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

American College of Allergy, Asthma & Immunology

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FEATURE ARTICLES

Two Pivotal Asthma Studies Put Benralizumab on the Map

Benralizumab is a monoclonal antibody directed against the alpha subunit of the interleukin-5 (IL-5) receptor. This trial evaluated benralizumab's effectiveness in reducing glucocorticoid requirement in patients with severe asthma and eosinophilia.

The randomized, placebo-controlled trial included 220 adults with severe asthma and persistent eosinophilia. Benralizumab dosage was 30 mg sc every 4 weeks or every 8 weeks; in the latter group, the first three doses were given every 4 weeks. The primary endpoint was reduction in oral glucocorticoid dose through 28 weeks while maintaining asthma control.

Median final glucocorticoid dose was reduced by 75% in the combined benralizumab group, compared to 25% in the placebo group. Patients taking benralizumab were four times more likely to have a reduction in glucocorticoid dose. Compared to placebo, annual exacerbation rate was 55% lower with benralizumab every 4 weeks and 70% lower with benralizumab every 8 weeks.

There was no significant difference in FEV_1; adverse effects were also similar between groups. Benralizumab was associated with improvements in some asthma symptom measures, but not all.

Benralizumab has a significant glucocorticoid-sparing effect in adult patients with severe asthma and eosinophilia. The study also suggests a reduction in exacerbation rate, but no effect on FEV_1 and mixed effects on asthma symptoms. The authors note that about 20% of patients had no reduction in oral glucocorticoid dose with benralizumab, for unknown reasons. • • •

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

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Previous trials have found that benralizumab lowers blood eosinophil counts and reduces exacerbation rates in patients with severe asthma. The authors report a phase 3 trial of benralizumab for patients with mild to moderate persistent asthma.

The multicenter, international BISE trial included 311 adults with mild to moderate, persistent asthma while on maintenance inhaled corticosteroids (ICS), which continued during study treatment. After stratification by blood eosinophil count (cutoff point 300 cells/μL), patients were randomly assigned to benralizumab 30 mg sc or placebo, every 4 weeks for 12 weeks. The primary endpoint was change in prebronchodilator FEV_1 from baseline to 12 weeks.

Prebronchodilator FEV_1 improved from 2,248 mL at baseline to 2,310 mL at 12 weeks in the benralizumab group, compared to no significant change in the placebo group. Benralizumab was associated with an 80 mL greater improvement (least-squares mean difference) in the primary outcome. Adverse events were similar between groups.

Benralizumab added to maintenance ICS shows a small improvement in prebronchodilator FEV_1 in patients with mild to moderate persistent asthma. The results suggest that benralizumab might affect modifiable disease processes in this group of patients. Although the improvement in lung function does not reach the minimum clinically important difference of 10%, further studies may be warranted.

COMMENT: In the ZONDA trial, benralizumab was four times more likely to reduce oral glucocorticoid dose compared with placebo, in adults with severe asthma associated with eosinophilia. In the BISE trial, benralizumab also reduced exacerbation rates in adults with mild to moderate persistent asthma, although it had no significant (minimally important) effect on FEV_1. Compared to the currently available anti-IL-5 agents, possible advantages of benralizumab are less frequent dosing (subcutaneous once every 4 weeks) and a potential to reduce exacerbations irrespective of the blood eosinophil count. Although improvements in asthma symptom scores and quality of life occur with all three biologics, randomized controlled trials directly comparing the three agents are needed to determine selection among these options for treatment of eosinophilic asthma.

C.D.

Nair P, Wenzel S, Rabe KF, et al: Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med. 2017;376:2448-2458.

Ferguson GT, FitzGerald JM, Laviolette M, et al: Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2017;5:568-576.

Keywords: asthma (adult). asthma (severe), anti-IL-5, biologics,

Mastery over Mast Cells May Mitigate AHR

In patients with severe asthma, airway mast cells are associated with poor disease control and quality of life. KIT is the major survival and growth factor for mast cells. This study evaluated the effects of imatinib, a KIT inhibitor, on airway hyperresponsiveness (AHR) and mast cells in patients with severe asthma.

The study included 62 patients with severe, poorly controlled asthma and AHR despite maximal medical therapy. Patients were • • •

randomly assigned to 24 weeks of treatment with imatinib—200 mg/d for 2 weeks, then 400 mg/d—or placebo. Change in AHR to methacholine was assessed, along with airway mast cell numbers and activation markers.

Imatinib was associated with greater reduction in AHR compared to placebo. Mean increase in methacholine PC_{20} was 1.73 doubling doses in the imatinib group, compared to 1.07 in the placebo group. There was also a significant decrease in mast cell activation; serum tryptase levels decreased by 2.02 ng/mL with imatinib versus 0.56 ng/mL with placebo. Mast cell numbers decreased in both groups, with a nonsignificant trend toward greater reduction with imatinib. Reductions in asthma exacerbations and patient-reported outcomes were numerically but not significantly different with imatinib.

The proof-of-principle study finds that KIT inhibition with imatinib reduces mast cell activation and AHR in patients with severe asthma. "These results suggest that KIT-dependent processes and mast cells contribute to the pathophysiologic basis of severe asthma," the researchers write.

COMMENT: In this phase 2 study, inhibition of KIT by the tyrosine kinase inhibitor imatinib shows cautious promise in decreasing AHR in severe asthma. As with other emerging biologic agents, we need to walk the fine line between preserving beneficial immune effects and attempting to reverse some of the deleterious effects. In this era of burgeoning precision medicine—as elegantly pointed out by Steve Galli (N Engl J Med. 2017;376:1983-1984)—selection of the right patient is the key.

C.D.

Cahill KN, Katz HR, Cui J, et al: KIT inhibition by imatinib in patients with severe refractory asthma.N Engl J Med. 2017;376:1911-1920.

Keywords: biologics, mast cells, severe asthma

Might 'Star Wars' Technology Solve Challenge of Asthma Heterogeneity?

Molecular and genetic markers, particularly in readily accessible specimens, may lead to new approaches to identifying patients for targeted therapies for severe asthma. This study used gene-expression profiles in peripheral blood to identify subgroups of patients with severe asthma.

The analysis included 610 asthmatic and control subjects from the Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) study. Important differences in blood transcript profiles and molecular pathways were assessed, including differences in subjects with mild/moderate and severe asthma and the effects of oral corticosteroid treatment. Patient clusters were created on the basis of gene expression patterns, independent of clinical findings.

The results showed differential expression of 1,693 genes for subjects with severe asthma versus nonasthmatic subjects. The differences between nonasthmatic subjects and the nonsmoking severe asthma and mild/moderate asthma subgroups were significantly related to each other, although with a greater effect size in the severe asthma subgroup.

On assessment of biologic pathways, most of the differences between subgroups reflected differences in circulating immune cells. Severe asthma was associated with increased chemotaxis, migration, and myeloid cell trafficking and decreased B-lymphocyte development and hematopoietic progenitor cells and lymphoid hypoplasia. Cluster analysis identified subgroups of patients with severe asthma who had differing responses to oral corticosteroids. The study identifies differences in peripheral blood gene expression for patients with asthma, including severe asthma, versus nonasthmatic subjects. Transcript profiles also identify subgroups of patients with severe asthma, including differential responses to oral corticosteroids. The study shows "major differences in the activity of circulating cells that do not follow the currently applied clinical classification based on severity of asthma."

COMMENT: This study used blood transcriptomic technology to characterize subgroups of asthmatics. The findings included a 1,700-gene severe asthma disease signature. This is a very important observation that opens the door to developing better diagnostic biomarkers and targeted therapies. Stay tuned!

B.E.C.

Bigler J, Boedigheimr M, Schofield JPR, et al: A severe asthma disease signature from gene expression profiling of peripheral blood from U-BIOPRED cohorts. Am J Respir Crit Care Med. 2017;195:1311-1320.

Keywords: asthma (adult), asthma (severe), transcriptome analysis

'Type 2 Innate Lymphoid Cells' Traffic to the Nose after Allergen Challenge

Recent studies have identified "type 2 innate lymphoid cells" (ILC2s) as a group of effector cells of the innate immune response that may play a key early role in initiating Th2 response to allergens. Increased ILC2 numbers have been found across various mucosal tissues in type 2-mediated disease, but their role in causing allergic airway inflammation and asthma remains unclear. The authors used a new noninvasive technique to evaluate the role of ILC2s to nasal allergen challenge.

Nasal allergen challenge was performed in 9 subjects with moderately severe asthma with allergic rhinitis and 8 healthy controls. Nasal curettage samples were obtained for flow cytometric analysis to assess ILC2 and granulocyte recruitment to the upper airways. Soluble mediators in the

nasal lining fluid were measured using nanosorption techniques.

Allergen challenge in the asthma/allergic rhinitis group induced rapid onset of nasal symptoms accompanied by increased recruitment of eosinophils, neutrophils, and ILC2s to the nasal mucosa. Analysis of nasal mediators showed increased production of interleukin-5, prostaglandin D2, and eosinophil and Th2 cell chemokines. Subjects with markers of type 2 responses, ie, higher serum IgE and airway eosinophilia, had greater ILC2 recruitment to the upper airway.

Using a new noninvasive sample collection technique, this study shows rapid recruitment of ILC2s to the upper airway in atopic patients after nasal allergen challenge. This effector is associated with important type 2 mediators and likely plays a key role in the early allergic response to aeroallergens. With further study of their role in the lower airways, ILC2s might become a new target for asthma therapies.

COMMENT: This study used a fascinating nasal allergen challenge model to help validate the importance of ILC2s, a recently characterized innate effector cell type. This important observation helps us better understand the mucosal allergic inflammation in asthma, including the relationship between innate and adaptive immune responses.

B.E.C.

Dhariwal J, Cameron A, Trujillo-Torralbo M-B, et al: Mucosal type 2 innate lymphoid cells are a key component of the allergic response to aeroallergens. Am J Respir Crit Care Med. 2017;195:1586-1596.

Keywords: airway inflammation, asthma (adult)

Single-Dose Oral Challenge to Peanut: A Safe Option for Risk Stratification?

The dose predicted to elicit a reaction in 5% of patients with peanut allergy (ED_{05}) is 1.5 mg of peanut protein. The authors sought to validate this ED_{05} value in a new single-dose challenge technique in an unselected group of children with peanut allergy.

The international Peanut Allergen Threshold Study (PATS) included 378 children with peanut allergy at three centers; subjects were recruited regardless of previous reaction severity. About half of patients (one-third in the United States and Ireland, three-fourths in Australia) said that they disregarded precautionary allergen labeling. The monitored open food challenge consisted of eating a cookie containing 1.5 mg of peanut protein.

Fifteen percent of children had mild, transient reactions that fell short of specified criteria for objective or likely reactions. Eight patients met criteria for mild reactions: a rate of 2.1%. Four patients were treated with antihistamines; none required epinephrine. Reactions were unrelated to skin prick test results or specific IgE levels. At 1-month follow-up, food allergy-related quality of life scores were significantly improved, regardless of the peanut challenge result.

This novel single-dose oral peanut challenge technique elicits mild or objective reactions in about 2% of peanut-allergic children, compared to the predicted rate of 5%. The single-dose challenge appears safe and acceptable to patients, and may provide a new approach to identifying the most highly dose-sensitive group of children. Validation of the predicted peanut ED_{05} has implications for policy and food labeling.

COMMENT: Parents of children with peanut allergy frequently ask if the child can eat foods manufactured in a factory that processes peanuts. The PATS helps address these concerns. It found that using a small, eliciting dose challenge with a small amount of peanut protein could distinguish between children with severe sensitivity and the 65% who had no reaction. Even those who reacted to a single cookie containing 1.5 mg of peanut protein had only mild reactions; none needed epinephrine. Although the eliciting dose was projected to have a 5% reaction rate, only 2.1% of patients had reactions. This may be explained by patient selection: some were too anxious to participate and some others didn't care about manufacturing labeling. The use of small eliciting doses in children with food allergy has potential utility for predicting safety for oral challenges and for product labeling.

S.M.F.

Hourihane JO'B, Allen KJ, Shreffler WG, et al: Peanut Allergen Threshold Study (PATS): novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy.
J Allergy Clin Immunol. 2017;139:1583-1590.

Keywords: food labeling, oral food challenge, peanut allergy

Diagnosing Peanut Allergy via the Eye!

Oral food challenge is often needed to confirm the diagnosis of peanut allergy, but is time-consuming and carries a risk of severe reactions. Conjunctival provocation testing (CPT) is an established test for inhalant allergies. This study evaluated the use of CPT for diagnosis of peanut allergy.

The cross-sectional study included 102 children and adolescents with suspected peanut allergy, based on positive skin prick tests or specific IgE levels, with or without possible clinical reactions; and 28 controls of similar age. Subjects underwent CPT using powdered, dried peanut extract, in dilutions starting at 1:80 and gradually increasing to 1:1. Maximum peanut dose was 8.5 mg per eye. Testing was discontinued if two or more symptoms (redness, itching, chemosis and tearing) appeared. Double-blind placebo-controlled oral peanut challenge was performed in the children with suspected peanut allergy, and open challenge in controls.

The CPT was positive in 98% of children with • • •

suspected peanut allergy and in one control subject. Oral peanut challenge was positive in 86% of children with suspected allergy. All 81 children with a positive oral challenge also had a positive CPT result. At a 1:10 dilution, CPT had a sensitivity of 96% and specificity of 83%. None of the children had severe adverse reactions to CPT, compared to 23 cases of anaphylaxis in response to oral peanut challenge.

Conjunctival provocation testing appears to be a feasible, safe, and accurate diagnostic test for children with suspected peanut allergy. The CPT result is positive in all patients with positive oral peanut challenge, and negative in about 90% of those with negative oral challenge. The CPT could be a useful supplemental test to oral peanut challenge.

COMMENT: This very interesting study evaluated conjunctival peanut challenge and compared it to DBPCFC in 102 children with suspected peanut allergy. Remarkably, CPT picked up all patients who were positive via oral challenge! Conjunctival challenge was much safer, with only 3% of patients having moderate reactions. In contrast, moderate to severe reactions occurred in 26% of patients with food challenges; 17% of all children undergoing peanut challenge required epinephrine. About 10% had false positive conjunctival challenges, all of whom were allergic to birch pollen. Further studies are needed to confirm these exciting findings. D.A.K.

Lindvik H, Carlsen KCL, Mowinckel P, et al: Conjunctival provocation test in diagnosis of peanut allergy in children.
Clin Exp Allergy. 2017;47:785-784.

Keywords: diagnosis, oral food challenge, peanut allergy

Three Trials of Early Egg Introduction: HEAP, STEP and BEAT

A few previous studies have evaluated early egg introduction to prevent the development of egg allergy (EA), with mixed results. The "Hen's Egg Allergy Prevention" (HEAP) study evaluated early egg introduction for primary prevention of EA in a general population of infants.

The study included 4- to 6-month-old infants free of egg sensitization, based on specific IgE (sIgE) levels. They were randomly assigned to receive verum egg white powder or placebo rice powder, added to weaning foods three times weekly up to age 12 months. The main study outcome was the development of egg sensitization, reflected by sIgE.

On screening, sIgE was detected in 23 of 406 infants. Food challenge confirmed EA in 16 of 17 tested infants, 11 of whom had anaphylactic reactions.

At 12 months, rates of egg sensitization were 5.6% in infants assigned to egg white powder versus 2.6% in those assigned to rice powder: relative risk (RR) 2.20. Rates of confirmed EA were 2.1% versus 0.6%, respectively: RR 3.30. Allergic symptoms related to study treatments were also more frequent in the egg white group: 7.1% versus 0.5%.

In a general population of infants at weaning age, early introduction of egg white does not prevent egg sensitization or allergy. Since many infants already have sIgE and EA, this intervention might even result in an increased number of allergic reactions, some of them severe. Screening on the basis of atopic eczema misses one-third of infants with early egg sensitization.

At a time of rising rates of egg allergy (EA), the optimal age to introduce egg into the infant's diet remains unclear. The "Starting Time of Egg Protein" (STEP) study evaluated the effects of early egg protein introduction for primary prevention of EA in infants at high hereditary risk.

The study included 820 infants, aged 4 to 6 months, whose mothers had a history of allergic disease or sensitization. To ensure that the study was evaluating a primary prevention effect, infants with eczema were excluded. The infants were randomly assigned to receive pasteurized raw whole egg powder or rice powder daily up to age 10 months. At that time, cooked egg was introduced to the diet in both groups. At 12 months, EA was assessed by raw egg challenge and sensitization was assessed by skin prick test.

At 12 months, there was no significant difference in the development of EA: 7.0% in infants assigned to egg powder and 10.3% in the control group. Rates of confirmed allergic reactions causing early discontinuation of study treatment were 6.1% in the egg powder group versus 1.5% in the rice powder group; none of these were anaphylactic reactions. Infants in the egg group had higher egg-specific IgG_4 levels at age 12 months: median 1.22 versus 0.07 mg_A/L.

In 4- to 6-month-old infants at hereditary risk of allergy but without eczema, early egg introduction does not reduce the risk of IgE-mediated EA by age 12 months. Routine testing for egg sensitization does not appear necessary before introduction of egg into the diet for this group of infants.

Some trials have suggested that early introduction of egg into the diet might reduce the risk of egg allergy (EA) in infants at high risk. The "Beating Egg Allergy Trial" (BEAT) evaluated the effects of early egg introduction in infants with a family history of atopy.

The study included 319 infants, aged 4 months, who had at least one first-degree relative with allergic disease. All were initially free of egg allergy, based on a skin prick test response of less than 2 mm to egg white; about one-fourth had eczema at baseline. Infants were randomly assigned to receive whole egg powder or placebo rice powder from age 4 to 8 months, at which time their diet was expanded. The main outcome was the presence of egg sensitization at 12 months, based on a skin prick test response of 3 mm or larger.

Fourteen infants had an allergic reaction to egg during the first week of the study. Twelve-month evaluation was performed in 254 infants; dropout rates were similar between groups. Rates of egg white sensitization at 12 months were 11% in the egg powder group versus

20% in the rice powder group: odds ratio 0.46. Early egg introduction was associated with an absolute risk reduction of 9.8%, with a number needed to treat of 11.

The egg powder group had higher IgG_4 to egg protein and higher IgG_4/IgE ratios. There was no significant difference in the rate of probable egg allergy, based on clinical, oral challenge, or skin prick test reactions: 8 cases in the egg powder group and 8 in the rice powder group.

The BEAT results suggest that early egg introduction can reduce egg white sensitization in infants at high risk of EA, including those with eczema. However, a significant percentage of these infants cannot tolerate this intervention. Introducing egg at low doses immediately after weaning might be beneficial, and does not show evidence of harm.

COMMENT: Three articles from the May issue of *JACI* assessed the impact of early introduction of egg protein in reducing the risk of developing allergy. In the HEAP study, 4- to 6-month-old infants with egg sIgE less than 0.35 kU/L were assigned to either verum powder (similar to raw egg) or placebo. Surprisingly, there was a 5.7% prevalence of EA even before randomization. In fact, the trial was stopped early because of the relatively high rate of allergic reactions at first exposure to verum powder. Not only did the authors conclude that consuming egg protein early did not prevent EA, they advised that it may be harmful.

In the STEP trial, infants of atopic mothers with no eczema were randomized at 4 to 6 months to either pasteurized raw egg powder or placebo. Although STEP was planned as a primary prevention study, there was no evidence that early egg feeding substantially reduced the risk of EA, as measured by an egg challenge at 1 year. There was an impressive rise in egg $sIgG_4$ in the egg powder-treated group; however, 6% stopped taking the egg powder because of allergic reactions. All children could introduce cooked egg into their diets at 10 months, which may have affected the outcomes. The authors suggest that use of cooked egg may be advisable.

The BEAT study was unique in that all of the infants had a family history of allergy and negative skin test results to egg at 4 months, with 26% presenting with eczema. This was also designed as a primary prevention study with infants receiving either egg white powder or placebo at 4 months—although 8.5% had reactions to the egg powder and could not continue. At 8 months, cooked egg could be added to the diet of all infants. The egg powder intervention resulted in EA in 10%, assessed by skin test at 12 months, compared to 20% in the group receiving placebo. There was also an impressive rise in egg sIgG4 in the treated group.

The take-home message from these studies is that early intervention with cooked egg at 4 to 6 months is reasonable and relatively safe, but may not result in definitive reduction in EA.

S.M.F.

Bellach J, Schwarz V, Ahrens B, et al: Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants.
J Allergy Clin Immunol. 2017;139:1591-1599
Palmer DJ, Sullivan TR, Gold MS, et al: Randomized controlled trial of early regular egg intake to prevent egg allergy.
J Allergy Clin Immunol 2017;139:1600-1607.
Tan JW-L, Valerio C, Barnes EH, et al: A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy.
J Allergy Clin Immunol. 2017;139:1621-1628.

Keywords: early introduction, egg allergy, food allergy, prevention

Does Hard Water Prevent Atopic Dermatitis?

Factors affecting skin barrier function might influence the risk of atopic dermatitis (AD). Previous reports have suggested higher rates of AD in areas with so-called hard water and among children born in fall or winter. This study looked for a possible synergistic relationship between these two AD risk factors.

The researchers analyzed data on nearly 53,000 children from the Danish National Birth Cohort. National data sources were used to gather birth data and information on domestic water hardness, which differs across Danish regions. Physician diagnosis of AD and other characteristics were assessed in parental interviews when the children were 6 and 18 months old.

Overall prevalence of AD was 15.0%. Prevalence ranged from 13.5% to 17.1% in regions with the softest versus hardest domestic water; relative prevalence of AD increased by 5% per 5-degree increase in water hardness. Hard water accounted for an estimated 2% of the population risk of AD.

Relative prevalence of AD was 24% higher for children born in fall and 18% higher for those born in winter. There was no evidence of interaction between season of birth and water hardness.

Both hard domestic water and fall/winter birth are associated with a higher prevalence of AD in early childhood. Risk of AD increases along with degree of water hardness, but there is no synergistic interaction between these two risk factors. Further studies are needed to see if water softening can reduce AD risk in infants.

COMMENT: Skin barrier impairment in newborns is a potential risk factor for AD. Water can be a skin irritant and hard water, with high calcium carbonate, could cause even more irritation. This report from the Danish National Birth Cohort is unique since the geology of Denmark is unusual, with the country separated by a "main stationary line" caused by glaciers. The risk for developing AD increased by 5% for each 5 degrees of domestic water hardness, suggesting that using softer water could potentially be a primary prevention measure. Although the prevalence of AD increased in infants born in the colder seasons as expected, there was no synergism with hard water exposure. Maybe we should pay closer attention to the hardness of our local water.

S.M.F.

Engebretsen KA, Bager B, Wohlfart J, et al: Prevalence of atopic der-

matitis in infants by domestic water hardness and season of birth: cohort study. J Allergy Clin Immunol. 2017;139:1568-1574.

Keywords: atopic dermatitis, risk factors

Small Ragweed Particles Contain Plenty of Allergen

On exposure to humidity or thunderstorms, ragweed pollen grains release respirable subpollen particles (SPP), which have been linked to allergy and asthma symptoms. The authors compared the proteomes and allergomes of short ragweed SPP and total pollen protein extract (TOT), including comparison with the effects of aqueous pollen protein extract (APE) in sera from sensitized patients.

Ninety-four percent of the short ragweed pollen allergome was found in the SPP fraction, including the largest amounts of minor Amb a 4 and major Amb a 1 and Amb a 11 allergens. The TOT fraction was richest in Amb 8, while APE was richest in Amb A 6, Amb A 5, and Amb a 3. The highest proportion of the most abundant proteins, ie, red-colored cells, was found in the TOT fraction, which were little different between SPP and APE. The study identified new candidate allergens—phosphoglycerate mutase and phosphoglucomutase—which were IgE-reactive in SPP, TOT, and APE.

The findings document the presence of the full range of major and minor short ragweed allergens within the SPP fraction. Thus SPP, which can reach the alveoli, plays an important role in the development of ragweed sensitization. The study also shows the rich content of NADH and other oxireductases in short ragweed SPP.

COMMENT: Since the seminal work by Busse and Reed in 1972, we have known that particles smaller than ragweed pollen are important in ragweed allergy and asthma. The authors performed a proteomic analysis on SPP of ragweed and confirmed that indeed these particles contain the full major and minor short ragweed allergen repertoire and can clearly reach the alveoli.

D.A.K.

Smiljanic K, Apostolovic D, Trifunovic S, et al: Subpollen particles are rich carriers of major short ragweed allergens and NADH dehydrogenases: quantitative proteomic and allergomic study. Clin Exp Allergy. 2017;47:815-828.

Keywords: pollen allergy, proteomic analysis, ragweed

Corticosteroid Response Identifies Severe Asthma Phenotypes

Previous studies have described differing characteristics of severe versus nonsevere asthma. These phenotypes may also be affected by differences in adherence to and correct use of corticosteroids. This study compared responses to intramuscular corticosteroid in patients with severe and nonsevere asthma.

The study included 526 adults and 188 children with asthma. Based on 2014 American Thoracic Society/European Respiratory Society guidelines, 315 of the adults and 107 of the children had severe asthma. Responses to a single dose of intramuscular triamcinolone were compared between groups after 3 weeks. Response was defined as at least a 10-point improvement in percent predicted FEV_1.

After systemic triamcinolone, percent predicted FEV_1 increased by a mean of 3.4% in adults with severe asthma and 2.6% in those with nonsevere asthma. In children, neither group had a significant mean improvement after treatment. In adults with severe asthma, FEV_1 and asthma control after triamcinolone continued to be lower than in adults with nonsevere asthma. In children, the only factor that distinguished severe from nonsevere asthma after triamcinolone was the prebronchodilator FEV_1.

Just 21% of adults and 20% of children had a 10-point improvement in percent predicted FEV_1. Except in children with nonsevere asthma, response to triamcinolone was predicted by initial bronchodilator response and by exhaled nitric oxide.

Most adults and children with severe asthma don't meet the study criterion for response to a single dose of intramuscular triamcinolone. Adults with severe asthma have persistent differences in airflow obstruction and asthma symptoms despite systemic corticosteroid. This suggests a pattern of corticosteroid nonresponsiveness different from that of pediatric severe asthma.

COMMENT: In this study, only 20% of adults and children with severe asthma responded to intramuscular triamcinolone. Baseline FEV_1 response to bronchodilator and exhaled nitric oxide predicted response in both age groups, but there were important age differences that need further investigation.

B.E.C.

Phipatanakul W, Mauger DT, Sorkness RL, et al: Effects of age and disease severity on systemic corticosteroid responses in asthma. Am J Respir Crit Care Med. 2017;195:1439-1448.

Keywords: asthma (severe), corticosteroid response, phenotypes

Coping Strategies in Young Patients with Food Allergy

Personality studies have found increased rates of alexithymia—difficulty in recognizing or describing emotions—among young patients with food allergies. This condition may affect clinical outcomes and coping strategies. The authors examined associations between coping strategies, alexithymia, and anxiety among young patients with

food allergies.

Validated measures were used to assess coping, alexithymia, and anxiety in 92 adolescents and young adults (mean age 18.6) seen at an Italian food allergy center. About 90% of patients had been prescribed self-injectable epinephrine; one-half had experienced episodes of anaphylaxis. Questionnaire responses indicated alexithymia in 15% of patients and borderline alexithymia in 32%.

On analysis of coping strategies, avoidance was the factor that contributed the most to explaining alexithymia, followed by trait anxiety, younger age, anaphylaxis, and social support. Higher alexithymia was associated with increased use of avoidance as a coping strategy, rather than other strategies such as problem-solving or positive thinking.

Many young patients with food allergies have evidence of alexithymia, which is largely explained by avoidant coping strategies. Recognizing that these patients cannot identify and express their emotions may have implications for communication and management strategies. In food allergy and other conditions, affect regulation may have important effects on health behaviors and coping strategies.

COMMENT: We advise our patients to avoid relevant foods, but may not fully appreciate the full impact of anxiety associated with the risk of life-threatening reaction from inadvertent exposure. These authors report on psychologic distress and affect disturbance in a cohort of adolescents and young adults with IgE-mediated food allergy. Alexithymia (literally: "no words for feelings") has been observed in a number of chronic conditions. It has also been associated with heightened physiological arousal, an awareness of and tendency to overreport physical symptoms, and compulsive behaviors. The findings seem to warrant periodic assessment of psychologic well-being in our patients with food allergy.

D.M.L.

Polloni L, DunnGalvin A, Ferruzza E, et al: Coping strategies, alexithymia and anxiety in young patients with food allergy. Allergy. 2017;72:1054-1060.

Keywords: coping, food allergy, psychological factors

Allergists Can Lead in Inpatient Penicillin Allergy Testing

Most patients who report penicillin allergy can tolerate penicillin. Despite its impact on antibiotic prescribing, testing for penicillin allergy is infrequently performed in hospitals. This study reports a multidisciplinary approach to inpatient penicillin allergy testing.

The program was implemented at an academic medical center, in a partnership between the allergy and pharmacy departments. Daily reports identified inpatients with reported penicillin allergy and prioritized them for evaluation. In appropriate cases, a specialty pharmacist performed diagnostic testing for penicillin allergy at the bedside. Of 1,203 patients screened over an 18-month period, 252 were interviewed by the allergy pharmacist. Penicillin allergy testing was performed in 247 patients and completed in 228.

Just 5 patients had positive penicillin allergy test results. Overall, the program led to removal of reported penicillin allergy in 90.5% of cases; often, this was achieved just by taking a detailed history. Negative test results led to significant changes in antibiotic prescribing, including prescribing of a penicillin or cephalosporin in more than one-third of cases. In about 7% of patients found not to have penicillin allergy, this label was added back on a later healthcare encounter. In most cases, the allergy pharmacist was able to clear these incorrect reports.

This experience shows that a dedicated inpatient penicillin allergy testing program is feasible and effective. The authors believe this is a practical and proactive approach to large-scale penicillin testing, which is readily adaptable to the needs of varying healthcare settings.

COMMENT: This very interesting study explored the use of a physician-pharmacist team to determine whether inpatients labeled with "penicillin allergy" could undergo a turnkey skin test and challenge protocol to remove this diagnosis, when inaccurate. Recent studies have demonstrated increased morbidity and costs in hospitalized patients with a label of penicillin allergy. Through this program, over 90% of patients were ultimately able to have the penicillin allergy label removed. The study provides a great framework for allergists to aid in improving antibiotic stewardship.

J.J.O.

Chen JR, Tarver SA, Alvarez KS, et al: A proactive approach to penicillin testing in hospitalized patients. J Allergy Clin Immunol Pract. 2017;5:686-693.

Keywords: antibiotics, drug allergy, penicillin allergy

New Understanding of NSAID Allergy

Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause adverse reactions including true allergic reactions and "pseudoallergic" hypersensitivity reactions (HSRs). The authors analyzed electronic health records data to identify the incidence of and risk factors for NSAID HSRs.

Novel informatics techniques were used to assess HSRs and other adverse drug reactions to prescription NSAIDs among adult outpatients in a large healthcare network. The database included more than 4 million active allergy records for more than 2 million patients over an 8-year period. Natural language processing was used to classify adverse reactions as HSRs or side effects.

A total of 1,035 adverse drug reactions were identified in 62,719 patients receiving prescription NSAIDs: a rate of 1.7%. Of these events, 18.3% were classified as HSRs. Rash was the most common HSR, 38.1%; followed by angioedema or swelling, 27.0%; urticaria or hives, 19.6%; itching, 14.8%; shortness of breath, asthma, or wheezing, 6.3%; and anaphylaxis or hypotension, 5.3%. Independent • • •

risk factors were previous history of HSR, odds ratio (OR) 1.8; female sex, OR 1.8; autoimmune disease, OR 1.7; and prescription for maximum-dose NSAIDs, OR 1.5.

Adverse drug reactions occur in nearly 2% of patients receiving prescription NSAIDs, and nearly 20% of these reactions are HSRs. The study identifies some patient- and drug-related factors associated with an increased risk of HSRs to NSAIDs.

COMMENT: Using data mining approaches, the authors examined adverse reactions associated with outpatient use of NSAIDS in a large academic healthcare system. They found that overall 1.7% of patients suffered an adverse drug reaction; of these, approximately 1 in 5 were consistent with an HSR. Risk factors for HSRs included prior drug HSRs, female sex, history of autoimmune disease, and maximal dose of NSAID. Interestingly, patients prescribed cyclo-oxygenase-2 antagonists had a similar overall incidence of adverse drug reactions but a greater risk of HSRs.

J.J.O.

Blumenthal KG, Lai KH, Huang M, et al: Adverse and hypersensitivity reactions to prescription nonsteroidal anti-inflammatory agents in a large health care system. J Allergy Clin Immunol Pract. 2017;5:737-743.

Keyword: drug allergy, hypersensitivity reactions, NSAIDs

Older Adults with Asthma Are Different

Some reports have suggested differing patterns of airway inflammation in older patients with asthma. This study compared characteristics of airway inflammation in older versus younger asthma patients, including associations with asthma control.

The prospective study included two groups of New York City asthma patients: 35 older patients and 37 younger patients, mean age 67.9 and 30.8 years, respectively. After a run-in period accounting for inhaled corticosteroid use, sputum samples were obtained for analysis of inflammatory markers. Control groups of older and younger subjects were studied to account for age-related differences in inflammation.

The older patients had lower asthma control and pulmonary function compared to younger patients: mean asthma control score was 15 versus 18 and mean FEV_1 percent predicted 69.1% versus 81.0%. The older patients also had higher neutrophils, 23.1% versus 6.9%; and higher eosinophils, 3.8% versus 1.2%. Interleukin-6 and IL-8 levels were also higher in the older asthmatic group.

All inflammatory markers were similar in older and younger controls. In older asthma patients, higher sputum IL-6 and higher macrophage inflammatory protein 3α/CCL20 levels were associated with worse asthma control. Hospitalization risk was higher for older patients with higher neutrophil count and higher IL-1β, IL-6, and macrophage inflammatory protein 3α/CCL20 levels.

Older adults with asthma have increased sputum neutrophils and eosinophils and higher levels of cytokines associated with neutrophil recruitment, compared to younger asthma patients. The differences in airway inflammation may contribute to decreased asthma control in older patients. The authors discuss the implications for further research and clinical management of inflammation in older asthma patients.

COMMENT: We can expect to be seeing older adults with asthma more frequently based on demographic changes in the US population. This study design is notable. Several comparator groups were included: younger subjects with/without asthma, and older subjects without asthma. Interestingly, markers of inflammation did not differ significantly between older and younger nonasthmatic subjects. Atopy was frequent in older asthmatics and more frequent in younger asthmatics. Older asthmatics had worse asthma control and a more pronounced pattern of neutrophilic and eosinophilic inflammation. Age-specific therapies for older asthmatics merit consideration, and investigation in future studies.

D.M.L.

Busse PJ, Birmingham JM, Calatroni A, et al: Effect of aging on sputum inflammation and asthma control.
J Allergy Clin Immunol. 2017;139:1808-1818.

Keywords: asthma (adult), inflammation, inner city, older adults

Antibiotic Stewardship–Job Security for Allergists!

Many patients are labeled with penicillin allergy, with a major impact on antibiotic use and patient outcomes. Adequate assessment of penicillin allergy and practitioner education are essential. Hospital practitioners were surveyed regarding penicillin allergy and its clinical management.

The electronic survey was distributed to 716 physicians, pharmacists, and nurse practitioners providing care to inpatients at two community teaching hospitals. The response rate was 39%. The largest category of respondents was attending physicians with more than 10 years of experience.

About half of respondents were unfamiliar with the cross-reactivity rates between penicillin, cephalosporin, carbapenem, and monobactam antibiotics. In case vignettes, only about 40% of respondents knew the appropriate role of penicillin skin testing while less than 20% knew the role of temporary induction of drug tolerance. The respondents acknowledged the need for allergy/immunology consultation in the case scenarios—yet a large majority said they never or infrequently obtained referrals. Pharmacists were better informed about penicillin allergy and cross-reactivity.

The survey highlights gaps in the knowledge of penicillin allergy and its management among hospital health- • • •

care professionals. The findings identify key areas for improvement of clinical management of penicillin allergy, and support expansion of multidisciplinary approaches involving allergists and pharmacists.

COMMENT: Antibiotic stewardship is becoming increasingly important in healthcare. Campaigns such as Choosing Wisely seek to properly identify patients with true allergy to penicillin; we as allergists play a key role in these quality measures. This survey of healthcare practitioners in two community-based teaching hospitals demonstrates the need for education about skin prick testing to penicillin and the true rates of cross-reactivity of penicillin with other antibiotics. We are essential in the care of patients "labeled" with penicillin allergy, and responsible for differentiating patients with true allergy from those who may tolerate penicillin.

V.H.-T.

Staicu ML, Soni D, Conn KM, Ramsey A: A survey of inpatient practitioner knowledge of penicillin allergy at 2 community hospitals.
Ann Allergy Asthma Immunol. 2017;119:42-47.

Keywords: antibiotics, drug allergy, penicillin allergy

Another Nail in the Coffin of the GERD-Asthma Link

Many patients with asthma have gastroesophageal reflux disease (GERD), but it is unclear whether this condition contributes to asthma severity. This study assessed the prevalence of aspiration in patients with asthma and its association with disease control.

The study included 78 patients with asthma, classified as mild, moderate, or severe. In bronchoalveolar lavage (BAL) specimens, pepsin was measured as a marker of aspiration. Propensity for reflux was assessed by barium swallow studies. Correlations between aspiration and measures of asthma control were assessed.

Pepsin was detected in BAL samples from 58.9% of patients. Pepsin levels were similar across asthma severity groups, and were unrelated to asthma control measures, including FEV_1 and exacerbation rate. The findings were unaffected by adjustment for other factors including body mass index, proton pump inhibitor use, or eosinophilia. More than half of patients had a positive barium swallow, but this was unrelated to pepsin level or asthma control.

Aspiration does not appear to be related to asthma control across the range of asthma severity. The findings question the effects of GERD on asthma control and exacerbation rate.

COMMENT: This ambitious study recruited 78 patients of various asthma severities to undergo bronchoscopy/BAL, barium swallow, and measurement of pepsin in BAL fluid as a marker for aspiration. Despite finding elevated pepsin in almost 60% of asthma patients, there was no correlation of aspiration with disease severity, asthma control, exacerbation frequency, or FEV_1. Dividing the cohort into those with and without positive barium swallows for reflux made no difference. The evidence linking GERD and asthma continues to vanish.

D.A.K.

Hunt EB, Ward C, Power S, et al: The potential role of aspiration in the asthmatic airway. Chest. 2017;151:1272-1278.

Keywords: asthma (adult), GERD

Polluted Air Kills

Long-term exposure to air pollution is associated with increased mortality. There are limited data on the effects of air pollution levels below current air quality standards or outside of urban areas. This study used Medicare data to assess the relationship between long-term air pollution exposure and mortality in older adults.

The cohort study included 61 million Medicare beneficiaries in the continental United States from 2000 through 2012, with more than 460 million person-years of follow-up. Annual average exposures to $PM_{2.5}$ and ozone were calculated using validated prediction models. Associations between pollutant exposure and death were assessed with adjustment for demographic factors, Medicaid eligibility, and area-level covariates.

The results showed pollutant-related increases in mortality at levels below national standards. All-cause mortality increased by 7.3% per 10 μg increase in $PM_{2.5}$ exposure and by 1.1% per 10 ppb in ozone exposure. On analysis limited to years of exposure to low pollutant levels—12 μ/m^3 for $PM_{2.5}$ and 50 ppb for ozone—risk of death increased by 13.6% and 1.0%, respectively. The mortality impact of $PM_{2.5}$ exposure was greater for men, black subjects, and those eligible for Medicaid.

Long-term exposure to particulate air pollution and ozone is associated with increased mortality in the Medicare population. These health effects are observed at exposure levels below current national air quality standards and are greater in racial minorities and disadvantaged groups. The authors discuss the implications for determining the health effects of low levels of air pollution and for setting air-quality standards.

COMMENT: This eye-opening, decade-long cohort study involved 61 million Medicare beneficiaries. It showed that long-term exposures to $PM_{2.5}$ and ozone were associated with an increased risk of death. Even more starkly, the increased risk was seen at levels below the current established safe standards! These findings have profound implications for regulatory health policy that can have important public health benefits. Allergists should rally together to work towards the goal of reducing air pollution. That's despite the sobering insight expressed in the provocative editorial

by Berger et al (N Engl J Med 2017; 376:2591-2592), that "Ironically, Pittsburgh is less than 30 miles from the Donora Smog Museum, where a sign reads 'Clean Air Started Here.'"

C.D.

Di Q, Wang Y, Zanobetti A, et al: Air pollution and mortality in the Medicare population. N Engl J Med, 2017;376:2513-2522.

Keywords: air pollution, mortality, older adults

The Science of Why Smoking Is Evil

Smokers with mild asthma may develop features more typical of severe asthma, including unstable disease and a neutrophilic pattern of airway inflammation. This study evaluated the role of interleukin-17A (IL-17A) in the development of neutrophilic airway inflammation in asthmatic smokers.

Comparison of endobronchial biopsy specimens showed increased expression of IL-17A, IL-6, IL-8 and increased neutrophil numbers in asthmatic smokers, compared to nonsmokers with asthma. Interleukin-17A expression was significantly correlated with IL-8 expression and neutrophil count. Among smokers, eosinophil count was correlated with IL-17A and IL-8 expression.

In further experiments, human tracheal epithelial cells were cultured with IL-17A in the presence and absence of cigarette smoke extract (CSE). Expression of IL-17A and IL-8 were increased in the presence of CSE and IL-17A, in dose-dependent and synergistic fashion. Further synergistic increases in IL-6 and IL-8 occurred in cells co-stimulated with CSE, IL-17A, and aeroallergens lacking intrinsic protease activity.

The study confirms the presence of neutrophilic airway inflammation in asthma patients who smoke, and suggests that IL-17A is "at least one key mediator" driving this pattern. In combination with smoke and other environmental stimuli, IL-17A seems to induce neutrophil chemotaxins from airway epithelial cells.

COMMENT: It has been known for some time that asthmatics who smoke are less steroid-responsive and may have upregulation of neutrophilic airway infiltration. The mechanism of this shift in inflammatory milieu is not well understood. Siew et al explored the potential role of IL-17A via immunohistochemical analysis of endobronchial biopsies of smoking and nonsmoking asthma patients. They found that IL-17A, IL-6, IL-8, and neutrophil numbers were significantly higher in the mucosa of asthmatic smokers compared to nonsmokers. The data supports the hypothesis that asthma patients who smoke develop a neutrophilic airway inflammatory response at least in part by smoke-induced production of IL-17. This certainly seems a good phenotype to consider IL-17A blockade. I am sure more is to come.

J.J.O.

Siew LQC, Wu S-Y, Ying S, Corrigan SJ: Cigarette smoking increases bronchial mucosal IL-17A expression in asthmatics, which acts in concert with environmental aeroallergens to engender neutrophilic inflammation. Clin Exp Allergy. 2017;47:740-750.

Keywords: airway inflammation, asthma (adult), smoking

Rethinking Antibiotic Use in COPD Exacerbation

Antibiotics don't improve short-term outcomes in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), but the possible long-term effects are unclear. This trial evaluated the effects of adding doxycycline to prednisolone on time to next exacerbation in patients with COPD.

The study included 301 outpatients with stage 1 to 3 COPD, enrolled at nine teaching hospital clinics and three primary centers in the Netherlands. At the time of exacerbation, patients were assigned to receive a 7-course of doxycycline 100 mg/d (200 mg the first day) or placebo, stratified by disease stage. Both groups received 10 days of oral prednisolone 30 mg/d. Time to next exacerbation was compared between groups.

Another exacerbation occurred within 2 years in 85% of the doxycycline group and 83% of the placebo group; median times to next exacerbation were 148 and 161 days. The two groups also had similar rates of adverse effects during the first 2 weeks and through 2 years of follow-up. Other outcomes were also comparable between groups, including deaths and total number of exacerbations. Total antibiotic use was twice as high in the doxycycline group.

The results show no two-year benefit of adding an antibiotic to oral corticosteroid treatment for outpatient COPD exacerbations. Time to next exacerbation is not shortened by doxycycline versus placebo, regardless of sputum purulence.

COMMENT: Previous studies have demonstrated that antibiotics do not reduce mortality or short-term treatment response in COPD exacerbation. However, little is known about the possible long-term impact of antibiotics. This Dutch study examining the long-term impact of antibiotic use in patients with mild to severe COPD during an exacerbation is therefore of great interest. All subjects received 10 days of prednisone, while half received a 7-day course of oral doxycycline in addition. Median time to next exacerbation was no different between groups; thus the findings do not support prescription of antibiotics for COPD in the outpatient setting. It should be noted that exclusion criteria included fever and hospitalization, but not sputum purulence.

van Velzen, ter Riet G, Bresser P, et al: Doxycycline for outpatient-treated acute exacerbations of COPD: a randomized double-blind placebo-controlled trial. Lancet Respir Med. 2017;5:492-499.

Keywords: antibiotics, COPD, exacerbations

Is There Really a Test to Predict Antihistamine Response in CSU?

Vascular endothelial (VE)-cadherin is an endothelial cell-specific molecule involved in angiogenesis and vascular permeability. Recent studies have suggested that histamine-induced release of soluble VE-cadherin might play a role in the pathogenesis of chronic spontaneous urticaria (CSU). This study assessed serum sVE-cadherin levels in patients with CSU, including the response to H_1 antihistamine treatment.

An enzyme-linked immunosorbent assay was used to measure serum sVE-cadherin levels in 54 patients with CSU, 28 patients with atopic dermatitis, and 42 healthy controls. Mean sVE-cadherin level was 8.84 ng/mL in the CSU group, compared to 6.67 in the atopic dermatitis patients and 6.35 ng/mL in controls. Serum sVE-cadherin level was associated with CSU severity based on the Urticaria Activity Score, and decreased after treatment with fexofenadine.

Cultured HMEC-1 cells released sVE-cadherin in response to antihistamine; this response was inhibited by H_1 but not H_2 antihistamine. In further experiments, H_1 antihistamine blocked histamine-induced phosphorylation of VE-cadherin.

The results show elevated serum sVE-cadherin levels in patients with CSU, and support a pathogenetic role of histamine-induced sVE-cadherin release via activation of the H_1 receptor. Serum sVE-cadherin levels are related to CSU severity, and decrease after treatment with H_1 antihistamine.

COMMENT: In a disease that is challenging for patients and health care providers alike, this study is the first to show increased levels of an endothelial cell-specific adhesion molecule in CSU. Treatment with antihistamines inhibited release of sVE-cadherin. For clinicians, the opportunity to obtain more information in this disease is interesting. Ultimately, the question is whether the findings apply to a broader population, if specific subsets of patients may be more likely to benefit from antihistamines, and if sVE-cadherin predicts overall disease progression.

V.H.-T.

Chen T, Guo Z-p, Wang W-j, et al: Increased serum soluble endothelial cadherin levels in patients with chronic spontaneous urticaria.
Ann Allergy Asthma Immunol. 2017;118:704-709.

Keywords: biomarkers, CSU

Mosquito Allergens May Predispose to Other Arthropod Allergies

Previous studies have reported cross-reactivity between mosquitoes and other arthropods, including house dust mite, cockroach, and shrimp. This study identifies some additional allergens involved in cross-reactivity between mosquitoes and other arthropods.

The study included 34 sera from patients with asthma and/or allergic rhinitis from an allergy clinic in Martinique. Cross-reactivity between *Aedes aegypti* and other arthropod species were analyzed, including molecules other than tropomysin.

About 82% of patients had positive IgE reactivity to one or more species of house dust mite and 65% to *A. aegypti.* About 29% reacted to American cockroach and 23.5% to shrimp. All of these arthropod species showed high cross-reactivity with mosquito: 96.6% for *Dermatophagoides pteronyssinus,* 95.4% for shrimp, 84.4% for the tropical dust mite *Blomia tropicalis,* and 75.4% for cockroach. Four novel cross-reactive allergens were identified: odorant binding protein, mitochondrial cytochrome C, peptidyl-prolyl cis-trans isomerase, and a gene product with a hypothetical magnesium ion binding function.

This study in a tropical population of allergy patients shows cross-reactivity between mosquito, house dust mite, cockroach, and shrimp. The study identifies four previously unreported cross-reactive allergens in *A. aegypti* extract. The authors call for further studies to clarify the role of these molecules in the tropics and other areas where mosquitoes are abundant.

COMMENT: Sensitization to mosquitoes has been well-described. In this population from Martinique, almost 65% had IgE positive to mosquitoes. Several novel mosquito allergens are described. In the tropics, the practicing allergist may consider the cross-reactivity of other arthropods in patients with asthma or allergic rhinitis. Further studies of atopic patients in other areas with abundant mosquitoes—and whether they are at risk of true sensitization or clinical allergy to house dust mite, shrimp or cockroach—would be beneficial.

V.H.T.

Cantillo JF, Puerta L, Lafosse-Marin, et al: Allergens involved in the cross-reactivity of *Aedes aegypti* with other arthropods.
Ann Allergy Asthma Immunol. 2017;118:710-718.

Keywords: arthropods, cockroach, house dust mite, mosquitoes

REVIEWS OF NOTE

COMMENT: We allergists frequently see patients with lung disease. This review reminds us that patients with bronchiectasis need to be studied for underlying immunodeficiency. The authors studied a cohort of patients with bronchiectasis. Because serious lung disease in patients with primary immunodeficiency is a poor prognostic factor, this study reveals important findings that are helpful to the practicing allergist. Although less than 1.4% of the patients needed gamma globulin replacement, our responsibility as healthcare providers includes consideration of antibody deficiency.

V.H.-T.

Ruffner MA, Aksamit TR, Thomashow B, et al: Frequency of untreated hypogammaglobulinemia in bronchiectasis.
Ann Allergy Asthma Immunol. 2017;119:83-87.