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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

Cockroach Sensitization Linked to Lower Allergic Rhinitis Severity

If the Hygiene Hypothesis is correct, then early childhood exposure to microbes may influence the severity of allergic rhinitis (AR) symptoms. This question was addressed in a controlled study of adult AR patients, using cockroach sensitization as a proxy for childhood microbial exposure.

Twenty-one adults with AR and allergy to house dust mite made total symptom score (TSS) ratings in the natural setting and in response to repeated 3-hour exposures to mite allergen in an allergen challenge chamber (ACC). T-cell activation and transcriptomic profiles were tested in peripheral blood and nasal cells. Three groups of patients with pollen allergy (mountain cedar, oak, and ragweed) were studied during out-of-season ACC exposure to these pollens. In all groups, the relationship between cockroach skin prick test and AR symptom severity was assessed.

Among mite-positive patients, symptom scores were highest for those with any pollen sensitization but without cockroach sensitization, followed by those with pollen plus cockroach sensitization, then neither sensitization, then negative pollen but positive cockroach sensitization. Among patients sensitized to both mite and pollen, immune and inflammatory responses resolved faster in those who were also sensitized to cockroach.

In the pollen-allergic groups, patients positive for cockroach had lower symptom scores both in the ACC and during pollen season. For all ACC studies combined, cockroach-sensitized patients were 2.8 times more likely to be in the lower-TSS cluster.

The study finds that positive cockroach skin tests are associated with lower symptom severity in polysensitized patients with AR. Cockroach sensitization may be related to • • •

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The following journals have been selected as the primary focus of review in the preparation of materials within "AllergyWatch®".

- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Journal of Asthama
- 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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reduced T-cell activation and more rapid termination of allergen-induced immune/inflammatory responses. Balancing treatment groups by sensitization status might reduce confounding in AR clinical trials, the authors suggest.

COMMENT: This cleverly designed study provides evidence that the Hygiene Hypothesis is correct. Challenging AR patients with both pollen and dust mite sensitivities, the authors confirmed that patients with more than one sensitivity had greater symptoms. Interestingly, when the allergic subjects were also sensitive to cockroach antigen there was a muted response after challenge, both for symptoms and immunologic cellular responses. This response was not found in subjects with a negative skin test to cockroach. The authors suggest that sensitivity to cockroach is a "proxy" for early-life exposure to microorganisms or other environmental factors that could potentially shift to a Th1-favored response—consistent with the Hygiene Hypothesis.

S.M.F.

He W, Jimenez F, Martinez H, et al: Does cockroach sensitization reduce symptoms from dust mite and pollen allergies?
J Allergy Clin Immunol. 2015;136:658-666.

Translating LEAP to Clinical Practice–Consensus Statement

The recent "Learning Early About Peanut Allergy" (LEAP) study provided evidence that early introduction of peanut lowered the risk of peanut allergy in high-risk infants. A consensus communication by 10 international specialty associations provides interim guidance on early-life, complementary feeding practices to reduce peanut allergy risk.

In the LEAP study, UK infants at high risk of peanut allergy were assigned to early peanut introduction, between 4 and 11 months of age, or complete avoidance through age 5. The results suggested an absolute 14% reduction in the risk of challenge-confirmed peanut allergy, with a relative risk reduction of 80%.

This study provides level 1 evidence that early peanut introduction is safe and effective for selected high-risk infants, in countries where peanut allergy is prevalent. Evaluation by an allergist or other specialist may help to guide decision-making for children with early-onset atopic disease. The LEAP study provides no data on the risk or benefit of early peanut introduction in general or low-risk populations, or on alternative approaches to peanut introduction.

Without intervention by health care providers, high-risk infants may remain at risk of delayed introduction of solid and allergenic foods, because of the common belief that these foods may exacerbate eczema. More extensive guidelines from the National Institute of Allergy and Infectious Disease and the European Academy of Allergy and Clinical Immunology are expected next year.

COMMENT: Representatives from multiple organizations convened to create interim guidance on clinical decision making following the provocative results of the LEAP study. Introduction of peanut-containing products into the diets of "high-risk" infants early in life (between 4 and 11 months) in areas of high prevalence was recommended to prevent onset of peanut allergy. While acknowledging limitations of the LEAP study, the authors also suggested that for infants with early-onset atopic disease, such as severe eczema, or egg allergy in

the first 4 to 6 months of life, physicians should consider evaluation by an allergist or similarly trained physician regarding the appropriateness of early peanut introduction. The evaluation may include peanut skin-testing, in-office observed peanut ingestion, or both, as deemed appropriate after discussion with the family.

C.D.

Fleischer DM, Sicherer S, Greenhawt M, et al: Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants.

Pediatrics. 2015;136:600-604.

Predictors of Biphasic Anaphylactic Reactions

Because of the risk of potentially fatal biphasic reactions, prolonged monitoring has been recommended for children with anaphylaxis. Having validated clinical predictors of biphasic reactions would help to guide monitoring time. Incidence of and risk factors for biphasic reactions were analyzed in a large series of children with anaphylaxis.

The retrospective study included 484 patients meeting diagnostic criteria for anaphylaxis at two Canadian academic pediatric emergency departments (EDs). Seventy-one children developed biphasic reactions—an incidence of 14.7%. About 72% of children with biphasic reactions were boys; the median age was 6 years. About three-fourths of delayed reactions occurred before ED discharge, with a median time of 4.7 hours. For those occurring after ED discharge, the median was 18.5 hours.

Respiratory and/or cardiovascular manifestations occurred in 69% of delayed reactions. Epinephrine was used in only 49% of children with biphasic reactions. Independent risk factors include age 3 to 6 years, odds ratio (OR) 3.60; ED presentation more than 90 minutes after onset of the initial reaction, OR 2.58; wide pulse pressure at triage, OR 2.92; more than one dose of epinephrine to treat the initial reaction, OR 2.7; and ED administration of inhaled β-agonists, OR 2.39.

Biphasic reactions are relatively common among children with anaphylaxis seen in the ED, and seem to be related to the severity of the initial reaction. The identified risk factors need to be validated in a larger study before being used as clinical prediction rules.

COMMENT: Nearly 15% of pediatric anaphylaxis cases in the ED involve biphasic reactions. In this study, clinical predictors of biphasic reactions include delay in ED presentation longer than 90 minutes after onset of the original reaction, requirement for more than one dose of epinephrine, and use of β-agonists in the ED. The accompanying editorial (Ann Allergy Asthma Immunol. 2015;115:165) reminds us prompt epinephrine administration reduces the risk of biphasic reactions, and that nonadherence to carriage of epinephrine persists (46%) despite financial incentives. Unfortunately, there is no consensus on management of biphasic reactions.

C.C.R.

Alqurashi W, Stiell I, Chan K, et al: Epidemiology and clinical predictors of biphasic reactions in children with anaphylaxis. Ann Allergy Asthma Immunol. 2015;115:217-223.

FOCUS ON DIAGNOSTIC TESTING

How Likely Are Systemic Reactions to Skin Prick Tests?

Skin prick testing (SPT) is regarded as a safe procedure with a low rate of systemic reactions. Rates and characteristics of systemic reactions to SPT were analyzed in a large UK experience.

The prospective study included an estimated 31,000 patients undergoing SPT at a specialist allergy clinic between 2007 and 2013. Systemic reactions occurred in 24 patients, mean age 23.5 years. Seventeen affected patients were female, and twelve had asthma. The overall rate of systemic reactions was 0.077%.

Food allergens were implicated in 18 reactions, with peanut involved in 7 cases. Various aeroallergens were involved in 4 reactions, and wasp venom and Tazocin (piperacillin/tazobactam) in 1 case each. Three-fourths of cases were characterized by an SPT wheal larger than 8 mm. The patient who reacted to Tazocin developed anaphylaxis within minutes after SPT.

Although most systemic reactions were mild cutaneous reactions, ten were severe reactions with airway involvement or hypotension. All reactions responded to immediate treatment in the clinic.

This large experience finds systemic reactions to SPT occurring at a rate of 77 per 100,000 patients. Three-fourths of reactions involve foods, most commonly nuts. Although the overall risk is small, systemic reactions to SPT are associated with a history of severe reaction and large skin test reactions.

COMMENT: In the current environment where increasing numbers of non-allergists are performing SPT, this UK study described the incidence of systemic reactions. The greatest number of reactions was to foods, and peanuts in particular. There was some correlation with history of a severe reaction and large SPT size, which may help guide us to use caution in these patients. The authors remind us that SPT should be performed in a controlled setting where staff are trained to treat severe allergic reactions.

V.H.-T.

Sellaturay P, Nasser S, Ewan P: The incidence and features of systemic reactions to skin prick tests.

Ann Allergy Asthma Immunol. 2016;115:229-233.

Can Metabolomics Distinguish Asthma from COPD?

It can be challenging to distinguish asthma from chronic obstructive pulmonary disease (COPD) and other causes of chronic airflow limitation in outpatient care. This pilot study evaluated a metabolomic approach to differentiating between asthma and COPD.

Clinical data and urine samples for nuclear magnetic resonance spectroscopy (NMR) analysis were collected from adult patients meeting criteria for asthma and COPD before (133 patients) and after (38 patients) exacerbations. Samples were also obtained from 54 patients with stable asthma and 23 with stable COPD. Data on levels of 86 metabolites per urine sample were used to create a metabolomic model to differentiate between asthma and COPD. Accuracy was assessed by blinded analysis of metabolomic data from a subset of patients.

The metabolomic model showed unique differences in certain metabolites for patients with asthma versus COPD. Based on a final list of 16 metabolites, the model differentiated between the two diagnoses among patients seen in the emergency department and during post-exacerbation follow-up. On blinded assessment, the model was more than 90% accurate in diagnosing asthma and COPD.

This preliminary study provides proof-of-concept for the use of urine metabolites to distinguish between the diagnosis of asthma or COPD. A forthcoming analysis will focus on comparing metabolites for exacerbation. With further development, a metabolomic approach could provide a new approach to clinical diagnosis of asthma versus COPD.

COMMENT: Metabolomics is the study of metabolic and biochemical changes in a living subject, induced by disease or even a therapeutic intervention. This is a report of a proof-of-concept study using NMR on urine samples to differentiate patients with asthma from those with COPD, during both exacerbations and follow-up when clinically stable. The model could correctly differentiate blinded urine samples from asthmatics from those from COPD patients with 90% accuracy. Although the sensitivity was 92.6% the specificity was 79.2%, which is still quite impressive. The authors suggest that metabolomic analysis of body fluids might eventually be helpful in the diagnosis and monitoring of patients with airway disorders.

S.M.F.

Adamko DJ, Nair P, Mayers I, et al: Metabolomic profiling of asthma and chronic obstructive disease: a pilot study differentiating diseases.
J Allergy Clin Immunol. 2015;136:571-580.

Diagnostic Accuracy of FEV_1/FVC in Asthma

On spirometry, the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) is used to assess airflow obstruction. This study evaluated the accuracy of the FEV_1/FVC *z* score for asthma diagnosis, including the impact of differing pretest probabilities.

The researchers analyzed data on 1,698 asthma patients, drawn from four Asthma Clinical Research Center trials. The patients' mean age was 39 years; 71% were female and 61% white. Measured and predicted FEV_1/FVC values were assessed, and *z* scores calculated for each patient. The diagnostic accuracy of FEV_1/FVC was assessed at different asthma prevalences and *z* score thresholds.

Mean FEV_1 was 83.0% predicted, with a mean FEV_1/FVC of 0.74. In symptomatic patients with a 50% pretest probability of asthma, peak accuracy of 68% was obtained at a *z* score threshold of 1.0. This represented the 16th percentile, associated with a 6-percentage-point reduction from predicted FEV_1/FVC.

By comparison, in a screening population with a 5% pretest probability, the optimal *z* score was 2.0: the 2nd percentile, with a 12 percentage point reduction from the predicted ratio. Disease control markers did not alter the findings on diagnostic accuracy of FEV_1/FVC.

While a reduced FEV_1/FVC may provide supporting evidence of asthma, the diagnostic accuracy of this ratio depends on the pretest probability. Based on their findings, the authors suggest a more specific FEV_1/FVC threshold for populations with a low pretest probability of asthma, but a more sensitive threshold when pretest probability is high.

COMMENT: Can we get more information from spirometry for monitoring our asthmatic patients? The FEV_1/FVC ratio has been used to help distinguish between airflow obstruction vs restriction. These authors used statistical analysis in over 1600 patients from 4 different research centers to determine more accurate criteria for diagnosing airway limitations. Calculating the *z* scores (the difference between measured and predicted FEV_1/FVC divided by the standard deviation for the populations studied) can be helpful, but depends on the type of patients. In known asthmatics, a more sensitive *z* score threshold (1.0 SD) should be used. In contrast, for general population screening, a more specific threshold (2.0 SD) is appropriate for predicting airflow obstruction. The bottom line is that it is important to evaluate spirometry in context of the clinical setting.

S.M.F.

A Lambert, MB Drummond, Wei C, et al: Diagnostic accuracy of FEV_1/forced vital capacity ratio *z* scores in asthmatic patients.
J Allergy Clin Immunol. 2015;136:649-653.

Amoxicillin Skin Tests Aren't Helpful in Kids with Non-Immediate Reactions

Non-immediate reactions to beta-lactams in children are generally mild and self-limited. Previous studies have suggested that skin testing provides little information in • • •

such cases. This study compared the utility of skin testing versus drug provocation testing (DPT) in children with non-immediate reactions to amoxicillin.

The retrospective study included 352 children, mean age 7.5 years, with a history of non-immediate reactions to amoxicillin—occurring between 1 and 36 hours after exposure. All had mild to moderate skin reactions, mainly consisting of maculopapular exanthema or urticaria. A series of skin prick and intradermal testing with amoxicillin was performed. Four children were excluded because of a history of a severe reaction, and parents refused further testing in 11 children. The remaining 337 children proceeded to amoxicillin DPT.

The DPT results were positive in 25 patients—a rate of 7.4%. All reactions were mild and were managed at home. Amoxicillin challenge was positive in 2 out of 3 children who had positive skin tests and proceeded to DPT. The sensitivity of skin testing was 8.0%, with specificity of 99.7%.

Most children with mild, non-immediate skin reactions to amoxicillin do not react to DPT. The results support a strategy of immediate DPT, avoiding costly and complex skin test regimens. Children with positive reactions to DPT should not receive the antibiotic again.

COMMENT: Most children with rashes after beta-lactams are not drug-related. However, skin testing is often used to determine tolerance. These Italian investigators evaluated the utility of amoxicillin skin tests with delayed readings followed by DPT in 337 children with histories of benign, non-immediate reactions to amoxicillin. Skin tests were positive in only 3 children (0.8%), 1 of whom tolerated the challenge. Despite negative skin tests, 23 children had positive challenges, all similar to their initial reaction. The sensitivity of skin tests was only 8%. This study adds to existing literature indicating that proceeding directly to challenge is safe and effective for this group of patients, with about 1 in 14 reacting. Whether skin testing with penicillin reagents would have improved the sensitivity is unknown.

D.A.K.

Barni S, Sarti L, Pucci N, et al: Utility of skin testing in children with a history of non-immediate reactions to amoxicillin.
Clin Exp Allergy. 2015;45:1472-1474.

Do Patients with EoE Have Seasonal Variations?

Previous reports have suggested that aeroallergens may contribute to seasonal exacerbations of eosinophilic esophagitis (EoE). This study evaluated the links between esophageal eosinophilia, EoE, and aeroallergen sensitization/allergic rhinoconjunctivitis in children.

The study used a database of 1,180 patients diagnosed with EoE at a children's hospital clinic from 2006 through 2014. Of these, 160 children (14%) met criteria for possible aeroallergen-induced EoE, based on reported symptom variation and changes in biopsy findings during pollen season.

Aeroallergen-induced EoE was confirmed in 32 children, with maximal eosinophil counts of 53.25 eos/hpf during pollen season versus 10.25 eos/hpf out of season. Eighty-four percent of affected patients were boys. All had clinical evidence of allergic rhinitis, while 75% had a history of asthma. Twenty-two of the 32 patients also had known food-induced symptoms. Another 75 patients had seasonal variation in esophageal eosinophil counts that could not be attributed to seasonal aeroallergen exposure alone.

Seasonal variations of EoE and esophageal eosinophilia may be related to aeroallergen sensitization. Further studies are needed to characterize this group of patients with aeroallergen-induced EoE; information on the allergens to which patients are sensitized may have therapeutic implications.

COMMENT: Patients with EoE may have allergies to food, aeroallergens, or both. This study evaluated children with EoE who had seasonal exacerbations; most had flares during the spring. The results highlight the importance of identifying aeroallergen triggers, in addition to food allergens, for many patients. While further prospective studies are needed, the authors raise the question of whether aeroallergen immunotherapy may control eosinophilia in these patients. As increasing numbers of patients with EoE are identified, further studies will help to guide diagnosis and treatment.

V.H.-T.

Ram G, Lee J, Ott M, et al: Seasonal exacerbation of esophageal eosinophilia in children with eosinophilic esophagitis and allergic rhinitis.
Ann Allergy Asthma Immunol. 2015;224-228.

Out-of-Pocket Cost Affects Adherence to Allergen Immunotherapy!

Allergen immunotherapy is an effective treatment for allergic rhinitis, but many patients discontinue immunotherapy before the recommended 3- to 5-year duration. This study evaluated economic barriers and other factors contributing to premature discontinuation of allergen immunotherapy.

The researchers identified 555 patients with allergic rhinitis, asthma, or both who discontinued allergen immunotherapy before completing the full prescribed regimen. Sixty-two percent of patients were women, mean age 28.6 years; and 38% men, mean age 34.8 years. When they stopped immunotherapy, 68% of patients were in the maintenance phase and 32% in the escalation phase.

Insurance copayments for allergen injections or extract were the most common reason for premature discontinuation of immunotherapy, cited by 40% of patients. This was followed by travel inconvenience, mentioned by 15% of patients. Less common factors included change of residence, other health problems, perceived ineffectiveness, or perceived lack of need to continue treatment. Local adverse effects were mentioned by 1% of patients and systemic reactions by 0.5%. Nearly one-fourth of patients gave no reason for stopping treatment.

The need for insurance copayments seems to be the most common reason for premature discontinuation of subcutaneous allergen immunotherapy. Full insurance coverage for allergy shots might lead to better patient outcomes, and likely to lower overall costs.

COMMENT: In this day of increasing fiscal responsibility for the patient, ways to improve patient adherence to therapy should include addressing third-party payer coverage of common procedures and treatments. This study looked at patients with allergic rhinitis and/or asthma who discontinued subcutaneous allergen immunotherapy before the recommended 3- to 5-year duration. Stopping immunotherapy early increased as patients' responsibility to pay for the treatment increased. The cost factor was the most likely reason for early termination of the treatment. The authors suggest that improved coverage of allergen immunotherapy will improve adherence as well as quality of life for patients with asthma and/or allergic rhinitis, thereby affecting overall costs related to the disease.

V.H.-T.

Vaswani R, Garg A, Parikh L, Vaswani S: Non-adherence to subcutaneous allergen immunotherapy: inadequate health insurance coverage is the leading cause.
Ann Allergy Asthma Immunol. 2015;115:241-243.

Response to Asthma Treatment Differs by Age

It's still unclear how asthma physiology, symptoms, and response to treatment are affected by age and sex. A large body of data from Asthma Clinical Research Network (ACRN) was analyzed to assess the impact of age and sex on response to treatments for mild to moderate asthma.

The researchers analyzed high-quality data on 1,200 unique patients enrolled in ten influential ACRN treatment trials. The median age was 30.4 years; 56.7% of patients were women. The effects of age and sex on asthma phenotypes and treatment failure rates were assessed.

The treatment failure rate was 17.3% for patients aged 30 years or older, compared to 10.3% for younger patients: odds ratio 1.82. Within the older group, risk increased with age: OR 1.02 per year and 1.13 per 5 years. Treatment failure was also associated with lower lung function and longer duration of asthma. Among patients aged 30 or older, those taking controller medications had a higher treatment failure rate.

On analysis of specific treatments, the risk of failure on inhaled corticosteroids also increased with age: OR 1.03 per year. Despite a somewhat higher FEV_1 in women (84.5% vs 81.1% predicted), asthma control was similar between the sexes. The overall treatment failure rate was not significantly different by sex: 15.2% for women and 11.7% for men. There was a trend toward increased rescue medication use by women: 36.2% vs 13.1%.

This large analysis of data from asthma clinical trials finds a higher risk of treatment failure for patients aged 30 years or older, with increasing risk at older ages. Further studies are needed to determine whether older patients may benefit from different treatment approaches. The lack of difference by sex is surprising, in light of previous observational studies.

COMMENT: This evaluation of several ACRN studies that were conducted from 1993 to 2003 gives us insight regarding the increased risk of treatment failure with age. The unexpected finding was that there were no differences in gender. These observations resonate with our clinical intuition, but the factors associated with lack of treatment response may be more complicated. Economic factors may lead to inability to maintain medication adherence in the older population.

B.E.C.

Dunn RM, Lehman E, Chinchilli VM, et al: Impact of age and sex on response to asthma therapy.
Am J Respir Crit Care Med. 2015;192:551-558.

Paving the Way for a National Nicotine Reduction Policy

Reducing the nicotine level of cigarettes may be a promising approach to making smoking less addictive. Only a relatively few, small studies have evaluated the effects of this approach. A six-week trial was performed to compare the effects of smoking cigarettes with varying levels of nicotine.

The randomized controlled trial included 840 adult cigarette smokers with no current interest in quitting. They were randomly assigned to smoke their usual brand of cigarettes or one of six investigational products, with nicotine content ranging from 0.4 to 15.8 mg/g. The main outcome of interest was the number of cigarettes smoked per day at week 6.

Seven hundred eighty smokers completed the trial. Average number of cigarettes smoked per day was significantly lower for subjects assigned to reduced-nicotine cigarettes: 15 to 17 per day at nicotine levels of 0.4 to 2.4 mg/g, compared with 21 to 22 per day for those receiving 15.8 mg/g cigarettes or their usual brand. There was no significant reduction for smokers assigned to cigarettes containing 5.2 mg/g of nicotine. The lower-nicotine cigarettes were associated with less nicotine exposure and dependence and fewer cravings during abstinence from smoking, with no difference in expired carbon monoxide or total puff volume.

Reduced-nicotine cigarettes can reduce nicotine exposure and dependence, compared to standard cigarettes. This may be a useful strategy to reduce smoking, without causing nicotine withdrawal or compensatory smoking.

COMMENT: In 2009, legislation was passed that permitted reduction in levels of nicotine, tobacco's primary addictive agent. A systematic but slow reduction of nicotine content was proposed, in an attempt to wean smokers off cigarettes, while minimizing hardship from withdrawal.

Reassuringly, this randomized trial of 840 adults using low-nicotine cigarettes—as low as 0.4 mg of nicotine/g of tobacco vs 15.8 mg/g for commercial cigarettes—suggests that reduction in a much shorter time frame may be possible. Of course, there are many variables that impact the end-goal of combating the devastating health consequences of combustible tobacco use, but this is a promising start! (See also the commentary by Fiore and Baker:
N Engl J Med 2015; 373:1289-1291.)

C.D.

Donny EC, Denlinger RL, Tidey JW, et al: Randomized trial of reduced-nicotine standards for cigarettes.
N Engl J Med. 2015;373:1340-1349.

New Data on Air Pollution and Childhood Wheeze and Asthma

It's still unclear how long-term exposure to traffic-related air pollution (TRAP) affects the development of asthma. The role of the timing and duration of TRAP exposure is a key question. This issue was addressed using data from a prospective birth cohort study with long-term follow-up.

The analysis included 617 children from the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), each with at least one atopic parent. Clinical follow-up from age 1 to 7 was used to assess parent-reported wheezing, along with wheezing phenotypes and childhood asthma. A land-use regression model was used to estimate TRAP exposure, which was analyzed for associated with wheezing and asthma outcomes.

Complete data were available for 589 children. Those with higher TRAP exposure at birth were at increased risk of both the transient and persistent wheezing phenotypes: adjusted odds ratio (OR) 1.64 and 2.31, respectively. High TRAP exposure from birth to age 1 and from age 1 to 2 was also associated with an increased risk of persistent wheezing: OR 2.26 and 1.89, respectively. Asthma risk was significantly increased only for those children with high average exposure from birth through age 7: OR 1.71

High exposure to TRAP during infancy is linked to an increased risk of persistent wheezing. For childhood asthma, long-term exposure to high levels of TRAP is the only significant association. The authors discuss the implications for understanding how air pollution affects asthma pathophysiology.

COMMENT: This is another publication from the very important, longitudinal CCAAPS. The results show that early-life and persistent exposure to TRAP is associated with not only the incidence of wheezing but also the persistence of asthma. The results complement the Southern California Children's Health Study, which showed impaired lung growth and asthma incidence associated with air pollution exposures that occur later in childhood. This is an extremely important public health observation worthy of our attention.

B.E.C.

Brunst KJ, Ryan PH, Brokamp C, et al: Timing and duration of traffic-related air pollution exposure and the risk for childhood wheeze and asthma.
Am J Respir Crit Care Med. 2015;192:421-427.

Continuing Conundrum: Causes of CAP in Adults

Previous estimates of the US incidence of community-acquired pneumonia (CAP) predate the availability of the pneumococcal conjugate vaccine and recent advances in molecular and antigen-based testing. This paper presents updated estimates of the incidence and microbiologic causes of CAP requiring hospitalization in US adults.

The "Etiology of Pneumonia in the Community" (EPIC) study used active surveillance to identify adults hospitalized for CAP at five hospitals in Chicago and Nashville from 2010 to 2012. The study included radiographic confirmation and culture, serologic testing, antigen testing, and molecular diagnostic techniques.

Of 3634 eligible patients, 2,488 were enrolled in the study. Of these, 2,320 (93%) had radiographic evidence of pneumonia. The patients' median age was 57 years; 21% required ICU care and 2% died. A pathogen was detected in 38% of 2,259 patients with specimens available for both bacterial and viral testing. One or more viruses were detected in 23% of patients, bacteria in 11%, bacteria and viruses in 3%, and fungi or mycobacteria in 1%.

The CAP incidence was 24.8 cases per 10,000 adults per year. Incidence increased to 63.0 cases per 10,000 in people aged 65 to 79, and 164.3 per 10,000 in those aged 80 or older. Incidence increased with age for each identified pathogen.

The study confirms the high burden of CAP in the United States, especially at the oldest ages. No pathogen is identified in most cases; the predominance of respiratory viruses in this study may partly reflect the benefits of bacterial vaccines.

COMMENT: We are well aware of the considerable burden of CAP requiring hospitalization in adults. It is an even bigger problem in older adults, with an incidence ranging up to 25 times higher in adults 80 years of age or older, compared to those aged 18 to 49 years. Unfortunately, despite concerted efforts to use newer, more sensitive and specific diagnostic methods, pathogens are detected in a minority of the patients—38% in this large population-based study. Of note, the most common pathogens were human rhinovirus (9%), influenza virus (6%), and *Streptococcus pneumoniae* (5%). These data shout out for improving the coverage and effectiveness of the currently recommended vaccines (eg, influenza and pneumococcal vaccines), and for developing better diagnostic tests to detect etiologic agents causing pneumonia.

C.D.

Jain S, Self WH, Wunderink RG, et al: Community-acquired pneumonia requiring hospitalization among US adults.
N Engl J Med. 2015;373:415-427.

Increased Herpes Zoster Risk in Asthmatic Children

A previous study reported an increased risk of vaccine-preventable diseases, including herpes zoster (HZ), among children with asthma. This population-based study looked at whether this association was consistent across differing criteria for childhood asthma.

The study included 221 children and adolescents with HZ in Olmsted County, Minn., between 1996 and 2001. These cases—mean age 9.7 years and 53% female—were matched for age and sex to 238 controls with no history of HZ. Asthma status was assessed based on the Asthma Predictive Index (API) criteria, for the first 3 years of life (original API) and beyond; the predetermined asthma criteria (PAC) used in a previous study; and documented physician diagnosis of asthma.

Based on the original API, asthma was already present before the HZ index date for 7.7% of cases versus 3.4% of controls. After controlling for varicella vaccine history and atopic status, the odds ratio for HZ in children with asthma defined by the API was 2.56. The association was consistent for the other definitions evaluated as well. Risk was consistently higher for children with atopy and lower for those with varicella vaccination.

Using different definitions of asthma, this study confirms the association between HZ and asthma in pediatric patients. Asthma status may be an important consideration in HZ vaccine studies; the mechanisms of the association remain to be determined.

COMMENT: Asthma has been associated with increased risk of infections. This study looked at a group of pediatric patients with HZ with and without asthma, using different criteria to define asthma. Atopic patients were at increased risk of HZ, and patients with asthma had younger age of HZ onset. This study reminds us to keep HZ in the differential diagnosis of asthmatic children, in order to ensure early detection and treatment.

V.H.-T.

Wi Ch-I, Kim B-S, Mehra S, et al: Risk of herpes zoster in children with asthma.
Allergy Asthma Proc. 2015;36:372-378.

Bariatric Surgery Reduces Asthma Exacerbations in Adults

Studies have reported only modest improvements in asthma control after the typically modest weight loss achieved by nonsurgical interventions. This study compared asthma exacerbation rates in a large series of patients undergoing bariatric surgery.

Using databases from three states, the researchers identified 2,261 obese asthma patients, aged 18 to 54 years, who underwent bariatric surgery. Rates of emergency department visits and hospitalizations for asthma were compared for two years before through two years after bariatric surgery.

During the reference period of 13 to 24 months before bariatric surgery, 22.0% of patients had an ED visit or hospitalization for asthma. This figure was not significantly different, 21.7%, for the 12-month period before surgery. However, the risk of events was 10.9% during the 12 months after bariatric surgery, and the same during the following year. For both periods, the odds ratio for asthma exacerbations was 0.42. By comparison, exacerbation risk was unchanged after non-bariatric surgery in obese asthma patients.

For obese patients with asthma, the rate of exacerbations leading to ED visits or hospital admission decreases by about half after bariatric surgery. The findings provide new evidence that large and sustained weight loss reduces asthma morbidity.

COMMENT: It is well known that obese patients have more problems with asthma control than nonobese asthmatics. These authors report data from three large state reported databases to compare ED and hospitalization rates for asthma exacerbations in the years before and after bariatric surgery. Although the study makes a variety of statistical assumptions, these compelling data show that post-bariatric surgery the risk for asthma exacerbation was reduced by one-half. These data might be helpful in discussions with our asthmatic patients with morbid obesity who are contemplating bariatric surgery.

S.M.F.

Hasegawa K, Tsugawa Y, Chang Y, Camargo CA Jr: Risk of an asthma exacerbation after bariatric surgery in adults.
J Allergy Clin Immunol. 2015;136:288-294.

Hospital Admissions for Food Allergy Reactions in Teens Are on the Rise

Data from developed countries around the world suggest increasing prevalences of food allergy and anaphylaxis in children. An Australian hospital database was used to analyze long-term trends in anaphylaxis admissions.

Using the Australian National Hospital Morbidity Database, the researchers compared rates of hospitalization for anaphylaxis for two 7-year periods: 2005-06 to 2011-12 vs 1998-99 to 2004-05. From 2005-06 to 2011-12, the overall population rate of admission for food-related anaphylaxis increased by 1.5-fold: from 5.6 to 8.2 per 10^5 population per year. The numbers were highest in children aged 0 to 4 years: from 21.7 to 30.3 per 10^5 population per year, a 1.4-fold increase. However, the proportional increase was 2.1-fold for children and adolescents aged 5 to 14: from 5.8 to 12.1 per 10^5 population per year.

Smaller increases of 1.5- and 1.3-fold were noted in the 15 to 29 and 30 and older age groups, respectively. The modeled year-on-year increase in admissions for food-

related anaphylaxis in all age groups increased from 0.35 per 10^5 population in 1998-99, to 0.49 in 2004-05, to 0.63 in 2011-12. The age-specific changes were significant only for the 5-to-14 and 15-to-29 age groups.

The data show continued increases in food-related anaphylaxis in Australia since the mid-2000s. While children up to age 4 account for most cases, the rate of increase might be fastest in those aged 5 to 14. This suggests that the burden is shifting to older adolescents and young adults, who are at highest risk for fatal anaphylaxis.

COMMENT: The increase in anaphylaxis admissions has been previously reported, but these data from an Australian national database confirm a steady increase. They show a 1.7-fold rise in the 7 years between 1998-99 to 2004-05, with a further 1.5 fold increase between 2005-06 and 2011-12. The interesting findings are that the largest increase was in anaphylaxis hospitalizations due to food allergies in children—particularly older children and teenagers. This has implications for re-emphasizing the importance of accurate diagnosis and proper education in this age group.

S.M.F.

Mullins RJ, Dear KBG, Tang MLK: Time trends in Australian hospital anaphylaxis admissions in 1998-1999 to 2011-2012.

J Allergy Clin Immunol. 2015;136:365-375.

Infliximab Adverse Reactions and Response to Desensitization

The monoclonal antibody infliximab has become an important treatment for inflammatory bowel disease (IBD) and other diagnoses. Past studies have reported nearly a 10% rate of acute infusion reactions to infliximab, with a 1% rate of serious reactions. The authors review their experience with adverse reactions to infliximab and the outcomes of desensitization.

The single-center study included 336 patients with IBD treated with infliximab from 2000 to 2014. Systemic adverse reactions to infliximab occurred in 30 patients, a rate of 8.9%. These reactions led to discontinuation of infliximab in 15 patients. Another 3 patients continued infliximab with pretreatment and/or a decreased infusion rate.

Infliximab desensitization was carried out in 12 patients, starting at a dilution of 0.1 mg/mL, increasing to the full treatment dose over 4 to 6 hours. This protocol was successful in all patients, who were able to receive the recommended therapeutic dose of infliximab.

Desensitization can allow continuation of therapy in IBD patients with systemic adverse reactions to infliximab therapy. Further study in larger numbers of patients is needed to demonstrate the safety and efficacy of this approach.

COMMENT: Infliximab is a chimeric IgG1 monoclonal antibody against tumor necrosis factor, and as such is an increasingly employed therapy in IBD, rheumatoid arthritis, and psoriatic arthritis. The authors review their experience with 68 completed desensitizations to infliximab. Their protocol should prove useful for future desensitizations by the allergist community.

C.C.R.

Mourad AA, Boktor MN, Yilmaz-Demirdag Y, Bahna SL: Adverse reactions to infliximab and the outcome of desensitization.

Ann Allergy Asthma Immunol. 2015;115:143-146.

Long-Term Omalizumab for Refractory Chronic Urticaria

Last year, the FDA approved omalizumab for treatment of refractory chronic urticaria (CU). The authors review their experience with long-term therapy with omalizumab for patients with refractory CU.

From 2005 to 2015, a trial of omalizumab was initiated for 17 patients with well-defined refractory CU. Ten patients responded to treatment: 5 men and 5 women, median age 44 years and median duration of CU 4 years. Eight patients had complete resolution of symptoms after reaching their optimal regimen, with a median treatment duration of 37 months. None of the responders required upward titration of dosage, increased treatment frequency, or add-on therapy. Symptoms recurred during tapering in 5 out of 8 patients, requiring omalizumab to be restarted. One patient required no maintenance therapy after successfully discontinuing omalizumab.

This small experience supports the safety and efficacy of long-term omalizumab therapy for some patients with refractory CU. Because spontaneous remission is possible, weaning should be attempted periodically. Larger, prospective studies are needed.

COMMENT: Patients with CU can be difficult to treat, and quality of life is an area of concern for many. This study looked at patients with refractory CU and treatment with omalizumab over a long-term course. The authors found this was a safe and effective option for many patients. Their recommendations include an attempt to discontinue omalizumab, as one patient had disease remission, and others tolerated resumption of the treatment. Monoclonal anti-IgE treatment appears to be an important option to consider in CU patients, who can be so difficult to treat.

V.H.-T.

Har D, Patel S, Khan DA, et al: Outcomes of using omalizumab for more than 1 year in refractory chronic urticaria.

Ann Allergy Asthma Immunol. 2015;115:126-129.

Chronic Bronchitis Patients Feel Worse than those with Emphysema!

Among patients with chronic obstructive pulmonary disease (COPD), those with emphysema and chronic airflow obstruction are thought to have lower quality of life • • •

(QOL) than those with chronic bronchitis. Data from two COPD cohort studies were used to compare QOL for these two groups.

The researchers analyzed data from the Lovelace Smokers' Cohort (LSC) and the COPD Gene Cohort (COPDGene). Patients reporting cough at least 3 months out of the year with a postbronchodilator FEV_1/FVC of 70% or greater were considered to have chronic bronchitis. Those with an FEV_1/FVC of less than 70% without evidence of chronic bronchitis were considered to have chronic airflow obstruction only. The St George's Respiratory Questionnaire (SGRQ) and 36-Item Short Form Health Survey (SF-36) were used to assess QOL.

From the LSC, the study included 341 patients with chronic bronchitis and 302 with chronic airflow obstruction. Patients with chronic bronchitis were younger, had a higher BMI, and less smoking history. The SGRQ Activity score and the SF-36 Role Physical and Physical Functioning scores were similar between groups.

However, the patients with chronic bronchitis had significantly worse SGRQ Symptoms and Impact scores, as well as lower scores for social and emotional measures on the SF-36. The differences remained significant after adjustment for the covariates of age, sex, smoking history, and FEV_1. The findings were validated in the COPDGene cohort of 523 patients with chronic bronchitis and 2,208 with chronic airflow obstruction.

Contrary to assumption, QOL may be worse for COPD patients with chronic bronchitis only, compared to those with chronic airflow obstruction. The difference is significant for symptoms and mental well-being, after adjustment for other factors. Despite their symptom differences, the two groups have similar physical activity.

COMMENT: It has always been assumed that patients with COPD with airflow obstruction would have lower QOL than those with chronic bronchitis and preserved lung function. This study from a New Mexico registry compared patients with chronic bronchitis (productive cough at least 3 months per year) with no airflow obstruction to other COPD patients with airflow obstruction. Despite having higher emphysema scores on CT, the patients with airflow obstruction had higher QOL and less symptoms than those with chronic bronchitis! The findings could not be attributed to the cough alone. Current COPD guidelines may not adequately address these more symptomatic patients.

D.A.K.

Meek PM, Petersen H, Washko GR, et al: Chronic bronchitis is associated with worse symptoms and quality of life than chronic airflow obstruction.

Chest. 2015;148:408-416.

Sleeping on Animal Fur–A New Way to Prevent Asthma?

Early-life exposures related to "growing up on a farm" may reduce the risk of childhood allergies and asthma. This study evaluated long-term immune and allergic disease outcomes associated with sleeping on animal fur during infancy.

The analysis included 2,441 children participating in a German birth cohort study. Among factors, parents reported data on whether the children slept on animal fur (eg, sheepskin) during the first 3 months of life. Fifty-five percent of the children did sleep on animal fur during infancy.

On adjusted analysis, children who slept on animal fur had lower rates of recurrent early wheezing at age 4 and current asthma at age 6: odds ratio 0.75 and 0.56, respectively. This group of children also had persistent stimulation of the interferon-γ response up to age 3. The associations were independent of the higher exposure to bacterial endotoxin in mattress dust for children who slept on fur.

Infants who sleep on animal fur may be at lower risk of asthma later in childhood, possibly associated with stimulated Th1 reactivity. With further study, this might be a new way to create environments associated with higher microbial exposure for infants.

COMMENT: This interesting study from Germany is a "proxy" for previous reports suggesting that early exposure to farm animals, through its effects on innate immune function, is protective against the development of asthma. Although sleeping on animal fur is not a common practice in the United States, these observations support the protective effects of early endotoxin exposure, probably mediated through the microbiome.

B.E.C.

Tischer C, Standl M, Lehman I, et al: Sleeping on animal fur is related to asthma outcomes in later childhood.

Eur Respir J. 2015;46:107-114.

New Tool for Assessing VCD Symptoms

Because it involves adduction of the vocal cords during inspiration, vocal cord dysfunction (VCD) is easily misdiagnosed as asthma. The authors developed and tested a clinical tool for monitoring symptoms and response to treatment in patients with VCD.

Symptoms of VCD were elicited from focus groups with patients and clinicians, then validated and ranked for importance. Twelve items were included in a VCD questionnaire, with each item scored on a five-point Likert scale (range 12 to 60). In a validation study, the questionnaire performed very well in differentiating 31 patients with endoscopically confirmed VCD from 29 asthma patients and 14 healthy controls.

The questionnaire also reflected improvement after treatment in 20 new patients with VCD: median score improved from 50.5 to 35.0. The minimal important difference in VCD questionnaire score was 4 points, corresponding to a patient rating of "minimally better."

The new questionnaire appears useful for assessing change in symptoms in patients with VCD. With fur-

ther study, this tool will be useful in refining and evaluating new treatments for this condition.

COMMENT: Fowler and colleagues provide us with a valid and responsive tool that can discriminate between VCD and asthma. This tool will likely prove quite useful for future research in the diagnosis and treatment of VCD.

J.J.O.

Fowler SJ, Thurston A, Chesworth B, et al: The VCDQ—a questionnaire for symptom monitoring in vocal cord dysfunction.
Clin Exp Allergy. 2015;45:1406-1411.

Inflammatory Mediators in CRS and AERD: New Data

Questions remain about the mechanisms of chronic rhinosinusitis (CRS) with and without nasal polyps versus aspirin-exacerbated respiratory disease (AERD). This study compared the inflammatory profiles of CRS with and without nasal polyps, and examined whether the differences between CRS with polyps and AERD reflect differences in inflammatory mediators.

Specimens of polyps from patients with CRS with nasal polyps shows increased expression of interleukin (IL)-5, IL-13, eotaxin-2, and monocyte chemoattractant protein (MCP)-4, compared to tissues from patients with CRS without polyps and controls. All groups of CRS patients showed similarly low interferon-γ mRNA or protein expression. Nasal polyps from AERD patients showed increased expression of eosinophil cationic protein, granulocyte-macrophage colony-stimulating factor, and MCP, compared to tissues from patients with CRS with nasal polyps. The AERD tissues also showed decreased gene expression of tissue plasminogen activator. Even though AERD was associated with higher eosinophilia, there was no increase in type 2 mediator protein levels.

The findings suggest that a type 2 inflammatory environment predominates in CRS with nasal polyps, but do not support a classic type 1 milieu in CRS without nasal polyps. Although AERD is associated with elevated ECP levels compared to CRS without nasal polyps, there are no associated elevations in traditional type 2 inflammatory mediators. Instead, the study implicates other inflammatory mediators in the pathogenesis of AERD, which may lead to new treatment strategies.

COMMENT: This very important study gives us significant insight into the mechanisms of CRS. As expected with nasal polyps, there is a robust expression of high-Th2 signature cytokines. The unexpected finding was that CRS without nasal polyps is likely not an adaptive T effector-driven disorder. Rather, it may result in a breakdown of innate immune function—leading to the spectrum of recurrent episodes of acute illness and extensive tissue remodeling, and thus to persistent symptoms. The authors enumerate factors that drive AERD in patients with CRS and nasal polyps, which may lead to advances in therapy for this refractory group of patients. See the accompanying editorial by Larry Borish: Am J Respir Crit Care Med. 2015;192:647-648.

B.E.C.

Stevens WW, Ocampo CJ, Berdnikovs S, et al: Cytokines in chronic rhinosinusitis: role in eosinphilia and aspirin-exacerbated respiratory disease.
Am J Respir Crit Care Med. 2015;192: 682-694.

Step-Down Therapy for Asthma: Longer-Term, 'Real World' Results

Current guidelines recommend step-down therapy for patients whose asthma is stable for at least 3 months. Yet the evidence for this recommendation is weak, with few data on long-term outcomes. This longitudinal study assessed the 24-month outcomes of stepping-down asthma medications, including the role of duration of asthma stability.

Using a large US claims database, the researchers analyzed time to events in 26,292 patients who stepped-down their asthma controller medications. A step-down event was defined as a 50% or greater reduction in days of supplied controller medications from one 4-month interval to the next, whether or not guided by a healthcare professional. Patients with no evidence of exacerbations and less than two claims for rescue inhalers were considered to have stable asthma, before as well as after step-down.

Thirty-two percent of patients had an asthma exacerbation during the 24-month period after stepping-down their controller medications. The rate of exacerbations leading to an ED visit or hospitalization was only 7%. Exacerbation risk was lower for patients with a longer period of asthma stability before step-down. Over 24 months, exacerbation rates were 44% for patients with less than 4 months' stability, 34% for 4 to 7 months, 30% for 8 to 11 months, and 21% for 12 months or longer.

This large claims-based study finds a 32% rate of exacerbations in the two years after stepping-down asthma controller medications. This risk appears to be greatly affected by the duration of asthma stability before step-down. Further studies should distinguish patients who step-down under the guidance of a healthcare professional from those who have a lapse in treatment adherence.

COMMENT: Step-down therapy is a key part of asthma guidelines, yet evidence is fairly limited on the best approach. This study looked at a health claims database and followed almost 27,000 asthmatics on controllers who had reductions in their medications over a 2-year period. Not surprisingly, those who remained on their entry controller therapy for a longer period of time had fewer exacerbations than those with shorter periods. An important limitation is that the reason for fewer fills of controllers (step-down) was unknown; thus nonadherence versus recommendations by health care providers to truly step-down could not be discerned.

D.A.K.

Rank MA, Johnson R, Branda M, et al: Long-term outcomes after stepping down asthma controller medications: a claims-based, time-to-event analysis.
Chest. 2015;148:630-639.

Near-Fatal Asthma–Who Is Likely To Have It?

Near-fatal asthma (NFA) is a heterogeneous condition that can occur in patients with several different profiles. This study used cluster analysis to identify differing phenotypes of NFA.

Of 179 patients with episodes of NFA at 33 Spanish hospitals over 2 years, 84 had complete data on 44 variables for cluster analysis. Cluster 1 included 33 patients, mean age 59.2 years. They had a high prevalence of severe persistent asthma and high rates of asthma medication use. Nearly half had at least 1 previous episode of NFA.

Cluster 2 included 28 patients, mean age 49.9 years, about half of whom were receiving inhaled corticosteroids. On arrival at the hospital, 82% of cluster 2 patients had impaired consciousness and 68% had respiratory arrest. Cluster 3 included 23 patients, mean age 42.4 years, with low rates of anti-inflammatory therapy and medical monitoring. This cluster had a relatively high rate of sensitization to allergens previously linked to NFA, such as *Alternaria alternata* and soybeans.

Three separate phenotypes of NFA are identified, with differences in age, asthma severity and treatment, and other characteristics. The findings may help in developing specific treatment strategies for the differing profiles of NFA.

COMMENT: The authors report three distinct clusters of NFA: older patients with severe asthma; patients with history of respiratory arrest, impaired consciousness, and/or need for mechanical ventilation; and younger patients receiving inadequate anti-inflammatory therapy with frequent sensitization to *A. alternata*. Certainly, we have long strived to identify the third cluster, as intervention in this group can easily prevent asthma exacerbations. The other two clusters reinforce the need to develop newer classes of medicines as well as better tools to aid in the earlier identification of exacerbations.

J.J.O.

Serrano-Pariente J, Rodrigo G, Fiz JA, et al: Identification and characterization of near-fatal asthma phenotypes by cluster analysis.
Allergy. 2015;70:1139-1147.

REVIEWS OF NOTE

COMMENT: This Practice Parameter provides both an evidence-based approach to the diagnosis and management of immune deficiencies and a series of algorithms on how to arrive at the appropriate diagnosis. It is a "must have" reference for allergy specialists.

S.A.T.

Bonilla, MD FA, Khan DA, Ballas ZK, et al: Practice parameter for the diagnosis and management of primary immunodeficiency.
J Allergy Clin Immunol. 2015; 136:1186-1205.e78.

COMMENT: This extremely well-articulated article translates guidelines into hands-on clinical care advice that primary care providers can give their patients with atopic dermatitis. My favorite take-home point is the concept of finger-tip unit (FTU) to help quantify for the child/adult the amount of ointment per body surface area that would be appropriate for them to use.

C.D.

Eichenfield LF, Boguniewicz M, Simpson EL, et al: Translating atopic dermatitis management guidelines into practice for primary care providers.
Pediatrics. 2015;136:554-565.

COMMENT: Does my patient have asthma? Does my patient have COPD? Or does my patient have both asthma and COPD? If you are not sure, then this excellent review on the emerging "asthma-COPD overlap syndrome" (ACOS), a condition where a person has clinical features of both asthma and COPD, is a must-read for you!

C.D.

Postma DS, Rabe KF: The asthma-COPD overlap syndrome.
N Engl J Med. 2015;373:1241-1249.

COMMENT: This document was assembled by a task force of the European Academy of Allergy and Clinical Immunology to examine the literature regarding contraindications of immunotherapy. The task force developed recommendations regarding the use of immunotherapy to venom and aeroallergens in patients with cardiac disease, autoimmune disease, immunodeficiency, and in patients requiring angiotensin-converting enzyme inhibitors, beta-blockers, and monoamine oxidase inhibitors. This very useful document deserves review by all allergists performing immunotherapy.

J.J.O.

Pitsios C, Demoly P, Bil MB, et al: Clinical contraindications to allergen immunotherapy: an EAACI position paper.
Allergy. 2015;70:897909.

COMMENT: This is a wonderful examination of the literature regarding anaphylaxis and its treatment in patients with cardiac disease. After careful review of the pros and cons associated with epinephrine use in these patients, the authors conclude that clinicians should be wary of potential adverse effects from epinephrine. These risks should be weighed against the possibility of death from untreated anaphylaxis, remembering that there is no absolute contraindication to the use of epinephrine for anaphylaxis.

J.J.O.

Lieberman P, Simons FER: Anaphylaxis and cardiovascular disease: therapeutic dilemmas.
Clin Exp Allergy. 2015;45:1288-1295.