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

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## FEATURE ARTICLES

# Think Twice Before Prescribing Acid-Suppressive Medications or Antibiotics to Infants

Early-life exposure to medications, including acid-suppressers and antibiotics, may affect childhood allergy risk by altering the microbiome. This study evaluated the use of acid-suppressive and antibiotic drugs during infancy for association with the risk of allergic diseases in early childhood.

The study included 792,130 children from the US Department of Defense's TRICARE Management Activity Military Health System database. All were born between 2001 and 2013, with continued enrollment from within 35 days of birth to at least age 1. Infants with an initial hospital stay of more than 7 days or with allergic conditions diagnosed before 6 months of age were excluded from the study.

During the first 6 months of life, a histamine-2 receptor antagonist ($H_2$RA) was prescribed for 7.6% of infants, a proton pump inhibitor (PPI) for 1.7%, and an antibiotic for 16.6%. These exposures were analyzed for association with diagnosis of allergic diseases at a median follow-up of 4.6 years.

Other than seafood allergy, risks of all allergic conditions evaluated were increased for children with exposure to $H_2$RAs or PPIs. For food allergy, adjusted hazard ratios (HRs) were 2.18 for $H_2$RA and 2.59 for PPI exposure. The increase in food allergy risk with acid-suppressive medications was dose dependent. Both classes of acid-suppressing drugs were also associated with increased risks of medication allergy, anaphylaxis, allergic rhinitis, and asthma.

Exposure to antibiotics during infancy was associated with increased risks of asthma, HR 2.09; allergic rhinitis, HR 1.75; anaphylaxis, HR 1.51; and allergic conjunctivitis, HR 1.42. Antibiotic prescription was associated with increased risks of cow's milk and egg allergy, but • • •



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- 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
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- 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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not peanut or seafood allergy.

Infants prescribed acid-suppressive or antibiotic medications in the first 6 months of life are more likely to develop childhood allergic diseases. The strongest associations are noted for acid-suppressing drugs and the risk of food allergies. Further studies will be needed to confirm the causal nature and determine the mechanism of these associations.

**COMMENT:** The question of whether using microbiome-perturbing medications in infancy alters the subsequent risk of allergic diseases bothers all of us. In the largest retrospective cohort childhood study to date, the hazard of developing an allergic disease was significantly increased in those receiving acid-suppressive medications or antibiotics during the first 6 months of life. Adjusted HRs in infants prescribed $H_2$RAs/PPIs and antibiotics were highest for food allergy and asthma, respectively. The take-home message is that acid-suppressive medications and antibiotics for infants should only be prescribed in situations of unequivocal clinical benefit.

C.D.

Mitre E, Susi A, Kropp LE, et al: Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. JAMA Pediatrics. 2018;172:e180315.

Keywords: acid-suppressive drugs, antibiotics, asthma (child), food allergy

## Woodstock and MTV Generations Still Breathing OK, But May Be Coughing More

As marijuana becomes more widely used and socially accepted, it is important to consider its potential health effects, especially on the respiratory system. The authors performed a systematic review and meta-analysis of the evidence on respiratory symptoms, obstructive lung disease, and changes in pulmonary function associated with marijuana use.

The review identified 22 observational and interventional studies evaluating pulmonary outcomes in adolescent or adult marijuana users. There were 10 prospective cohort studies and 12 cross-sectional studies, including 1,255 participants with more than 10 "joint-years" of marijuana exposure. Data sufficient for meta-analysis was present for five outcomes.

Based on two prospective studies, marijuana users were at increased risk for cough and sputum production: risk ratio (RR) 2.04 and 3.84, respectively. Meta-analysis of four cross-sectional studies suggested significant associations with cough (RR 4.37) and sputum production (RR 3.40), along with wheezing (RR 2.83) and dyspnea (RR 1.56). There were insufficient data for analysis of changes in pulmonary function or development of obstructive lung disease; studies of these issues were limited by low exposure and young study populations.

Based on weak evidence, marijuana smoking may be linked to increased risks of cough, sputum production, and wheezing. Associations with pulmonary function and obstructive lung disease remain unknown. The researchers conclude: "Given rapidly expanding use, we need large-scale longitudinal studies examining the long-term pulmonary effects of daily marijuana use."

**COMMENT:** As more states legalize marijuana, we may be seeing

patients with respiratory symptoms related to pot smoking. The findings of this systematic review imply that smoking marijuana more than once per week for at least 1 year is associated with increased cough, sputum production, dyspnea, and wheezing. There was insufficient evidence for an association with impaired lung function, although (low-strength) evidence suggested an increase in airway resistance with marijuana use. As the effects of tobacco smoking may not be evident for decades, long-term studies examining the effects of marijuana use are needed.

D.M.L.

Ghasemiesfe M, Ravi D, Vali M, et al: Associations between marijuana use and cardiovascular risk factors and outcomes: a systematic review. Ann Intern Med 2018;169:106-115.

Keywords: marijuana, pulmonary function, respiratory symptoms

## Let's Toast to Aspirin Desensitization

Previous reports have suggested that most patients with aspirin-exacerbated respiratory disease (AERD) also develop upper and lower respiratory symptoms after ingesting alcohol. This study prospectively evaluated changes in symptoms of alcohol intolerance after aspirin desensitization therapy in patients with AERD.

The study included 45 consecutive patients undergoing aspirin desensitization for AERD, confirmed by aspirin challenge, at two centers. The patients were 27 women and 18 men, mean age 44 years; all reported nasal and/or lower respiratory symptoms within 24 hours after consuming alcohol. Symptoms included nasal congestion in 95.6% of patients, rhinorrhea in 46.7%, and wheezing in 40.0%. All patients underwent endoscopic sinus surgery followed by aspirin desensitization. Changes in alcohol-induced respiratory symptoms were assessed by a before-and-after questionnaire.

Thirty-seven patients completed the study. After aspirin desensitization, 86.5% of patients reported improvement in their ability to tolerate alcohol without upper or lower respiratory symptoms. Seventy percent said that treatment was very to extremely helpful in terms of their ability to tolerate alcohol, and most reported an increase in the volume of alcohol needed to cause symptoms. Four patients reported no change in alcohol-induced respiratory symptoms.

Adding to previous anecdotal reports, this study suggests improvement in alcohol-induced respiratory symptoms after aspirin desensitization in patients with AERD. Further study is needed to determine the mechanism of this effect. The findings may provide a useful additional piece of information for decisions about aspirin desensitization.

**COMMENT:** We have recently appreciated that alcohol-induced respiratory symptoms are observed more frequently in patients with AERD than in aspirin-tolerant asthma patients. In some cases, even small amounts of alcohol are sufficient to promptly provoke symptoms. Alcohol inhibits the catabolism of leukotrienes, and AERD patients are much more sensitive to LTE4-induced bronchospasm. This study demonstrates yet another aspect of quality of life that improves with aspirin desensitization.

D.M.L.

Glicksman JT, Parasher AK, Dogrhamji L, et al: Alcohol-induced respiratory symptoms improve after aspirin desensitization in patients with aspirin-exacerbated respiratory disease. Int Forum Allergy Rhinol. 2018;10:1093-1097.

Keywords: alcohol, AERD, aspirin desensitization, NSAIDs

## Accidental Food Allergy Reactions: Products and Undeclared Ingredients

Allergen avoidance is a critical part of management of food allergies, but reactions due to accidental ingestions remain common. Precautionary allergen labeling (PAL), or "may contain" labels, are of questionable accuracy and often ignored. This prospective cohort study analyzed the types of food products and allergens involved in unexpected allergic reactions.

The study included 157 adults, mean age 35 years, with a physician-confirmed diagnosis of food allergy. Over 1 year of follow-up, 73 patients had one or more allergic reactions involving accidental ingestion of food allergens. Thirty-seven patients submitted a total of 51 triggering food products, which were analyzed for the unintended presence of culprit allergens.

The submitted food products consisted largely of chocolates, breads and rolls, cookies, meats, or combined dishes. Two-thirds were prepackaged foods. Thirty-seven percent of analyzed products contained one to four allergens that were not among the listed ingredients. The unintended allergen content was highest for peanut, milk, and sesame; milk proteins carried the highest estimated risk of reactions.

The amount of allergen ingested varied between patients. When unintended allergens were detected, intake exceeded the reference dose for one or more allergens, or there was a culprit allergen with no known reference dose. Patients neglected the PAL information in some cases, while in others there was no PAL statement.

The study lends insights into the triggering foods and culprit allergens that may be involved in accidental food allergy reactions. Peanut, milk, and sesame are the most common culprits, with milk being the most likely to cause reactions. The authors note that all of the eight allergens detected but not declared on the ingredient list are representative of allergens regulated in the European Union.

**COMMENT:** Patients with food allergy live with the fear of potential reactions following accidental ingestion of their allergenic food. In this well-designed prospective study in adults with food allergy, 46% of patients had an aver-

age of two unexpected reactions over the 1 year studied. Most patients had multiple food sensitivities, but the main culprits were milk, peanut, and sesame. The foods triggering reactions were mainly bread, cookies, chocolates, and meals outside the home. Although some patients admittedly were not diligent reading the PAL, many of the PAL statements did not list the offending allergen. Our food allergy patients need better assurances that PAL will more accurately predict contents of allergen, so we can help them evaluate their risk for reaction.

S.M.F.

Blom WM, Michelsen-Huisman AD, van Os-Medendorp H, et al: Accidental food allergy reactions: products and undeclared ingredients. J Allergy Clin Immunol. 2018;142:865-875.

Keywords: accidental ingestion, allergen avoidance, food allergy

## Early-Life Immune Signatures of Persistent Food Allergy

Childhood food allergies resolve over time in some patients, but little is known about the mechanisms by which food allergy develops or resolves. Recent evidence suggests that activation of the innate immune system in early life might play a causal role in predisposing to food allergy. This study examined innate immune profiles associated with the development of egg allergy and natural tolerance in childhood, including the effects of serum vitamin D.

The study used peripheral blood mononuclear cell samples longitudinally collected from 54 infants enrolled in the population-based HealthNuts study: 36 who had egg allergy at age 1 year and 18 with no food allergy. At age 2 to 4 years, egg allergy had resolved in 22 children subjects and persisted in 14. Innate immune responses associated with the development and resolution or persistence of egg allergy were analyzed.

The analysis identified a unique innate immune signature associated with persistent egg allergy. Compared to infants with transient egg allergy, the persistent group had increased numbers of circulating monocytes and dendritic cells at baseline as well as in response to in vitro endotoxin exposure. This pattern was associated with greater production of interleukin (IL)-1β and IL-8 at baseline, as well as increased tumor necrosis factor-α and IL-8 in the presence of endotoxin.

This innate immune signature, including elevated production of inflammatory cytokines, was still present at follow-up in the children with persistent egg allergy. The innate immune profiles associated with resolution of food allergy were correlated with increased serum vitamin D levels. At follow-up, 54% of children with persistent egg allergy had vitamin D deficiency (50 nmol/L or less), compared to 13% of the transient group.

Innate immune function in infancy is not only associated with the development of food allergy, but may also predict whether food allergy persists or resolves later in childhood. The findings also suggest an immunomodulatory role of increased vitamin D levels in the development of natural tolerance to egg. The findings may prove helpful in identifying high-risk infants whose food allergy is likely to be persistent in childhood.

**COMMENT:** "Will my infant outgrow their food allergy?" We struggle with this question daily. In this study, children with increased inflammatory cytokines and circulating monocytes were less likely to outgrow their egg allergy. Interestingly, increased vitamin D levels were correlated with natural resolution of egg allergy, suggesting that vitamin D may play an immunomodulatory role in the development of natural allergen tolerance. Although we can't definitively answer our patients' question, there may be markers that help us predict an infant's innate immune function in the future.

S.M.F.

Neeland MR, Koplin JJ, Dang TD, et al: Early life innate immune signatures of persistent food allergy. J Allergy Clin Immunol. 2018;142:857-864.

Keywords: food allergy, innate immune function, vitamin D

## Respiratory Viruses Mess with Treatment Response in Kids with Asthma Exacerbations

Respiratory viral infections are a common trigger of childhood asthma exacerbations. We still know little about how respiratory viruses affect the severity of asthma attacks or their response to treatment. These questions were addressed using data from a large cohort study of children with moderate to severe asthma exacerbations.

The study included 958 children, aged 1 to 17, from the "Determinants of Oral Corticosteroid Responsiveness in Wheezing Asthmatic Youth" (DOORWAY) study. Patients were seen for moderate or severe asthma exacerbations in five Canadian emergency departments, where they received standardized therapy with corticosteroids and inhaled bronchodilators.

Respiratory pathogens were identified by reverse transcription polymerase chain reaction assay of nasopharyngeal specimens. Exacerbation severity was rated by the Pediatric Respiratory Assessment Measure. Treatment failure was defined as hospital admission, ED stay longer than 8 hours, or return ED visit.

Two-thirds of patients were male; median age was 3 years. At least one respiratory pathogen was detected in 61.7% of patients. The most common pathogens were rhinovirus and respiratory syncytial virus: prevalence 29.4% and 17.9%, respectively. Treatment failure rate was 16.9%.

Pathogen detection was unrelated to exacerbation severity but was associated with a higher treatment failure rate: 20.7% versus 12.5%, for a rate difference of 8.2%. Among

children with a detected pathogen, the rate difference was higher for pathogens other than rhinovirus: 8.8% for RSV, 24.9% for influenza virus, and 34.1% for parainfluenza virus.

Most children seen in the ED for moderate to severe asthma exacerbations have at least one detected respiratory pathogen. While no pathogen is associated with greater exacerbation severity, treatment failure is more likely with pathogens other than rhinovirus. The authors discuss the implications for managing pediatric asthma exacerbations, especially in the presence of RSV, influenza, or parainfluenza virus infection.

**COMMENT:** In this large-scale prospective cohort study of children presenting to the ED with moderate or severe asthma exacerbations, viral detection was surprisingly unrelated to greater severity on presentation. On the other hand, the presence of specific pathogens – namely RSV, influenza, and parainfluenza – identified children with worse outcomes and suboptimal response to standard treatment. The findings suggest that severity on presentation and treatment response are two discrete aspects of how viruses affect acute asthma exacerbations. Strategies to address the problem include influenza prevention, pathogen identification, and treatment intensification for children with viral infections placing them at higher risk of treatment failure.

C.D.

Merckx J, Ducharme FM, Martineau C, et al: Respiratory viruses and treatment failure in children with asthma exacerbation. Pediatrics. 2018;142:e20174105.

Keywords: asthma (child), emergency department, exacerbations, respiratory viruses.

## Can Poor Asthma Control Cause A-fib?

Amid the growing epidemic of atrial fibrillation (AF), studies of new risk factors for this sustained cardiac arrhythmia are needed. Because they share some pathophysiologic mechanisms, a relationship between asthma and AF is possible. Data from a Norwegian population-based study were used to examine this potential association.

The study included data on 54,567 adults enrolled in two previous waves of the ongoing Nord-Trøndelag Health Study (HUNT), all initially free of AF. The occurrence of AF was determined by linkage to records from the two hospitals in the study area. Patient-reported asthma and asthma control – classified as controlled, partly controlled, and uncontrolled, based on Global Initiative for Asthma guidelines – were analyzed for association with the risk of developing AF.

Based on self-report, 10.9% of participants had ever had asthma, 7.2% had been diagnosed with asthma, and 4.6% had active asthma. During a mean 15.4 years' follow-up, 3.8% of participants were diagnosed with AF. On adjusted analysis, those with physician-diagnosed asthma were at higher risk of AF, compared to those without asthma: hazard ratio 1.38. There was also a dose-response association between asthma control and AF: odds ratios were 1.74 for participants with uncontrolled asthma and 1.42 for those with partly controlled asthma, with no significant association for those with controlled asthma. The associations were not explained by cardiovascular risk factors or comorbid conditions.

These population-based data suggest that adults with asthma are at increased risk of developing AF. Risk appears greatest in those whose asthma is active or uncontrolled. The researchers write, "Given the high prevalence of asthma, clinicians should be aware of this connection and closely examine AF risk factors in this patient group."

**COMMENT:** One potential novel risk factor for AF is asthma, since high levels of systemic inflammatory biomarkers have been reported in both conditions and $\beta_2$-agonists increase heart rate and the risk of arrhythmias. In this large prospective cohort study, self-reported asthma was indeed associated with a 38% increased risk of diagnosed AF. Furthermore, there was a dose-response association between levels of asthma control and AF. The good news is that there was no clear link with the use of $\beta_2$-agonist medications. Further studies are needed to validate these findings and to explore the underlying mechanisms and causal pathways linking asthma and AF.

C.D.

Cepelis A, Brumpton BM, Malmo V, et al: Associations of asthma and asthma control with atrial fibrillation risk: results from the Nord-Trøndelag Health Study (HUNT). JAMA Cardiol. 2018;3:721-728.

Keywords: asthma (adult), asthma control, atrial fibrillation

## Prenatal Antibiotics May Increase Childhood Asthma Risk

Antibiotic exposure during infancy may be a risk factor for childhood asthma. Less is known about the potential impact of prenatal antibiotics. Canadian health data were used to evaluate the association between maternal antibiotic use and childhood asthma in offspring.

The population-based cohort study included data on 213,661 maternal-newborn dyads in Manitoba between 1996 and 2002. Prenatal antibiotic exposure was analyzed as a risk factor for childhood asthma, with adjustment for maternal asthma, postnatal antibiotic treatment, and other confounders.

Overall, 38.6% of mothers were treated with antibiotics during pregnancy and 45.2% of infants received antibiotics during the first year of life. Childhood asthma (after age 5) developed in 10.1% of children. Asthma risk was higher in children with prenatal antibiotic exposure: adjusted hazard ratio (HR) 1.23. Risk appeared to increase with the number of antibiotic courses: HR 1.15 for one course, 1.26 for two courses, and 1.51 for three or more courses. Sensitivity analysis showed a similar increase in risk with maternal antibiotic use 9 months before pregnancy and 9 months post-

partum: HR 1.27 and 1.32, respectively.

Prenatal antibiotic exposure is associated with an increased risk of childhood asthma, with evidence of a dose-response. Risk appears similar for maternal antibiotic treatment before and after pregnancy, suggesting that the association is not causal and not specific to pregnancy. The authors highlight the need for further study of the association, including the role of intrapartum antibiotic exposure.

**COMMENT:** During pregnancy or in the immediate postpartum period, upwards of 40% of women receive a course of antibiotic. This is a controllable risk factor for asthma and may be due to permutations of the microbial community in both the mother and offspring. Prenatal antibiotic exposure was found to increase the risk of childhood asthma in a dose-dependent manner. One interesting finding was a difference in the incidence of asthma in rural versus urban populations, the reason for which is not clearly definable. The importance of using antibiotics judiciously during pregnancy and the postpartum period must continue to be brought forward in the obstetric and pediatric community. (Also see the accompanying editorial by Zhang et al: Eur Respir J. 2018;52:1801007.)

B.E.C.

Loewen K, Monchka B, Mahmud SM, et al: Prenatal antibiotic exposure and childhood asthma: a population-based study.

Eur Respir J. 2018;1702070.

Keywords: antibiotics, asthma (child), pregnancy

## Support for Early Introduction of Food...Even in Preterm Infants!

Increasing evidence supports early introduction of solid foods to promote oral tolerance and reduce the risk of food allergy. Although 3 to 7 months seems to be the optimal age in term infants, there are few data on introduction of complementary foods in preterm infants. This study assessed the effects of very early introduction of semisolid foods on the risk of allergic diseases in preterm infants.

The retrospective study included 464 preterm infants born at a Finnish university hospital from 2008 to 2012. The main outcome was the timing of introduction of complementary feeding in preterm infants, compared to matched term infants from the general population. The authors hypothesized that early introduction of semisolid foods would not be associated with an increased prevalence of food allergy or atopic dermatitis (AD) by age 1 to 2 years.

Median chronologic age at introduction of semisolid food was 3 months in preterm infants versus 4 months in term controls. Median corrected age at introduction was 1.4 months for all preterm infants. 1.9 months for late preterm infants (32 to before 37 weeks), 0.9 months for very preterm infants (28 to before 32 weeks), and 0.1 months for extremely premature infants (before 28 weeks). At age 1 and 2 years, there was no difference in the cumulative incidence of food allergy or AD for preterm versus term infants. Preterm infants who developed food allergy had significantly later introduction of semisolid foods. There was no increase in feeding problems among preterm infants who started semisolid foods early versus later.

The authors report their experience with "exceptionally early" introduction of complementary feeding in preterm infants. Even in extremely premature infants, this practice does not increase the risk of food allergy or AD, compared to term infants. The researchers write: "The key determining factor for the window of opportunity to develop oral tolerance is likely the time outside the womb rather than the corrected age (ie, developmental age) of the baby."

**COMMENT:** With recent changes in recommendations, parents of preterm infants may raise concerns regarding early introduction of solid foods. In this retrospective study, median age at semisolid food introduction in preterm infants was 3 months. None of the extremely premature infants developed food allergy, and only 3 out of 125 very premature infants had cow's milk allergy by age 1. Semisolid food was introduced later in children who developed food allergy. There was no increase in AD. Pediatric healthcare providers can use this study to support our recommendations and reassure parents that even premature infants with very early introduction of semisolid foods did not have increase in allergic disease.

V.H.T.

Yrjänä JMS, Koski T, Töröla H, et al: Very early introduction of semisolid foods in preterm infants does not increase food allergies or atopic dermatitis.

Ann Allergy Asthma Immunol. 2018;121:353-359.

Keywords: atopic dermatitis, early food introduction, food allergy, premature infants

## To Screen or Not to Screen for Peanut Allergy? That Is the Question!

Early introduction of peanut reduces the risk of peanut allergy in high-risk children. National guidelines on early peanut introduction vary, particularly in regard to recommendations for allergist referral and testing. The authors performed a simulation and cost-effectiveness study to compare these competing early peanut introduction and testing strategies.

The simulation compared three national strategies for early in-office peanut introduction in high-risk infants (those with severe atopic dermatitis and/or egg allergy). The US/Canadian strategy recommends peanut skin prick testing or specific IgE measurement, while the Australia/New Zealand and UK strategies recommend introduction without screening.

Any approach to early peanut introduction was cost-effective, compared to delayed introduction. Among the

competing early introduction strategies, no screening had the advantage over screening in terms of number of cases of peanut allergy prevented, quality-adjusted life-years (QALYs), and healthcare costs. Screening strategies were associated with a slight reduction in the rate of allergic reactions to peanut per patient.

Over a 20-year horizon, the per-patient cost of early peanut introduction without screening was about $6,557, compared to $7,576 for skin testing screening before introduction. Within the US population, screening high-risk children before peanut introduction would cost more than $654 million and identify 3,208 additional cases of peanut allergy. Simulations also supported current recommendations to defer screening in low-risk infants.

Comparison of national recommendations for early peanut introduction finds that screening of high-risk children is dominated by a no-screening strategy. Screening increases costs without improving QALYs, while preventing fewer overall cases of peanut allergy. The authors discuss the implications for developing and implementing early peanut introduction strategies.

**COMMENT:** As a consequence of the LEAP study, recommendations stress the early introduction of peanuts into the diets of high-risk infants. While US guidelines recommend screening tests such as skin or specific IgE testing, UK and Australian guidelines do not recommend any screening or in-office evaluation prior to peanut introduction. This simulation and cost-effectiveness analysis found that screening was associated with higher healthcare costs, without improvement in quality of life. Although screening slightly reduced overall lifetime reactions to peanut, this came at the cost of increased unnecessary peanut avoidance due to false-positive screening results. This paper makes us question our approach to early peanut introduction in the high-risk population.

J.J.O.

Shaker M, Stukus D, Chan ES, et al: "To screen or not to screen": comparing the health and economic benefits of early peanut introduction strategies in five countries. Allergy. 2018;73:1707-1714.

Keywords: early introduction, peanut allergy, prevention

## Reactions to Mosquitoes May Be due to Dust Mite Allergy

Previous studies have shown cross-reactivity between house dust mite (HDM), crustaceans, and insects, including mosquitoes. The authors have demonstrated that tropomysins from *Aedes aegypti* mosquitoes cross-react with HDM tropomysins. This study assessed humoral and cellular cross-reactivity of *A. aegypti* tropomysins with tropomysin from HDM.

In immunoassays, IgE antibodies from 15 HDM-allergic patients sensitized to Der p 10 showed humoral cross-reactivity with two recombinant tropomysins from *A. aegypti*. One of these mosquito tropomysins (Aed a 1 10.01) was a more potent inhibitor of IgE binding to Der p 10 than the other (Aed a 10.02), which is expressed only by mosquitoes, not other arthropods. Aed a 1 10.01 was also a stronger activator of basophils sensitized with Der p 10-specific IgE.

Mouse antibodies against both mosquito tropomysins also cross-reacted with Der p 10, with the Aed a 1 10.01-specific antibody showing stronger cross-reactivity. In the mouse model, cross-reactivity involved five cross-reactive T cell-activating regions.

These experiments show humoral and cellular cross-reactivity between HDM and mosquito tropomysins. Aed a 10 in particular – which has higher sequence similarity with Der p 10 – might induce allergic reactions to a wide range of tropomysins.

**COMMENT:** Tropomyosins are panallergens found in a number of animals including house dust mites, crustaceans, and mollusks. They are also found in mosquitoes. These investigators from Austria studied 15 HDM-allergic patients with minimal exposure to *A. aegypti* mosquitoes and found that all patients had specific IgE to recombinant *A. aegypti* tropomysins. Murine studies also showed T cell responses between mosquito and HDM tropomyosin. Could this cross-reactivity explain why some patients develop exaggerated reactions to mosquito bites?

D.A.K.

Cantillo JF, Puerta L, Fernandez-Caldas E, et al: Tropomysins in mosquito and house dust mite cross-react at the humoral and cellular level. Clin Exp Allergy. 2018;48:1354-1363.

Keywords: arthropods, house dust mite, mosquitoes, tropomysins

## Are Allergies/Food Allergy Associated with Autism Spectrum Disorder?

Immune dysfunction might be a link between environmental risk factors and autism spectrum disorder (ASD). Previous studies of the association between ASD and allergic diseases have been inconclusive. This study examined associations between food allergy and other allergic conditions with ASD in a nationally representative study of US children.

The study used cross-sectional data on 199,520 children, aged 3 to 17 years, from the National Health Interview Survey. About 49% of children were non-Hispanic white, 29% Hispanic, and 15% black. Allergic conditions were defined by parent/guardian responses to questionnaire items regarding food or digestive allergy, respiratory allergy, and eczema or skin allergy over the past 12 months.

Based on reported diagnosis by a physician or other health professional, the prevalence of ASD was 0.95%. Food allergy was reported for 11.25% of children with ASD versus 4.25% for those without ASD. The presence of ASD was also associated with higher rates of respiratory allergies, • • •

18.73% versus 12.08%; and skin allergies, 16.81% versus 9.84%. Associations with ASD remained significant on adjusted analysis, with odds ratios of 2.29 for food allergy, 1.28 for respiratory allergy, and 1.50 for skin allergy.

The results suggest positive associations between ASD and allergic conditions among US children, with food allergy showing the strongest association. Further studies are needed to confirm the associations and to clarify their causality and underlying mechanisms.

**COMMENT:** This cross-sectional, population-based study of children found a significant positive association of common allergic conditions, particularly food allergy, with autism spectrum disorder. A key weakness of the study is that while ASD was diagnosed by health professionals, allergies were defined based on parental questionnaire responses. Another weakness is that the study included all children regardless of age; hence there was no information regarding the onset of the allergic conditions or the timing of ASD diagnosis. While these results assuredly need validation, we can expect to get referrals for allergy evaluation of children with ASD, particularly for food allergy.

C.D.

Xu G, Snetselaar LG, Jing Jin, et al: Association of food allergy and other allergic conditions with autism spectrum disorders in children.

JAMA Network Open. 2018;1:e180279.

Keywords: autism, childhood allergies, food allergy

## Do Patients with Anaphylaxis to Venom Get Appropriate Treatment?

Although venom-induced anaphylaxis (VIA) accounts for less than 5% of cases, it comprises some of the most severe reactions. There are few data on uptake of guidelines for management of VIA. This study assessed the short- and long-term management of patients with VIA.

Using a Canadian national anaphylaxis registry, the researchers identified 112 VIA reactions in 115 patients treated in Montreal and western Quebec between 2013 and 2017. About three-fourths of reactions were treated by emergency medical services. Treatment included epinephrine administered by a healthcare professional in 63.5% of cases. Treatment without epinephrine was more likely for VIA occurring at home and for less-severe reactions without hypotension, hypoxia, or loss of consciousness.

Of 48 patients who responded to a follow-up questionnaire, 95.8% were prescribed an epinephrine autoinjector. Consultation with an allergist was reported by 68.8% of patients and allergy was confirmed in 63.6%. Eighty-one percent of patients with confirmed allergy received immunotherapy. Patients with known ischemic heart disease were less likely to see an allergist.

The population-based study reveals shortcomings in short- and long-term management of VIA. Substantial numbers of patients do not receive epinephrine, allergy consultation and confirmation, or immunotherapy for confirmed allergies. The authors call for educational interventions to bridge the "knowledge-to-action gap" in management of VIA.

**COMMENT:** This article from Canada describes patients with VIA from a national registry. Not surprisingly, less than two-thirds of patients were treated with epinephrine. Another area of concern is that only two-thirds saw an allergist. Of patients with positive results on allergy testing, 20% did not receive immunotherapy. None of the six patients who tested negative had repeat testing, as recommended by current guidelines. Only 20% patients had measurement of baseline tryptase levels. This article supports the need for increased education of healthcare providers in emergency settings, as well as patients.

V.H.-T.

Tritt A, Gabrielli S, Zahabi S, et al: Short- and long-term management of cases of venom-induced anaphylaxis is suboptimal.

Ann Allergy Asthma Immunol. 2018;121:229-234.

Keywords: anaphylaxis, venom allergy, venom immunotherapy

## Predicting Exacerbations in Severe Asthma: Is Exhaled NO the Answer?

Previous studies have found that past exacerbation status is the strongest predictor of future exacerbation risk. This factor should be considered in studies evaluating potential biomarkers for exacerbation risk. This study evaluated several Th2 biomarkers of exacerbation risk in patients with severe asthma, compared with exacerbation history alone.

The study included 105 patients from a Japanese severe asthma cohort. Of these, 39 had no exacerbations over 3 years. Fifteen were "consistent frequent exacerbators," with two or more exacerbations within 1 year; the remaining 51 patients were considered "infrequent exacerbators." Biomarkers were assessed as predictors of exacerbation category, including exhaled nitric oxide, blood eosinophil count, serum total and specific IgE, and serum periostin.

Sixty-three percent of patients had at least one asthma exacerbation over three years. On multivariate analysis including past exacerbation status, exhaled NO was an independent factor associated with the "consistent frequent exacerbator" status. Exhaled NO was significant both at baseline and after the first year. Aspirin-exacerbated respiratory disease was more common in frequent exacerbators, but other asthma comorbidities – including sinusitis, obesity, and gastroesophageal reflux disease – were not.

Exhaled NO may be a useful predictor of the frequent exacerbation phenotype in severe asthma. The predictive value of this biomarker appears independent of the patient's past exacerbation history.

**COMMENT:** Patients with severe asthma tend to have the highest frequency of exacerbations, and past exacerbations often predict future exacerbations. In this small Japanese

study, 105 severe asthma patients were divided into groups with frequent, intermittent, or no exacerbations over 3 years. Exhaled NO was the marker most associated with more exacerbations. The study included only 15 patients with frequent exacerbations; while all patients stated they were adherent, it is difficult to know how this was determined. The data also conflict with larger studies of severe asthma, where exhaled NO did not predict exacerbations.

D.A.K.

Kimura H, Konno S, Makita H, et al: Prospective predictors of exacerbation status in severe asthma over a 3-year follow-up.

Clin Exp Allergy. 2018;48:1137-1146.

Keywords: asthma (severe), exacerbations, exhaled NO, predictors

## Reassuring Results on Local Anesthetic Allergy

Allergists consider that immediate-type allergic reactions to local anesthetics are rare. However, this risk continues to be overestimated by other healthcare professionals as well as by patients. The authors report their experience in patients referred for evaluation of suspected immediate-type allergy to local anesthetics.

From 2010 to 2014, a total of 164 patients were referred to a regional allergy clinic for suspected immediate allergy to local anesthetics. The patients underwent a total of 189 provocations with local anesthetics, most commonly lidocaine. All of these tests were negative. Twelve percent of patients underwent skin tests, also with negative results. Other allergens, most commonly antibiotics, were identified in 10% of patients.

The study supports the belief that immediate-type allergy to local anesthetics is very rare. The authors note that most of these reactions have a nonallergic mechanism, such as vasovagal reactions; or are caused by other exposures such as chlorhexidine and latex.

**COMMENT:** This study reinforces our belief that allergic reactions to local anesthetics are exceedingly rare. None of the 164 patients referred for presumed local anesthetic allergy were found to be truly allergic.

J.J.O.

Kvisselgaard AD, Mosbech HF, Fransson S, Garvey LH: Risk of immediate-type allergy to local anesthetics is overestimated – results from 5 years of provocation testing in a Danish allergy clinic.

J Allergy Clin Immunol. 2018;6:1217-1223.

Keywords: anesthetic allergy, drug allergy

## Understanding the Components of House Dust Mites

A wide range of allergen components have been shown to be involved in house dust mite (HDM) sensitization. This study sought to further define the allergenicity and clinical implications of major and minor allergen components of HDM.

The researchers developed nine recombinant *Dermatophagoides farina* allergens: Der f 1, Der f 2, Der f 10, Der f 11, Der f 13, Der f 14, Der f 30, Der f 32, and Der f Alt a 10. They then analyzed IgE reactivity in sera from 160 Korean patients with confirmed HDM allergy. The findings were compared in three groups of patients: 67 with allergic airway disease, 41 with allergic airway disease plus atopic dermatitis (AD), and 52 with AD alone.

The main HDM allergens were Der f 1, recognized by IgE in serum samples from 88.1% of patients; and Der f 2, recognized in 78.1% of samples. Patients with allergic airway disease were mainly sensitized to these major allergens. By comparison, patients with AD "showed broader recognition to multiple HDM component allergens," including Der f 11, Der f 13, Der f 32, and Der f Alt a 10. Whereas about 80% of patients with allergic airway disease were sensitized to one or two allergens, 54% of those with AD reacted to three to five allergens. Patients sensitized to any of the minor allergens tended to be sensitized to multiple component allergens.

Among patients with HDM allergy, those with respiratory allergies appear to be sensitized to major allergens while those with AD are sensitized to a wider range of component allergens. The researchers suggest that Der f 11, Der f 13, Der f 32, and Der f Alt a 10 might be immunologic markers for AD, with potential implications for diagnosis and immunotherapy.

**COMMENT:** As we progress to more focused allergy testing with component-resolved diagnosis, one has to wonder what gains are to be made in the case of HDM sensitivity. This study demonstrates, not surprisingly, that most patients recognize Der f 1 and 2 and that these are the major epitopes in respiratory allergy. However, patients with AD demonstrated polysensitization to major as well as minor epitopes of Der F. These findings may aid in optimization of HDM immunotherapy.

J.J.O.

Park KH, Lee J, Lee J-Y, et al: Sensitization to various minor house dust mite allergens is greater in patients with atopic dermatitis than in those with respiratory allergic disease. Clin Exp Allergy. 2018;48:1050-1058.

Keywords: atopic dermatitis, component-resolved diagnosis, house dust mite allergy

## New Severe Asthma Questionnaire: Final Validation

Only 5% to 10% of asthmatic patients have severe asthma, but they account for a high share of asthma morbidity and costs. The authors previously reported the qualitative development and content validation of the new Severe Asthma Questionnaire (SAQ). This paper reports the final quantitative validation of the SAQ.

The SAQ is a 16-item questionnaire addressing various aspects of life related to severe asthma, producing a 0= to-100 SAQ score. It also includes a global question on overall quality of life, rated on a 100-point scale. In the present study, 160 patients completed the SAQ, along with the Asthma Control Test, Mini Asthma Quality of Life Questionnaire, and EQ-5D-5L quality of life scale.

Correlations were greater than 0.60, demonstrating convergent validity between the SAQ and other scales. Factor analysis of the 16 items showed construct validity. Both the SAQ and SAQ-global scores demonstrated discriminant validity, with the ability to discriminate between different levels of treatment. Both scores showed good test-retest reliability. With all outcome measures, there was a trend toward lower quality of life with higher oral corticosteroid doses.

The quantitative analysis completes the FDA-required procedures required for validation of the SAQ. The new tool appears useful for assessing the quality of life impact of symptoms and treatment for severe asthma. Further studies are needed to determine the SAQ's sensitivity to change and minimal clinically important difference.

**COMMENT:** The construct of the Severe Asthma Questionnaire allows for more discrete understanding of the impact on quality of life and symptoms in patients. The SAQ will help us better understand the burden of severe asthma and expand the indications for the use of alternative therapies (biologics and bronchial thermoplasty).

B.E.C.

Hyland ME, Jones RC, Lanario JW, Masoli M: The construction and validation of the Severe Asthma Questionnaire. Eur Respir J. 2018;52:1800618.

Keywords: asthma control, asthma (severe), quality of life

## Allergic Rhinitis Is Nothing to Sneeze At!

With a substantial impact on quality of life and work/school performance, allergic rhinitis (AR) is an important public health issue. The authors present a synthesis and critical analysis of previous research on the effects of AR on work productivity.

A systematic review identified 19 observational surveys and 9 interventional studies providing data on the work productivity impact of AR. On pooled analysis of studies using the validated Work Productivity and Activity Impairment questionnaire, AR was associated with approximately 36% impairment in productivity at work, ie, presenteeism. In contrast, AR-related work absenteeism was only about 4%. Productivity loss from AR was comparable to that of other chronic conditions, including depression, chronic obstructive pulmonary disease, irritable bowel syndrome, and arthritis.

Severity was a major determinant of the productivity loss from AR. Conjunctivitis and sleep disturbances had an impact beyond that associated with nasal symptoms. Randomized trial data showed that treatment with oral antihistamines and nasal sprays reduced productivity loss due to AR.

Available data suggest substantial work productivity losses associated with AR. Most of the burden is due to indirect costs from decreased productivity while at work; treatment with nonsedating antihistamines can reduce this impact. The researchers conclude their findings "provide an evidence-base to assist health care payers and policy makers implementing interventions to reduce the socioeconomic burden of AR."

**COMMENT:** This is a very important study for allergists, and a must-read for policymakers and payers. It demonstrates through systematic review that AR has a significant impact on work performance, with greater disease severity correlating with greater loss in productivity. Treatment of AR demonstrates improved work performance.

J.J.O.

Vandenplas O, Vinnikov D, Blanc PD ,et al: Impact of rhinitis on work productivity: a systematic review.

J Allergy Clin Immunol Pract. 2018;6:1274-1286.

Keywords: allergic rhinitis, productivity

## High QOL and Mental Health Burden of Atopic Dermatitis

Little is known about how atopic dermatitis (AD) and its severity influence the quality of life (QOL) impact of this chronic inflammatory disease. Data from a population-based study were used to examine the relationships between AD severity, associated comorbidity, and QOL.

The cross-sectional analysis included 602 adults meeting modified UK criteria for AD. Participants were drawn from the Atopic Dermatitis in America study, which found a 7.3% population prevalence of AD. Severity of AD was rated using a self-reported global score, the Patient-Oriented Eczema Measure (POEM), Patient-Oriented Scoring AD (PO-SCORAD), and the PO-SCORAD itch and sleep subscores. Two QOL scales were used: the Short Form-12 and the Dermatology Life Quality Index (DLQI).

More than one-fourth (25.8%) of adults with AD rated their overall health as fair to poor, compared to 15.8% of those without AD. Percentages reporting being somewhat to very dissatisfied with life were 16.7% and 11.4%, respectively. Adults with AD had lower weighted mean SF-12 physical (53.0 versus 53.5) and mental health subscores (45.9 versus 50.9) and a higher DLQI score (4.9 versus 1.1).

On multivariable analysis including adjustment for comorbid conditions, higher AD severity (global score, POEM, and PO-SCORAD) was associated with decreasing SF-12 physical and mental health scores and increasing DLQI score. Severe AD based on PO-SCORAD, POEM, or PO-SCORAD itch was associated with poor mental health (SF-12 mental health score of 34.7) and low skin-related QOL (DLQI score 24.7).

More than half of participants reported lifestyle limitations due to AD, while about 40% reported avoidance of social interactions and effects on activities. Itching was the most burdensome symptom, followed by skin dryness/scaling and redness/inflammation.

The study demonstrates the substantial QOL burden of AD. Especially at higher levels of severity, the QOL impact of AD is greater than for chronic conditions including heart disease and diabetes. The findings highlight the importance of assessing QOL in patients with AD, possibly with screening for mental health disturbances.

**COMMENT:** Atopic dermatitis is a challenge for patients; QOL is increasingly identified as important in patients with chronic illness. In the adult participants of this cross-sectional, population-based QOL study, even mild AD impaired QOL scores. As the severity of AD increased, QOL decreased. The presence of AD was associated with both avoidance of social interaction and limitation of the patients' lifestyle. Mental health scores in patients with moderate and severe AD were lower than in patients with conditions like diabetes, high blood pressure, and heart disease. Assessment of QOL is essential to identify patients at risk of mental disorders and to improve the overall lives of patients with AD.

V.H.-T.

Silverberg JI, Gelfand JM, Margolis DJ, et al: Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121:340-347.

Keywords: atopic dermatitis, mental health, quality of life

## Tips for Discontinuing Omalizumab in Chronic Urticaria

Omalizumab is a safe and effective treatment for chronic spontaneous urticaria (CSU), but symptoms often recur after treatment is withdrawn. Clinical trials have shown rapid and slow patterns of symptom return. This study evaluated potential predictors of the speed of symptom return after omalizumab discontinuation.

The study used data on omalizumab- and placebo-treated patients from two phase III randomized trials of omalizumab for CSU: 319 patients from ASTERIA I and 323 from ASTERIA II. A total of 746 variables were included in a least absolute shrinkage and selection operator model. Two variables were identified as predictors of symptom return pattern: baseline urticaria score over 7 days (UAS7) and early response to omalizumab, based on early area above the UAS7 curve. Patients with higher baseline UAS7 and a slower decrease in symptoms after starting treatment were more likely to have rapid return of symptoms after stopping omalizumab. The model's predictive accuracy was confirmed using data on 336 patients from the GLACIAL trial.

Baseline symptoms and initial response to omalizumab for CSU can accurately predict which patients will have rapid return of symptoms after treatment withdrawal. The authors suggest that these variables may provide a simple tool to improve clinical management of CSU.

**COMMENT:** It is often easier to determine when to begin a therapy versus when to stop it. This study demonstrates that in patients receiving omalizumab for chronic CSU, those with more significant baseline symptoms (higher UAS7) and those with slower improvement after starting omalizumab are more likely to suffer rapid symptom return with discontinuation.

J.J.O.

Ferrer M, Giménez-Arnau A, Saldana G, et al: Predicting chronic spontaneous urticaria symptom return after omalizumab treatment discontinuation: exploratory analysis. J Allergy Clin Immunol Pract. 2018;6:1191-1197.

Keywords: biologics, CSU, omalizumab

## Improved Understanding of Inflammatory Measures in Asthma

While both exhaled nitric oxide and blood eosinophils (B-Eos) are markers of type 2 inflammation, they may reflect different mechanisms. Population-based data were used to examine the association of simultaneously elevated exhaled NO and B-Eos with asthma-related outcomes, including the effects of differing cutoff points.

The study included 1,419 children and adults with asthma, age range 6 to 79 years, from the National Health and Nutrition Examination Survey 2007-12. All had available data on exhaled NO and B-Eos, as well as $FEV_1$. Simultaneous elevations of exhaled NO and B-Eos were evaluated for association with self-reported asthma events in the past year. Elevated exhaled NO was defined as 20 ppb or higher in children younger than 12 and 25 or higher for adolescents and adults; the study definition of elevated B-Eos was 300 cells/μL or higher. The analysis included the effects of differing cutoff points and age groups.

Compared to participants with normal levels of both biomarkers, those with simultaneous elevation of exhaled NO and B-Eos were about twice as likely to have an $FEV_1$ of less than 80% of predicted and wheeze disturbing sleep: odds ratio (OR) 2.15 and 1.88, respectively. However, there was no association with asthma attacks in the past year. On its own, elevated B-Eos was associated with increased asthma attacks and increased emergency department (ED) visits for asthma: OR 1.57 and 1.88, respectively.

Simultaneous elevations of exhaled NO and B-Eos are associated with reduced lung function and increased wheezing in children and adults with asthma. Elevated B-Eos is linked to increased asthma attacks and ED visits for asthma, independent of exhaled NO. These two biomarkers may provide complementary information in patients with asthma, including a possible link between active inflammation and impaired lung function.

**COMMENT:** This study examined whether exhaled NO and blood eosinophils are signals for different inflammatory pathways in asthma. While simultaneous elevations in both measures were correlated with reduced lung function, only elevated blood eosinophils were related to more severe asthma, asthma attacks, and emergency department visits. A significant limitation was the lack of testing for allergic sensitization, which may be a confounding variable of these measures. The utility of routine exhaled NO in severe asthma remains an enigma, especially as we try to justify its routine measurement.

J.J.O.

Mogensen I, Alving K, Jacinto T, et al: Simultaneously elevated FeNO and blood eosinophils relate to asthma morbidity in asthmatics from NHANES 2007-12. Clin Exp Allergy. 2018;48:935-943.

Keywords: asthma (adult), asthma (child), biomarkers, eosinophils, exhaled NO

## Does C1-INH Work Better in Certain Parts of the Body during HAE Attacks?

Human recombinant human C1 esterase inhibitor (C1-INH) is approved for treatment of acute hereditary angioedema (HAE) attacks. Attacks may occur at or spread to multiple anatomic locations. This study assessed time to response to C1-INH therapy in different attack regions.

Using data from two randomized trials, the analysis included data on 451 HAE attacks: 412 (in 127 patients) treated with recombinant human C1-INH, 50 IU/kg, and 39 (in 43 patients) treated with placebo. Abdominal and peripheral attacks were most common, followed by oro-facial-pharyngeal-laryngeal (OFPL) and urogenital attacks. Time from symptom relief to persistent reduction in visual analog severity score (20 mm or greater) was compared across anatomic locations.

Median time to the start of symptom relief in abdominal attacks was 60 minutes with C1-INH versus 240 minutes with placebo. For peripheral attacks, the medians were 105 versus 303 minutes, respectively. Based on smaller numbers, C1-INH was also faster for OFPL attacks, 64.5 versus 119 minutes; and urogenital attacks, 306 versus 320 minutes.

Recombinant human C1-INH is efficacious in hastening symptom resolution of HAE attacks in different anatomic regions. For all locations, median time to symptom relief is about 1 hour with C1-INH versus 4 hours with placebo; times are shortest for abdominal and longest for urogenital attacks.

**COMMENT:** We have recently seen increased treatment options for our patients with HAE. In this article, recombinant human C1-INH was efficacious in the treatment of HAE attacks, compared to placebo, in all attack locations. The shortest onset of symptom relief was in patients with abdominal symptoms, and the longest median time in urogenital attacks. Recurrence of HAE attacks was rare: in 93% of attacks, response was maintained at 72 hours. This is important information we can use to reassure our patients with HAE. The study evaluated a single dose of 50 IU/kg and included only moderate to severe HAE attacks presenting within 5 hours of symptom onset. The findings further support the efficacy of recombinant human C1-INH in the treatment of acute HAE attacks.

V.H.-T.

Baker JW, Bernstein JA, Harper JR, et al: Efficacy of recombinant human C1 esterase inhibitor across anatomic locations in acute hereditary angioedema attacks. Allergy Asthma Proc. 2018;39:359-354.

Keywords: C1 esterase inhibitor, hereditary angioedema

## REVIEWS OF NOTE

**COMMENT:** These authors present an excellent review of the many causes of cough, stressing the pathophysiology, diagnosis, and treatment.

J.J.O.

Mazzone SB, Chung KF, McGarvey L: The heterogeneity of chronic cough: a case for endotypes of cough hypersensitivity.
Lancet Respir Med. 2018;6:636-646.

**COMMENT:** This comprehensive review looked at multiple studies of minimally invasive biomarkers in patients with eosinophilic esophagitis (EoE). The positive news is that most studies were performed after 2014, supporting the recent increased interest in the disease. The most frequent biomarkers measured were blood-based. Further studies looking at both minimally invasive markers and assessment of clinical symptoms will likely provide useful information. Unfortunately, the different biomarkers do not distinguish EoE from other forms of atopic disease, although it is promising that many studies are investigating the disease from different angles. This reviewer is hopeful that the practicing allergist will have a minimally invasive option for our EoE patients in the not too distant future.

V.H.-T.

Hines BT, Rank MA, Wright BL, et al: Minimally invasive biomarker studies in eosinophilic esophagitis: a systematic review.
Ann Allergy Asthma Immunol. 2018;121:218-228.