predict responsiveness.

Inflammatory biomarkers measured before steroid treatment can predict ICS responsiveness in patients with asthma. In this study of three biomarkers, the combination of exhaled NO and urinary BrTyr shows the highest predictive value.

COMMENT: Which asthmatic patients are more likely to respond to ICS? The authors analyzed data on 46 steroid-dependent asthma patients from a previous study, using three biomarkers to predict responsiveness to treatment with ICS. The odds of response to ICS increased with elevations of all biomarkers—but when exhaled NO and urinary BrTyr were combined, the likelihood of response to ICS doubled. Biomarkers of Th2, eosinophilic-driven asthma may be helpful in predicting which patients will respond to our therapeutic recommendations.

S.M.F.

Cowan DC, Taylor DR, Peterson LE, et al: Biomarker-based asthma phenotypes of corticosteroid response.

J Allergy Clin Immunol. 2015;135:877-883. ●

Lipid Levels and Lipoprotein Particles Affect FEV₁ in Asthma

Apolipoproteins play a key role in normal lung development, as well as in adaptive immune responses and host defense. Previous studies comparing apolipoprotein and lipid levels in patients with and without asthma have yielded conflicting results. This study assessed the relationship of serum lipids, apolipoproteins, and lipoprotein particles with severity of airflow obstruction in asthma.

The study used serum samples from 159 patients with atopic asthma, as well as 74 atopic and 80 nonatopic, nonasthmatic controls. Standard measures of serum lipid and lipoprotein levels were analyzed for association with FEV₁ predicted. Nuclear magnetic resonance spectroscopy was performed to assess the size and concentration of specific lipoprotein particle subgroups.

In the atopic asthma patients, but not in nonasthmatic controls, serum lipid levels were significantly correlated with airway obstruction. High-density lipoprotein (HDL) cholesterol and apolipoprotein A-I (apoA-I) were positively correlated with FEV₁, while negative correlations were found for serum triglycerides, low-density lipoprotein (LDL) cholesterol, apolipoprotein B (apoB), and apoB/apoA-I ratio.

On NMR spectroscopy, HDL particle size was positively correlated with FEV₁ in the atopic asthma patients. Positive correlations were also noted for the concentration of large HDL particles and for total intermediate-density lipoprotein (IDL) particles. Low-density lipoprotein particle size and concentrations of LDL and very-low-density lipoprotein particles were

also negatively correlated with FEV₁ among the subjects with atopy and asthma.

Serum lipids and specific lipoprotein particles are related to FEV₁ in patients with atopic asthma. The findings suggest possible protective effects of apoA-I and HDL-C, whereas triglycerides, LDL-C, and apoB may be associated with greater airflow obstruction. The authors call for confirmatory studies in larger patient samples.

COMMENT: These data shed light on the correlation and possible protective effects of nonatherogenic lipids in the preservation of FEV₁ in patients with asthma. The findings may raise interesting considerations regarding systemic disorders that affect asthma, such as obesity, and further stimulate research to increase levels of less-atherogenic lipids in patients with asthma. See the accompanying editorial by Fessler: Am J Respir Crit Care Med. 2015;191:969-970.

B.E.C.

Barochia AV, Kaler M, Cuento RA, et al: Serum apolipoprotein A-I and large high-density lipoprotein particles are positively correlated with FEV₁ in atopic asthma.

Am J Respir Crit Care Med. 2015;191:990-1000. ●

In Obese Kids, Asthma Symptoms Are Different

Obesity is associated with an increased risk of asthma in children. The relationship between body weight and asthma phenotype remains unclear, as do the reasons why overweight/obese children have worse asthma control. This study compared the pattern and severity of asthma symptoms for overweight/obese versus lean children.

The cross-sectional study included 10- to 17-year-old children with persistent, early-onset asthma. Of these, 35 were overweight/obese, body mass index (BMI) 85% or higher; and 21 were normal-weight, BMI 20% to 65%. The results of a detailed history, quantitative and qualitative symptom assessment, and lung function testing were compared between groups.

Lung function results were similar between overweight/obese and normal-weight children. The overweight/obese group had lower exhaled nitric oxide levels and reduced methacholine responsiveness, but more frequent use of rescue therapies: 3.7 versus 1.1 per week.

For overweight/obese children, the main symptom associated with loss of asthma control was more likely to be shortness of breath, odds ratio (OR) 11.8; and less likely to be cough, OR 0.26. Overweight/obese children had higher gastroesophageal reflux scores, which may have mediated the differences in asthma symptoms.

The finding suggest worse asthma control and a qualitatively different pattern of symptoms in overweight/obese children with asthma. Gastroesophageal reflux symptoms may be a key mediator of the difference in shortness of breath and use of β -agonist use. The authors discuss the implications for management of dyspnea and body ● ● ●

weight in overweight/obese children with asthma.

COMMENT: The association of obesity and asthma has been well established but the underlying mechanism is still not clear. These researchers found that obese children with persistent asthma had more symptoms, compared to lean controls. Interestingly, the obese group had increased symptom reporting and increased use of rescue medications, despite minimal differences in spirometric findings. This suggests that obese children with persistent asthma may have a heightened perception of dyspnea, contributing to their increased symptom reporting.

S.M.F.

Lang JE, Hossain MJ, Lima JJ: Overweight children report qualitatively distinct asthma symptoms: analysis of validated symptom measures.

J Allergy Clin Immunol. 2015;135:886-893. ●

Weight Loss Helps Obese Adults with 'Real' Asthma

Despite the well-established link between obesity and asthma, it's still unclear whether weight loss can improve asthma control. Studies of this issue are limited by a lack of confirmatory tests for asthma-obese patients are commonly misdiagnosed with asthma. This study assessed the effects of weight loss on airway hyperresponsiveness (AHR) in patients with appropriately diagnosed asthma.

The prospective study included 22 obese adults, mean body mass index 45.7, with asthma confirmed by the presence of AHR, defined as a methacholine PC₂₀ of less than 16 mg/mL. Another 22 potentially eligible patients were tested but did not have AHR.

Sixteen obese patients with confirmed asthma went through a 3-month behavioral weight reduction program using liquid meal replacement supplements. The intervention was associated with mean weight loss of 16.5 kg, compared to a 0.6 kg weight gain in 6 control patients. Methacholine PC₂₀ improved from 5.02 to 10.2 mg/mL in the weight loss group, compared to an increase from 6.6 to 7.7 mg/mL in controls. Weight loss was also associated with a 5% improvement in FEV₁ and FVC, along with improvements in asthma control and quality of life. One patient in the weight loss group was able to stop taking asthma medications.

In this study of very obese patients with confirmed asthma, an effective behavioral weight management intervention leads to improvement in AHR and other asthma outcomes. One-half of obese patients reporting physician-reported asthma have negative results on methacholine challenge testing. Within its limitations, the study supports the need for healthy weight-loss interventions in obese adult asthma patients.

COMMENT: Many studies have explored the relationship between obesity and asthma. This relatively small study focused on AHR and the impact of weight loss on asthma. Like other studies, the results showed that 50% of obese patients diagnosed with asthma had normal AHR! A group of super obese patients with confirmed asthma underwent a 3-

month diet and exercise program. This group had significant improvements in AHR, asthma symptoms, lung function, and quality of life. In contrast, the control group had no improvements and actually gained some weight. The two key messages are: (1) AHR may help determine if dyspnea is from obesity or asthma and (2) weight loss strategies will likely help both issues!

D.A.K.

Pakhale S, Baron J, Dent R, et al: Effects of weight loss on airway responsiveness in obese adults with asthma: does weight loss lead to reversibility of asthma?

Chest. 2015;147:1582-1590. ●

Peanut SLIT and OIT-Latest Clinical Trials

A previous randomized trial of sublingual immunotherapy (SLIT) for peanut allergy found good safety outcomes, with modest clinical and immunologic improvements at 1 year. This report presented 3-year follow-up outcomes of peanut SLIT.

The study included 40 patients, aged 12 to 40 years, receiving daily peanut SLIT. At 2 and 3 years, patients underwent a 10 g peanut powder oral food challenge. Treatment was discontinued at 3 years; 8 weeks later, the peanut powder challenge was repeated and response to open feeding of peanut butter was assessed.

Of more than 18,000 peanut SLIT doses, about 98% caused no more than oropharyngeal reactions—none of the patients developed severe symptoms or required epinephrine. More than half of enrolled patients discontinued SLIT. At re-evaluation after the end of SLIT, 4 patients were fully desensitized to 10 g of oral peanut powder. All 4 patients had sustained unresponsiveness. Patients with responses at 2 years had decreased peanut-specific activation and skin prick test responses.

This follow-up study confirms a modest desensitizing effect of SLIT in patients with peanut allergy. Long-term safety outcomes are good, and responders show favorable immunologic outcomes over 3 years.

Studies have reported encouraging results with both SLIT and oral immunotherapy (OIT) for peanut allergy, but there have been few direct comparisons of these approaches. A placebo-controlled trial of SLIT versus OIT for peanut-allergic children is reported.

Twenty-one children with peanut allergy were randomly assigned to active SLIT/placebo OIT or active OIT/placebo SLIT. Final doses were 3.7 mg/d for SLIT and 2,000 mg/d for OIT. Double-blind challenges were performed after 6 and 12 months of maintenance therapy, after which patients were eligible for another 6 months of treatment. Those who did not respond to challenge at 12 or 18 months were taken off treatment for 4 weeks, then re-challenged.

Of 16 children who completed the study, all had more than a tenfold increase in challenge threshold at 12 ● ● ●

months. The increase in median challenge dose was 141-fold in the active OIT group, compared to 22-fold in the active SLIT group. Both treatments were associated with changes in skin test results and peanut-specific IgE and IgG₄ levels, with OIT producing larger changes. Adverse events were generally mild in both groups, but more frequent with OIT. At the end of the study, 4 children had sustained unresponsiveness to peanut.

For children with peanut allergy, OIT is more effective than SLIT. Oral immunotherapy is also associated with greater adverse reactions and a higher withdrawal rate. Only a few patients have sustained unresponsiveness 4 weeks after the end of treatment.

COMMENT: The quest for an efficacious treatment for peanut allergy continues, but it is always helpful to have long-term follow-up data from previous trials. This first study reports follow-up data from the CoFAR group, who initially reported that 70% of peanut-allergic children receiving SLIT for 1 year could tolerate small amounts of peanut protein. This extension confirms that SLIT is safe and induces a modest level of desensitization—although less than 15% of patients achieved sustained unresponsiveness. The authors suggest that peanut sIgG₄ might be a useful marker for successful desensitization, but it did not achieve statistical significance. The 4 children who did achieve sustained unresponsiveness also had changes in skin tests and basophil activation. A high dropout rate is attributed to difficulty of adhering to daily SLIT therapy.

The next study, from Johns Hopkins, was smaller but compared SLIT to OIT for peanut allergy. The results show a more robust immunologic and protective response with OIT. The authors suggest that it might be better to use OIT following SLIT, since there could be a reduction in the frequent local side effects from OIT. The quest for an effective treatment for our patients with food allergies continues on an optimistic course.

S.M.F.

Burks AW, Wood RA, Jones SM, et al: Sublingual immunotherapy (SLIT) for peanut allergy: long-term follow-up of a randomized multi-center trial.

J Allergy Clin Immunol 2015;135:1240-1248

Narisety SD, Frischmeyer-Guerrero PA, Keet CA, et al: A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy (OIT) for the treatment of peanut allergy.

J Allergy Clin Immunol 2015;135:1275-1282. ●

Outgrowing Peanut Allergy: Follow-up and Predictive Cutoffs

There are few prospective data on the natural history of childhood peanut allergy. A group of children diagnosed with peanut allergy at age 1 underwent follow-up evaluations at age 4.

The study included 156 children who were 1 year old when diagnosed with challenge-confirmed peanut allergy as part of a longitudinal study. One hundred four children were

followed up at age 4, including food challenges, skin prick testing (SPT) and specific IgE measurement. All sensitized children were tested at age 1 and 4, regardless of risk profile. The researchers sought to develop SPT and specific IgE cutoff points with high predictive value for persistent or resolved peanut allergy.

Twenty-two percent of children were no longer allergic to peanut at age 4. Peanut tolerance was predicted by decreasing wheal size, and persistent allergy by increasing wheal size. At age 1, an SPT response of 13 mm or greater and a specific IgE level of 5.0 kU/L or greater had a 95% positive predictive value (PPV) for persistent peanut allergy. At age 4, the 95% PPV values were 8 mm or greater for PPV and 2.1 IU/L for specific IgE. Nonsignificant factors included sensitization to Ara h 2, tree nut, and house dust mite; other food allergies; and presence of eczema or asthma.

These population-based data suggest that about 20% of 1-year-olds with confirmed peanut allergy are no longer allergic at age 4. The PPV values presented in this study are unique in that all children in the study underwent food challenges at diagnosis and follow-up, regardless of their SPT results and specific IgE levels.

COMMENT: How many times do we hear parents of children with newly diagnosed peanut allergy ask, "Will my child outgrow their allergy?" The HealthNuts study in Australia provided a unique opportunity to evaluate 4-year-olds who presented with peanut allergy, confirmed by oral challenge, at 1 year. Similar to previous reports, these researchers found that 22% of the children had developed tolerance at 4 years old. When the skin test wheal was 13 mm or greater or specific IgE to peanut was 5 kU/L or greater at 1 year, there was a 95% likelihood that peanut allergy would persist at age 4. Interestingly, the presence of eczema, asthma, co-existing food allergy, or even dust mite allergy did not predict persistent peanut allergy. The authors suggest that these data points may be helpful in monitoring children with peanut allergy and deciding when oral challenge would be safe.

S.M.F.

Peters RL, Allen KJ, Dharmage SC, et al: Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment.

J Allergy Clin Immunol 2015;135:1257-1266. ●

Chemically Modified Peanut Extracts Show Reduced Allergenicity

Subcutaneous peanut immunotherapy has an unacceptably high rate of serious adverse events. A new chemically modified, hypoallergenic preparation of Ara h 2 and Ara h 6 has demonstrated low IgE binding with preserved immunogenicity. The authors used an in vitro assay to test the allergenicity of chemically modified peanut proteins.

The chemically modified extracts consisted of reduced and alkylated (RA) native Ara h 2/6, with or without additional glutaraldehyde treatment (RAGA), and RA crude peanut extract (CPE). A mediator-release assay based ● ● ●

on the rat basophilic leukemia (RBL) cell line transfected with human Fcε receptor was used to test sera from 26 patients with peanut allergy. The median peanut-specific IgE level was 233 kU/L. Release of β-N-acetylhexosaminidase release (NHR) was used as a marker of RBL degranulation (as a percentage of total degranulation caused by Triton X).

In the mediator release assay, 19 of 26 patients were responders, with at least 10% NHR. Compared to native Ara h 2/6, responders showed significant reductions in NHR with both RA and RAGA extracts. The chemically modified proteins were associated with a later onset of activation by 10- to 100-fold in concentration, as well as a lower maximum release level. Modified RA-Ara h 2/6 and RAGA-Ara h 2/6 resulted in lower maximum mediator release than native Ara h 2/6, at protein concentrations of 0.1, 1, and 10 ng/mL.

The RA-CPE modified protein resulted in lower maximum NHR than native CPE, at concentrations of 1 and 10 ng/mL. Responders had high rAra h 2 IgE levels and a higher NHR in response to native Ara h 2/6 versus CPE, suggesting that Ara h 2/6 were the most important allergens in these patients.

Chemically modified Ara h 2 and Ara h 6 are associated with sharply reduced mediator release in an in vitro assay using sera from peanut-allergic children. The modified extracts show decreased allergenicity, which encourages their further development as potentially safe alternatives for use in peanut immunotherapy.

COMMENT: With increasing numbers of patients with peanut allergy and increased interest in treatment options, this study investigated the use of chemical modification of purified native Ara h 2 and Ara h 6. The results showed a 100-fold decrease in mediator release by patient sera. The modified proteins had lower maximum mediator release as well as later onset activation. Some nonresponder sera, with high specific IgE to peanut and rAra h 2, did induce low mediator release. The authors comment that this may be due to lower IgE antibody affinity or a dilution effect, since high total IgE antibodies were present. This appears to be a promising alternative for safe peanut immunotherapy, although careful patient selection should be considered.

V.H.-T.

Bencharitiwong R, van der Kleij HP, Koppelman SJ, et al: Effect of chemical modifications on allergenic potency of peanut proteins.

Allergy Asthma Proc. 2015;36:185-191. ●

Do VIT Patients Really Need to Stop Beta-Blockers and ACE Inhibitors?

There is ongoing debate over possible risks of using cardiovascular medications during Hymenoptera venom immunotherapy (VIT). This study evaluated the effects of two widely used medication classes—beta-blockers and angiotensin-converting enzyme (ACE) inhibitors—on the safety and outcomes of VIT.

The researchers analyzed follow-up questionnaires from

225 patients receiving VIT. When the questionnaires were completed, at a median VIT duration of 46 months, 55.6% of patients were taking some type of cardiovascular medication. Data on the course of VIT were collected, representing 3,397 months of maintenance therapy while taking an ACE inhibitor and 1,418 months while taking a beta-blocker.

Cumulative rates of VIT-related reactions were 9.1% per cycle and 0.31% per injection when subjective symptoms were included, and 1.7% per cycle and 0.06% per injection for objective reactions only. Adverse events were more frequent among patients who experienced systemic reactions during VIT buildup.

However, reactions were actually less frequent in patients taking any type of cardiovascular medication, or in those taking an ACE inhibitor. Repeat Hymenoptera stings occurred in 42.7% of patients and sting-induced objective reactions in 7.3%. Neither of these outcomes was increased for patients taking cardiovascular medications.

The retrospective study finds no evidence that continued use of cardiovascular medications—including beta-blockers and ACE inhibitors—lowers the safety or effectiveness of Hymenoptera VIT. The patient's individual risk should be carefully considered before changing established ACE inhibitor or beta-blocker therapy in patients receiving VIT.

COMMENT: Use of beta-blockers and ACE inhibitors during VIT has been a concern. This retrospective study investigated patients with cardiovascular disease receiving Hymenoptera VIT. Patients with systemic effects during the build-up phase were at increased risk for anaphylaxis during maintenance. Interestingly, anaphylactic reactions were significantly lower in patients treated with any cardiovascular medication or during VIT treatment with ACE inhibitor. Beta-blockers were substituted before VIT was started; however, increased numbers of patients were treated with beta-blockers during the maintenance phase. The authors conclude that there is limited evidence that beta-blockers or ACE inhibitors interfere with VIT. Further studies are essential to further elucidate the safety of concurrent beta-blocker and ACE inhibitor use during VIT.

V.H.-T.

Stoevesandt J, Hosp C, Kerstan A, Trautmann A, et al: Hymenoptera venom immunotherapy while maintaining cardiovascular medication: safe and effective. *Ann Allergy Asthma Immunol.* 2015;114:411-416. ●

Four-Injection Cat Peptide Immunotherapy: Still Working at 2 Years?

A previous study reported improvement in cat allergy symptoms after a short course of treatment (four injections) with Cat-PAD. This product is the first in a new class of synthetic peptide immuno-regulatory epitopes (SPIREs), comprising seven synthetic peptide T-cell epitopes with sequences derived from Fel d 1. The current report presents the results of allergy challenge 2 years after Cat-PAD treatment.

The study included 51 patients who received Cat-PAD—eight doses of 3 nmol or four doses of 6 nmol, given ●●●

intradermally over 3 months-or placebo. At 2 years' follow-up, patients underwent standardized cat allergen challenge in an environmental exposure chamber. Rhinoconjunctivitis symptoms and other outcomes were compared with those of baseline and end-of-treatment measurements.

Patients receiving the four-dose Cat-PAD treatment had a nonsignificant 3.85-point reduction in total rhinoconjunctivitis symptom score, compared to the placebo group. However, there was a significant difference in this outcome at the end of day 4, when cumulative allergen challenge was greatest-a prespecified secondary outcome. The four-dose treatment group also had consistent reductions in nasal symptoms between 2 and 3 hours on all four challenge days. The eight-dose Cat-PAD regimen showed no evidence of benefit.

These results suggest a lasting and clinically significant reduction in rhinoconjunctivitis symptoms in cat-allergic patients 2 years after a four-dose course of Cat-PAD treatment. The study provides initial evidence of long-term benefit of SPIREs as a new approach to allergen immunotherapy.

COMMENT: Immunotherapy using four intradermal injections of a group of seven synthetic peptide T-cell epitopes derived from Fel d 1 was shown to be clinically effective 1 year later using a controlled cat challenge model. This study provides follow-up data on 51 subjects who underwent a similar environmental exposure cat allergen challenge 2 years after treatment. Eleven patients received higher-dose and 17 received lower-dose peptide immunotherapy, while 22 received placebo. Although the study did not meet its primary endpoint (reduction of total rhinoconjunctivitis symptom score), other secondary endpoints were met. Given the small number of subjects, the study seems underpowered to reach meaningful conclusions. However, the limited data presented are somewhat promising for long-term immunomodulatory effects from just four injections.

D.A.K.

Coroux P, Patel D, Armstrong K, et al: Fel d 1-derived synthetic peptide immunoregulatory epitopes show a long-term treatment effect in cat allergic subjects. *Clin Exp Allergy*. 2015;45:974-981. ●

New Test for Basophil Suppression after Immunotherapy

Basophil histamine release is a potentially useful indicator of the response to allergen immunotherapy, but current assays to measure histamine release are challenging. This study assessed intracellular fluorochrome-labeled diamine oxidase (DAO) as an alternative biomarker of response to immunotherapy.

The study included 14 patients receiving grass pollen subcutaneous immunotherapy (SCIT), 12 receiving sublingual immunotherapy (SLIT), and 6 who had completed 3 years of grass pollen SLIT. Twenty-four patients with untreated seasonal allergic rhinitis and 12 nonatopic controls were studied as well. All groups underwent measurement of intercellular

fluorochrome-labeled DAO in whole-blood basophils. The results were compared with surface markers as an indicator of basophil activation. Clinical responses to immunotherapy and other immunologic markers were assessed as well.

The three groups of immunotherapy-treated patients had higher proportions of DAO-positive, chemoattractant receptor-homologue molecule expressed on Th2 lymphocytes (CRTh2)-positive basophils than those with untreated allergic rhinitis. There were also significant reductions in CRTh2-positive basophils expressing the cell surface markers CD203c^{bright}, CD63, and CD107a. These differences were associated with reduced rhinitis symptoms. The immunotherapy groups also showed increased serum inhibitory activity for IgE-allergen complex binding to B cells and basophil histamine release.

Expression of intracellularly labeled DAO by basophils may be a promising new approach to assessing tolerance and efficacy of allergen immunotherapy. The results show similar levels of basophil suppression in patients receiving grass pollen SLIT or SCIT, suggesting long-term immune tolerance 1 or 2 years after stopping SLIT.

COMMENT: Basophil histamine release is a good marker for response to allergen immunotherapy, but its measurement has been quite cumbersome. This study reports the use of DAO levels detected using flow cytometry on whole blood as a tool to measure basophil responsiveness with immunotherapy. The results show impressive reduction in basophil responsiveness and symptoms after both SLIT and SCIT. After further study and improved availability, we might consider using DAO in the future to monitor our patients on allergen immunotherapy.

S.M.F.

Shamji MH, Layhadi JA, Scadding GW, et al: Basophil expression of diamine oxidase: a novel biomarker of allergen immunotherapy response.

J Allergy Clin Immunol. 2015;135:913-921. ●

Steroid Bursts: Are Adverse Effects Overblown?

Short-term oral corticosteroid therapy is commonly prescribed for patients with acute asthma exacerbations. Patients often express concern over side effects-especially weight gain and increased appetite-but a recent report questioned whether oral corticosteroids actually cause these adverse effects. A placebo-controlled trial was performed to assess side effects of short-term oral steroid therapy for asthma.

The study included 55 adults with stable asthma. In random order, they received 10 days of double-blind treatment with oral prednisolone, 50 mg, and placebo. Side effects were compared between treatment periods, including body weight, changes in the appetite control hormone leptin, dietary intake, and appetite.

Adherence to prednisolone treatment was con- ● ● ●

firmed by reductions in blood eosinophils. Serum leptin levels were not significantly different with prednisolone versus placebo. There was also no difference in patient-rated appetite, dietary intake, or body weight. Measures of body composition showed no change in body fat. Women had a significant increase in waist circumference during steroid treatment.

However, some other types of adverse effects were more common during prednisolone treatment. The most frequent was sleep disturbance, reported by three-fourths of patients during the steroid period. Nearly half of patients reported reflux symptoms on prednisolone. Mood changes were similar between treatments.

The results show no increase in appetite, dietary intake, body weight, or body composition during a short course of prednisolone in asthma patients. Informing patients that such side effects are unlikely may help increase adherence to short-term oral steroids for asthma.

COMMENT: Steroid bursts are commonly prescribed for different allergic diseases. Patients are often reluctant to take them due to adverse effects such as weight gain and increased appetite. This double-blind, placebo-controlled crossover study of 55 adults with asthma assessed objective and subjective outcomes after treatment with prednisolone, 25 mg twice a day, or placebo for 10 days. Interestingly, no changes in weight, body fat, appetite, dietary intake or leptin levels were observed after prednisolone. However, sleep disturbances, often moderate to severe, were reported by 75% of patients taking the steroid. Mild reflux was also common. This study has clear implications for educating patients about what to expect (or not) with a steroid burst.

D.A.K.

Berthon BS, Gibson PG, McElduff LK, et al: Effects of short-term oral corticosteroid intake on dietary intake, body weight and body composition in adults with asthma - a randomized controlled trial.

Clin Exp Allergy. 2015; 45:908-919. ●

Atopy Affects Exhaled NO Levels in African American Children

Exhaled nitric oxide is a potentially useful marker of airway inflammation, but its appropriate use in clinical management of asthma is still unclear. A better understanding of airway pathophysiology and genetics is needed to address health disparities in minority populations with asthma. This study analyzed demographic, environmental, and physiologic factors affecting exhaled NO in African American children, with or without asthma.

The study included 128 African American children and adolescents, 44% with asthma, in Ypsilanti, Mich. All underwent exhaled NO measurement, skin prick testing, spirometry, and questionnaire assessments. Variables associated with exhaled NO levels were analyzed.

Mean exhaled NO was 24.4 ppb overall, 30.9 ppb in children with asthma, and 19.3 ppb in those without asthma.

On logistic regression analysis of all children, higher exhaled NO was significantly associated with atopy, reduced spirometric values, and current asthma. Among the asthmatic children, elevated NO was associated with inhaled corticosteroid use, recent respiratory infection, and atopy on univariate analysis.

However, on regression analysis, atopy was the only significant factor. Children with more positive skin prick tests had higher exhaled NO levels, with or without asthma.

Atopy has a major effect on exhaled NO levels in African American children, whether or not they have asthma. To maximize the benefits of exhaled NO measurement in this patient population, guidelines that incorporate information on atopic status are needed.

COMMENT: Eosinophilic asthma is highly responsive to corticosteroids, as is nitric oxide. Exhaled NO is influenced by age, sex, race, genetics, and atopy. This study corroborates that in African Americans—who have a 2- to 4-fold greater incidence of asthma compared to other populations—exhaled NO is elevated in the presence of atopy, with and without asthma. The practicing allergist should be cognizant that exhaled NO elevation may indicate atopy but not necessarily asthma exacerbation or poor adherence with or response to steroid therapy—particularly in African American patients.

C.C.R.

Baptist AP, Li L, Dichiaro CA: The importance of atopy on exhaled nitric oxide levels in African American children.

Ann Allergy Asthma Immunol. 2015;114:399-403. ●

Shared Patient Portal Can Improve Asthma Outcomes

Shared decision making is seen as an important approach to improving management of chronic health conditions in children. Patient portals linked to electronic health records (EHRs) may facilitate shared decision making between families and pediatricians. This randomized trial evaluated an EHR-linked shared decision-making portal for families of children with asthma.

Sixty families of children with persistent asthma, mean age 8.3 years, were randomly assigned to the "MyAsthma" shared decision-making portal, or to usual care. The MyAsthma portal monitored the family's asthma treatment concerns and goals, the child's asthma symptoms, and medication side effects and adherence, while providing decision support for clinicians as well as parents. Study outcomes included the portal's feasibility and acceptability and impact on the children's clinical outcomes.

In the intervention group, 57% of parents used MyAsthma during at least 5 of the 6 study months. Three-fourths of parents of children with moderate to severe asthma were "frequent users" (five or more times), compared to about half of whose children had mild persistent asthma. The portal detected 17 instances of poorly controlled or uncontrolled asthma in 13 children. ● ● ●

Ninety-two percent of parents were satisfied with MyAsthma. They felt it improved communication with the pediatrician's office, improved their ability to manage asthma, and increased awareness of ongoing attention to asthma treatment. The MyAsthma group reported lower rates of asthma flares and fewer missed work days due to asthma.

The MyAsthma portal is well-accepted by parents of children with asthma, and may be associated with meaningful improvements in clinical outcomes. Shared decision-making portals linked to EHRs have the potential to improve patient care and outcomes in pediatric asthma.

COMMENT: There is increasing interest in involving patients and families in shared decision making in the care of chronic diseases such as asthma. A 6-month, randomized placebo-controlled trial of 60 families using MyAsthma—an EHR-linked patient portal supporting shared decision-making for pediatric asthma—was conducted at three primary care practices. Parents reported a 92% satisfaction rate. They felt that their communication with the office, ability to manage asthma, and ongoing attention to treatment improved. There was a lower frequency of asthma flares and parents missed fewer days of work due to asthma. Not surprisingly, parents of children with moderate to severe persistent asthma used the portal more than others. Providers need to start getting familiar and comfortable with the use of secure technology to facilitate patient care.

C.D.

Fiks AG, Mayne SL, Karavite DJ, et al: Parent-reported outcomes of a shared decision-making portal in asthma: a practice-based RCT.

Pediatrics. 2015;135:e965-973. ●

Cognitive Function and Health Literacy Affect Adherence in Older Asthma Patients

Lower levels of health literacy have been linked to worse asthma self-care and asthma outcomes. This study looked at how cognitive skills influence the association between health literacy and asthma medication use and adherence in older adults.

The study included 425 patients, aged 60 years or older (mean 68 years), participating in the prospective "Asthma Beliefs and Literacy in the Elderly" (ABLE) study. Behaviors related to asthma medication use were assessed, including adherence and proper techniques of metered-dose inhaler (MDI) and dry powder inhaler (DPI) use. Participants also underwent assessment of health literacy and cognitive function. Cognitive assessment included fluid ability (ie, working memory, processing speed, and executive function) and crystallized (ie, verbal) ability.

Most participants were Hispanic or black, and half had a high school education or less. About 79% used an asthma controller medication. Health literacy was rated limited in 36% of subjects, and 27% had cognitive impairment based on the Mini-Mental State Examination.

Health literacy was correlated with all cognitive measures,

but more strongly with fluid versus crystallized abilities. Limited health literacy was associated with lower adherence to asthma controller medication, 23% versus 46%; and lower rates of proper DPI technique, 29% versus 43%, and MDI technique, 36% versus 66%. Fluid abilities independently predicted all three outcomes: odds ratio 1.63, 1.94, and 1.52, respectively.

Cognitive function explains much of the association between health literacy and asthma medication self-management in older adults. The findings are consistent with age-related declines in fluid abilities, whereas verbal ability is relatively preserved. The authors discuss strategies to account for variations in cognitive ability when educating older patients with asthma.

COMMENT: Low adherence and improper use of inhalers are common in asthma patients, and even more so in older patients. This study investigated the role cognitive skills may play in health literacy and adherence. Lower health literacy was observed in 36% of older patients, and this group had lower adherence and lower rates of proper DPI and MDI technique. All of these were significantly reduced compared to patients with adequate health literacy. Health literacy correlated with all cognitive measures—particularly "fluid abilities" requiring active information processing. The authors suggest that when we educate older patients, we limit the amount of information provided in one educational session and "chunk" similar information into a few smaller sections.

D.A.K.

O'Connor R, Wolf HS, Smith SG, et al: Health literacy, cognitive function, proper use, and adherence to inhaled asthma controller medications among older adults with asthma.

Chest. 2015;147:1307-1315. ●

Does Asthma Knowledge Correlate with Asthma Control in the Elderly?

Patient education seems important in improving asthma control, but there are few data on how asthma knowledge affects disease control in older adults. This issue was addressed in a study of Turkish older adults with asthma.

The 82 patients—76 women and 6 men, mean age 65 years—were interviewed by the same allergist. Patients completed an asthma knowledge questionnaire and Asthma Control Test and underwent skin prick testing, spirometry, and assessment of inhaler technique.

The patients had low education and a high rate of obesity. Twenty-one percent had atopy, most commonly to house dust mite. Sixty-three percent of patients had uncontrolled asthma, while only 27% demonstrated proper inhaler technique.

Asthma knowledge was rated "limited" for 48% of patients. However, there was no significant association between asthma knowledge and asthma control. The physician was the main source of asthma knowledge for 81% of patients. ● ● ●

This Turkish population of elderly asthma patients shows low asthma knowledge and "largely insufficient" asthma care, but no significant association between asthma knowledge and asthma control. The researchers highlight the need for asthma education programs for older adults, tailored to their educational level and asthma characteristics.

COMMENT: Asthma in elderly patients is often uncontrolled. Many factors contribute to this, including coordination, visual, hearing, and memory difficulties. In this study of elderly asthma patients in Turkey, more than half had uncontrolled asthma and nearly half had limited knowledge of their disease. The level of asthma control was not significantly associated with patients' knowledge of asthma. The sample was limited—more than 90% were women and almost two-thirds had not worked professionally. The patients did not use the Internet; physicians were their main source of information. The authors recommend education efforts for elderly patients with asthma, targeted to their educational level. It would also be interesting to have larger studies in other countries.

V.H.-T.

Ozturk AB, Pur LO, Kostek O, Keskin H: Association between asthma self-management knowledge and asthma control in the elderly.

Ann Allergy Asthma Immunol. 2015;114:480-484. ●

Link between Childhood Asthma and ADHD?

Asthma and attention-deficit/hyperactivity (ADHD) are both common chronic health conditions in children. While some studies have reported an association between these two problems, others have found no link. Swedish registry data were analyzed to seek associations between childhood asthma and ADHD.

The study included data on 20,072 twins enrolled in the Swedish Twin Register. Parental questionnaire responses when the twins were 9 or 12 years old were linked to other health registries. Associations between asthma and ADHD were analyzed, including the impact of asthma severity and medications. Comparisons between twins were performed to assess the relative roles of genes and environment.

The results suggested a 50% increase in ADHD risk among children with asthma: odds ratio (OR) 1.53. The association was not limited to either the inattentive or hyperactive/impulsive dimension of ADHD. Risk of ADHD was highest for children with more severe asthma, defined as four or more attacks in the past year. There was no association with asthma treatment. Cross-twin comparisons suggested only a weak genetic contribution to overlap between the two disorders.

Children with asthma, especially severe asthma, may be at higher risk of ADHD. Allergists should be aware of this overlap, and ensure that asthma care is integrated with appropriate evaluation and treatment for ADHD.

COMMENT: How often have parents shown concern

regarding their child's asthma or use of medicine to treat their asthma as a potential trigger of ADHD? Via this study by Holmberg and colleagues, we have some data. The authors analyzed parental questionnaires on 20,072 twins enrolled in the Swedish Twin Register, linked to the Swedish Medical Birth Register, National Patient Register, and Prescribed Drug Register, to determine if there was an association between asthma and ADHD. Interestingly, the results found an association of childhood asthma—especially severe asthma—with ADHD. Asthma medication did not seem to increase the risk of ADHD. These findings highlight the need for optimal clinical care of children with asthma to be integrated with effective management strategies for ADHD symptoms.

J.J.O.

Holmberg K, Lundholm C, Anckarsäter H, et al: Impact of asthma medication and familial factors on the association between childhood asthma and attention-deficit/hyperactivity disorder: a combined twin- and register-based study. Clin Exp Allergy. 2015;45:964-973. ●

Longitudinal Outcomes of Adult Asthma: 7-Year Follow-Up

Little is known about the course and prognosis of adult asthma, including the chances of remission and the factors associated with it. This longitudinal study assessed the 7-year prognosis of patients with adult-onset asthma.

The study included 160 patients diagnosed with adult-onset asthma in 2006 at a Turkish allergy clinic and contacted for follow-up in 2013. Ninety percent of patients were women; mean age at follow-up was 53 years. Seventy percent were diagnosed with asthma before age 40. Asthma control status was uncontrolled in 22% of patients, partially controlled in 29%, and completely controlled in 48.8%.

At follow-up, 11.3% of patients were in remission—defined as complete asthma control and no use of asthma treatments for at least 2 years. Mean age was 45.8 years for patients in remission versus 55.9 years in the uncontrolled group, and 53.0 years in the partially and completely controlled groups. Patients in remission and those with completely controlled asthma had a shorter duration of asthma. Remission was also associated with a lower rate of asthma and fewer comorbid conditions, although these differences weren't statistically significant.

At 7 years' follow-up, 1 out of 9 patients with adult-onset asthma has gone into remission. In addition to younger age, lower comorbidity, and other factors mentioned above, remission may be more likely for patients with a higher FEV₁, lower body mass index, and a higher rate of allergic rhinitis.

COMMENT: In this follow-up study of 160 individuals with adult-onset asthma, the remission rate is 11.3% at 7 years. Remissions occurred predominantly in a younger age group with a shorter duration of asthma, increased incidence of atopy, and fewer comorbidities than the overall group.

C.C.R. ● ● ●

Sözener ZC, Aydın Ö, Mungan D, Mısırlıgil Z: Prognosis of adult asthma: a 7-year follow-up study. *Ann Allergy Asthma Immunol*. 2015;114:370-373. ●

Can Diagnostic Codes Help Us Identify Chronic Urticaria?

Patients with chronic idiopathic urticaria or spontaneous urticaria (CIU/CSU) have debilitating hives and angioedema of unknown cause. The lack of a specific *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code contributes to the difficulties of studying this condition. This study reports the development and validation of an ICD-9-CM-based algorithm for identification of patients with CIU/CSU.

Records from four US allergy/immunology centers were reviewed to identify a random sample of patients identified by their physician as having CIU/CSU or who met a diagnosis-based algorithm of (1) at least two outpatient ICD-9-CM diagnosis codes 708.1, 708.8, or 708.9 occurring at least 6 weeks apart or (2) one outpatient diagnosis of 708.1, 708.8, or 708.9 and one diagnosis of 995.1 at least 6 weeks apart. Sensitivity and positive predictive value were assessed, and the algorithms were tested in an insurance claims database.

The sample included 149 patients, mean age 41 years; about three-fourths were women and 70% were white. One hundred fifteen patients were identified using the diagnosis-based algorithm while 90 had "known CIU/CSU" (56 were in both groups). Mean duration of CIU/CSU was about 3 years in both cohorts. The most frequent diagnoses were idiopathic urticaria, unspecified urticaria, and other specified urticaria. The algorithm based on ICD-9 codes had positive predictive value of 90.4% and sensitivity of 71.1%. Adding a medication-based component to the algorithm increased sensitivity to 88.3%.

The algorithm used in this study identifies a group of patients highly likely to have CIU/CSU and identifies most patients with this condition. Especially with further refinement, the diagnosis-based algorithm will be useful in claims-based research of CIU/CSU.

COMMENT: Some atopic diseases, like CIU/CSU, are difficult to treat. The use of ICD-9 codes may be helpful for conducting research and identifying patients with certain diseases, although CIU/CSU lacks a specific code. Algorithms using ICD-9 for these patients have not been validated, so the authors conducted a multicenter chart review to validate and revise previous algorithms. All patients used antihistamines; mean disease duration was 2.9 to 3.1 years. The authors tried three different algorithms, with similar accuracy in diagnosing CIU/CSU. The simple two-part algorithm was useful in accurately identifying these patients. This offers an opportunity for claims-based research, with improved patient identification and insights into the epidemiology and treatment of CIU/CSU.

V.H.-T.

Cherepanov D, Raimundo K, Chang E, et al: Validation of an ICD-9-based claims algorithm for identifying patients with chronic idiopathic/spontaneous urticaria.

Ann Allergy Asthma Immunol. 2015;114:393-398. ●

REVIEWS OF NOTE

COMMENT: This review of monitoring of childhood asthma gives the appropriate benchmark to be applied, within the limits of local resources.

B.E.C.

Pijnenburg MW, Baraldi E, Brand PLP, et al: Monitoring asthma in children. *Eur Respir J*. 2015;45:906-925.

COMMENT: This feature article by Nelson highlights the need for concern regarding hookah smoking. Compared to cigarettes, hookah smoking has a sweeter smell and a more appealing taste, which gives the impression that it is less harmful. This has been corroborated by a survey of university students in Florida, which found that while approximately 75% felt cigarette smoking could be harmful to their health, only approximately 54% felt similar concerns regarding the hookah. Like cigarettes, the hookah is associated with lung cancer and other respiratory diseases, and also carries the risk of infectious disease transmission from sharing a mouthpiece. We allergists should be asking our patients, especially adolescents and young adults, whether they are using hookahs and if so, providing education regarding their potential danger.

J.J.O.

Nelson R: Hookah smoking seduces US young adults. *Lancet Respir Med*. 2015;3:277.