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

American College of Allergy, Asthma & Immunology

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Editor's Note

I am humbled and honored to start my tenure as Editor in Chief for Allergy Watch. I follow previous Editors Bud Bardana, the founder of *Allergy Watch*; and Tony Montanaro and Steve Tilles, who helped raise the bar and improve the quality of our reviews. This issue is our first 2019 Maintenance of Certification review, where our Editors focus on articles selected by the American Board of Allergy and Immunology for its MOC CAP (Continuous Assessment Program) examination. I am fortunate to have wonderful Editors who work hard to provide all College members with useful reviews of the current literature.

S.M.F.

The article summaries and editor comments provided are not endorsed by the publishers, authors, or the American Board of Allergy & Immunology (ABAI), and therefore do not represent their views. The sole purpose of these summaries is to provide diplomates with an overview of content relevant to the ABAI's new Continuous Assessment Program (CAP).

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Head and Neck

Ellis AK, Tenn MW, Steacy LM, et al: Lack of effect of Timothy grass pollen sublingual immunotherapy tablet on birch pollen-induced allergic rhinoconjunctivitis in an environmental exposure unit. Ann Allergy Asthma Immunol. 2018;120:495-503.

Timothy grass pollen allergy tablets are approved for standardized sublingual immunotherapy (SLIT) of allergic rhinitis and conjunctivitis due to grass pollen allergy. Some evidence suggests that timothy grass SLIT might also reduce symptoms related to coexisting birch pollen allergy. This study evaluated the effects of timothy grass SLIT on birch pollen-induced allergic rhinitis (AR) in patients sensitized to both grass and birch pollen.

The phase 4 trial included 93 adults with confirmed allergy to both timothy grass and birch, studied in an environmental exposure unit. All participants had a total nasal symptom score (TNSS) of at least 6 of 12 on challenge with birch pollen. They were randomly assigned to receive 4 months of timothy grass SLIT or placebo. Changes in symptom scores in response to posttreatment birch pollen challenge were assessed, along with secondary outcomes.

There was no significant difference in TNSS reduction between the timothy grass SLIT and placebo groups. Ocular and rhinoconjunctivitis scores were also similar between groups. Symptoms of watery eyes were slightly better with placebo; otherwise, individual symptom scores were not significantly different between groups. Active timothy grass SLIT was well tolerated, with no serious adverse events.

This exploratory study finds no "bystander effect" of four months of timothy grass SLIT on symptoms related to coexisting birch pollen allergy. The effects of this SLIT product appear allergen-specific; it should be used mainly in patients with AR and conjunctivitis symptoms that are clearly worst during grass-pollen season.

COMMENT: This pilot study explored whether patients with allergy to both birch and grass pollen treated with • • •

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SANOFI GENZYME REGENERON

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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 Asthma
- Thorax
- Archives of Pediatric and Adolescent Medicine
- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
- American Journal of Medicine
- European Respiratory Journal
- Pediatric Allergy and Immunology

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timothy grass SLIT tablets demonstrate any bystander effect on their birch-induced AR. Assessment in an environmental exposure unit demonstrated that grass SLIT did not reduce birch-induced symptoms in this co-sensitized population. The rationale for performing this study was that earlier studies with the grass SLIT tablet indicated potential reduction in birch-associated symptoms, suggesting a non-specific immunologic effect.
J.J.O.

Bachert C, Sousa AR, Lund VJ, et al: Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial.
J Allergy Clin Immunol. 2017;140:1024-1031.

Many patients require surgery for nasal polyps, with a high risk of recurrence postoperatively. Interleukin-5 (IL-5) appears to be an important contributor to eosinophilic nasal polyposis. This trial evaluated anti-IL-5 therapy with mepolizumab for treatment of recurrent nasal polyposis.

One hundred five patients with recurrent nasal polyposis who met indications for repeat surgery were randomly assigned to treatment with mepolizumab, 705 mg IV every 4 weeks for six doses, or placebo. The main outcome was the proportion of patients who no longer required surgery after treatment, based on a composite of endoscopic nasal polyp score and nasal polyposis severity visual analog scale (VAS) score.

At 25 weeks, surgery was no longer required in 30% of patients assigned to mepolizumab, compared to 10% in the placebo group. The mepolizumab group had reductions in endoscopic and VAS scores, as well as improvement in all individual symptom scores and in the patient-reported Sino-Nasal Outcome Test score. The improvement in outcomes became significant at 9 weeks. Adverse events were similar between groups.

Anti-IL-5 therapy with mepolizumab reduces the need for surgery in patients with severe, recurrent nasal polyposis. Mepolizumab also improves symptom scores, compared to placebo. The investigators conclude, "[M]epolizumab treatment has the potential to improve the quality of life of and reduce the surgery-associated burden for patients with nasal polyposis."

COMMENT: This trial examined the efficacy of mepolizumab in reducing the need for surgery in patients with severe, recurrent bilateral nasal polyps who failed topical corticosteroid therapy. The group receiving six doses of mepolizumab (750 mg IV every 4 weeks) had a significantly reduced likelihood of needing surgery 4 weeks after discontinuing therapy, compared to the placebo group. Active therapy was associated with improvement in secondary endpoints, including symptoms and quality of life scores. It is important to remember that when considering recurrence of nasal polyposis, a previous study reported that 15% of patients required four to six procedures over an 8-year period. Although oral corticosteroid therapy may be effective, it is fraught with side effects. That reinforces the need to find novel intervention for this illness.
J.J.O.

Chang EH, Stern DA, Willis AL, et al: Early life risk factors for chronic sinusitis: a longitudinal birth cohort study.
J Allergy Clin Immunol. 2018;141:1291-1297

Many patients with chronic rhinosinusitis (CRS) have irreversible structural changes to the sinus mucosa, which contribute to persistent symptoms and poor treatment response. Primary and secondary prevention strategies are needed, but little is known about the natural history of the disease. Long-term follow-up data were used to assess early-life risk factors for CRS.

The analysis included subjects from the Tucson Children's Respiratory Study, enrolled as healthy infants in 1980-84. Of 772 participants with available data, 10.8% had physician-diagnosed sinusitis at age 6 and 12.2% had active sinusitis at age 22 to 32 (based on self-report plus physician-ordered sinus x-rays). Three sinus phenotype groups were identified: 57 with transient childhood sinusitis only, 68 with late-onset adult sinusitis only, and 26 with early-onset chronic sinusitis, beginning in childhood and continuing into adulthood.

Childhood sinusitis was the single strongest risk factor for adult sinusitis: odds ratio (OR) 4.2. The association remained significant after adjustment for known risk factors for childhood sinusitis, including atopy, asthma wheeze, allergic rhinitis (AR), eczema, and colds: OR 3.2.

Risk factors for early-onset sinusitis included elevated serum IgE levels, developing as early as 9 months; atopy, as diagnosed by skin-prick test; along with childhood eczema and AR, frequent colds, maternal asthma. Children with sinusitis were also more likely to have concurrent asthma. No early-life risk factors were associated with the late-onset adult sinusitis phenotype.

The study identifies several risk factors for early-onset chronic sinusitis by age 6, including frequent colds and other viral infections and asthma/allergic diseases. Childhood sinusitis is the main risk factor for adult sinusitis. Studies of the molecular mechanisms of this progressive disease phenotype are needed to develop effective preventive strategies.

COMMENT: Chronic rhinosinusitis is a common problem in the United States, with a prevalence rate of 10% and an estimated cost of 60 billion dollars annually. Approximately 25% of patients with CRS demonstrate no significant clinical improvement despite maximal medical/surgical treatment. Some postulate that this may be the result of irreversible structural changes in the sinus mucosa. If so, we need to better understand the natural history of this illness, focusing on time of inception of the different sub-phenotypes and factors that may determine its persistence. The study identifies three longitudinal patterns of expression of sinusitis: transient childhood sinusitis (11%), early-onset sinusitis with persistence (3%), and late-onset adult sinusitis (9%). Of the two adult subtypes, early onset was associated with type 2 immune response as well as susceptibility to viral infections and asthma. In the late-onset group, no early-life risk factor could be identified. Identification of molecular endotypes responsible for these two sinusitis subtypes may lead to therapies that could potentially prevent the progression to recalcitrant disease.

J.J.O.

Dermatologic

Hamad A, Jithpratuck W, Krishnaswamy G: Urticarial vasculitis and associated disorders.
Ann Allergy Asthma Immunol. 2017;118:394-398.

Some patients with urticarial eruptions seen in allergy practice may have urticarial vasculitis (UV), one of its three variant conditions, or Schnitzler syndrome. The authors review the differential diagnosis and treatment of these conditions.

Urticarial vasculitis is a leukocytoclastic vasculitis with burning, painful, and/or pruritic cutaneous lesions. Lesions may persist for longer than 24 hours and sometimes leave skin bruises. About 40% of patients have angioedema; musculoskeletal, pulmonary, renal, and gastrointestinal complications sometimes develop.

The authors discuss three variants of UV. Patients with normocomplementeric UV (NUV) have similar skin lesions, but normal complement levels and few noncutaneous manifestations. In some cases, no treatment is needed. Hypocomplementeric UV (HUV) is characterized by low complement component levels and elevated C1q autoantibodies. Extracutaneous manifestations include arthritis/myalgia, abdominal pain, and asthma symptoms. Treatment options include hydroxychloroquine or colchicine. Hypocomplementemic UV syndrome (HUVS) is a severe UV variant that can lead to serositis, renal or neurologic disease, or cardiopulmonary complications. It may overlap with the recently reported IgG4 disease; rituximab is an effective treatment for both conditions.

The authors review the mechanisms of UV and its variants; diagnosis includes skin biopsy and laboratory tests, including autoantibody measurement. The authors note that HUV can overlap with or evolve into systemic lupus erythematosus. The review also addresses Schnitzler syndrome, a condition associated with a neutrophilic urticarial eruption and fever, often with myalgia/arthralgia, bone pain, or lymphadenopathy. The authors present guidelines for the treatment of UV, including recommendations for mild, moderate, and severe disease and the role of biologic agents.

COMMENT: For allergists/immunologists evaluating patients who present with chronic urticaria, it is important to recognize the subset who actually have urticarial vasculitis. This is an informative review of UV and its variants, including Schnitzler syndrome, NUV, and HUV.

D.M.L.

Czarnowicki T, Krueger JG, Guttman-Yassky E: Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march.
J Allergy Clinic Immunol. 2017;139:1723-1734.

Atopic dermatitis (AD) is a very common childhood disease that often persists into adulthood. Disruption of the skin barrier is thought to play a key role in the devel-

opment of AD. The authors review the components of the skin barrier and their contributions to the AD phenotype, along with the association between AD and ensuing atopic march.

The authors discuss the components of the skin barrier and the abnormalities associated with AD. The stratum corneum is the major component of the epidermal barrier. Atopic dermatitis has been linked to disruption of the lipid layer; restoring cutaneous lipids has benefits for patients with AD. Tight junctions play an important role in keratinocyte adhesions. Their impairment affects lipids and filaggrin (FLG) processing within the epidermis. This filament-aggregating protein is the main structural component of the stratum corneum. Both lesional and nonlesional AD skin has low expression of FLG, even when FLG mutations are not present.

Environmental factors affecting the pathogenesis of AD include proteases and skin pH; an acidic pH is needed to maintain the integrity of the stratum corneum and several aspects of skin barrier function. Patients with AD have dysbiosis of the normal commensal skin microflora, including decreased microbial diversity. The authors discuss the complex interrelationship between immune dysregulation and skin barrier defects in AD.

Especially when increased IgE levels are present, AD may lead to the development of other allergic diseases, including food allergies, asthma, and allergic rhinitis. Functional impairment of the skin barrier may be a critical factor in the development of AD, with Th2 expansion and activation in the blood and skin promoting the occurrence of IgE isotope switching in immature B cells. This raises the possibility of early interventions to prevent AD and thus the subsequent atopic march.

Primary prevention approaches to inhibit development of AD include the use of moisturizers to support and supplement skin barrier function. Moisturizers have been shown to reduce the incidence of AD in high-risk infants, although the mechanisms of this effect remain to be demonstrated. So far, there are few data on secondary prevention of the atopic march once overt AD has developed.

COMMENT: This informative review summarizes skin barrier components and abnormalities, the AD phenotype, primary and secondary prevention strategies, and the role of AD as a gateway to development of other atopic conditions – aka, the atopic march.

D.M.L.

Yosipovitch G, Ständer S, Kerby MB, et al: Serlopitant for the treatment of chronic pruritus: results of a randomized, multicenter, placebo-controlled phase 2 clinical trial.
J Am Acad Dermatol. 2018;78:882-891.

Recent years have seen advances in understanding of the neural and cellular factors involved in pruritis, including the role of tachykinin substance P and its receptor, neurokinin 1 receptor (NK_1R). This multicenter trial evaluated serlopitant, an NK_1R antagonist, for the treatment of chronic pruritis.

The phase 2 study included 257 patients with chronic pruritis who did not respond to antihistamines or topical steroids. Patients were randomly assigned to oral placebo or serlopitant, 0.25, 1.0, or 5.0 mg once daily for six weeks, alone or with middle-potency steroids and emollients. Change in pruritis visual analog scale score was analyzed, along with safety outcomes.

Serlopitant reduced pruritis scores in dose-dependent fashion. At 6 weeks, 26% of placebo-treated patients had a 4 cm decrease in pruritus score, compared to 43% with serlopitant 0.25 mg, 38% with serlopitant 1.0 mg, and 53% with serlopitant 5.0 mg. Improvement in pruritis remained significant at 4 weeks' follow-up after the end of treatment. There was improvement in some domains on the Dermatology Life Quality Index score, and significant improvement in insomnia in the 1.0 and 5.0 mg dose groups. Safety and tolerability were similar between groups.

The NK_1R inhibitor serlopitant produces clinical improvement in chronic refractory pruritis. Further studies of serlopitant for chronic pruritis are underway.

COMMENT: We are seeing more patients in allergy/immunology practice with chronic pruritus, a distinct entity from chronic urticaria. These patients have unmet management needs; antihistamines and topical corticosteroids frequently lack efficacy. This randomized double-blind, placebo-controlled study assessed efficacy and safety of the NK_1R antagonist serlopitant. The data imply serlopitant is a promising agent for treatment of chronic pruritus that merits further study.

D.M.L.

Lung

Dicker AJ, Crichton ML, Pumphrey EG, et al: Neutrophil extracellular traps are associated with disease severity and microbiota diversity in patients with chronic obstructive pulmonary disease.
J Allergy Clin Immunol. 2018. 141:117-127.

Previous studies have reported the presence of neutrophil extracellular traps (NETs) in the airways of some patients with chronic obstructive pulmonary disease (COPD). Little is known about the clinical and pathophysiologic implications of this finding. This study examined the relationship between airway NET release and COPD severity, microbiome composition, and airway neutrophil function.

The study included multiple methods of quantifying NETs in sputum and serum from COPD patients, with samples obtained during periods of stable disease and exacerbations. Measures of sputum NETs (DNA-elastase and histone-elastase complexes) were correlated with COPD severity, as evaluated by the composite Global Initiative for Obstructive Lung Disease scale. The presence of NET complexes was

modestly associated with FEV_1, symptoms of COPD, and exacerbation frequency. Higher NET concentrations during exacerbations were linked to noneosinophilic exacerbations and decreased bacterial diversity, including increased presence of *Haemophilus* spp. In ex vivo studies, bacterial phagocytosis by airway neutrophils was lower in specimens from patients with higher concentrations of NET complexes.

The findings support the presence of increased NET formation in the airways of patients with COPD. The presence of NETs is associated with greater disease severity and more frequent exacerbations. The observed association with microbial dysbiosis raises the possibility of clinical effects of NET modulation.

COMMENT: Allergists are seeing more COPD patients in the office for diagnosis and management. The role of defining the microbiome and perturbations that occur with increased disease activity and treatment are evolving. The authors describe sputum NETs that predict severity and response to treatment. These changes result in decreased FEV_1 and increased presence of *Haemophilus influenzae.* These NETs in sputum are probably related to decreased lung function, poor quality of life, and increased disease progression.
B.E.C.

Mukherjee M, Bulir DC, Radford K, et al: Sputum autoantibodies in patients with severe eosinophilic asthma.
J Allergy Clinical Immunol. 2018; 141(4):1269-1279.

In patients with severe asthma, chronic airway inflammation may lead to frequent immune cell degranulation and peroxidase enzyme release, which has known immunogenic properties. This study evaluated the possibility of an autoimmune mechanism – triggered locally in the lungs and targeting eosinophil-specific antigens – associated with severe asthma.

The retrospective study included groups of patients with inhaled or oral corticosteroid-dependent eosinophilic asthma, mixed-phenotype eosinophilic asthma, and neutrophilic infective asthma, along with healthy controls. Anti-eosinophil peroxidase (EPX) immunoglobulins were identified in the airways of patients with eosinophilic asthma, most pronounced in the oral corticosteroid-dependent group. Sputum IgG autoantibodies against several antinuclear antigens not present in the circulation were detected as well. Sputum cytokine profiling showed a Th2-dominated microenvironment, along with increased signaling molecules (B-cell activating factor and B cell-attracting chemokine 1), linked to the formation of ectopic lymphoid structures. In vitro, sputum IgGs from patients with increased airway autoantibodies induced eosinophil degranulation, leading to the release of histone-rich extracellular traps, which were not inhibited by dexamethasone.

The findings suggest a "polyclonal autoiummune event" in the airways of patients with corticosteroid-dependent eosinophilic asthma, which might contribute to steroid nonresponsiveness in this asthma phenotype. This autoimmune severe asthma endotype is characterized by the presence of autoantibodies against EPX and autologous cellular components. Further studies are needed to identify better therapeutic options for these patients, who might account for one-third of those with severe eosinophilic asthma.

COMMENT: The advent of anti-IL-5 therapy has given greater exposure to eosinophil as a biomarker of disease activity, not only as a target for therapy. The use of anti-IL-5 medications predicts responses of 50% to 70% to decrease in exacerbations. The notion that autoimmunity may relate to increased disease activity has been investigated. The presence of autoantibodies in sputum may help to explain disease severity and incomplete response to therapy. Clinically available validation of this mechanism of eosinophilic disease activity in asthma and CRS is evolving.
B.E.C.

Desai M, Oppenheimer J, Tashkin DP: Asthma-chronic obstructive pulmonary disease overlap syndrome: what we know and what we need to find out. Ann Allergy Asthma Immunol. 2017:241-245.

The term asthma-COPD overlap syndrome (ACOS) reflects the clinical reality that some patients have features of both conditions. Although the clinical course may differ for patients with ACOS, there is no single definition and no firm treatment guidelines. The authors review current knowledge of ACOS and discuss emerging approaches and treatment options.

The recent GINA/GOLD report described ACOS as a condition of persistent airflow limitation with some features of asthma and some of COPD. The authors acknowledge the existence of multiple ACOS phenotypes, and offer a practical approach to patient identification. The clinical overlap likely reflects pathophysiologic overlap of the inflammatory mechanisms of disease. Smoking and exposure to air pollution are among the best-studied factors affecting the overlap phenotype. Further studies to clarify the natural history and prognosis of ACOS will likely classify individual patients as to whether asthma or COPD is the "predominant and preceding illness."

In the absence of firm treatment recommendations, decisions are often guided by whether the disease appears more "asthma-like" or "COPD-like." Treatment generally starts with asthma therapy, ie, inhaled corticosteroids. Step-up therapy may be considered earlier than in patients with asthma alone. Biologic agents are emerging as a therapeutic option for asthma, but there is less information on their role in COPD. While prevention is an important goal, there are currently no strong predictors of which patients with asthma will experience airway remodeling and no convincing evidence that early treatment can prevent remodeling.

Dedicated clinical trials of therapy for patients with ACOS are needed. The authors highlight the need to identify clinical phenotypes that will predict treatment response, opening the way to personalized therapy.

COMMENT: As allergists see more complex patients with COPD, it is key that an evidence-based approach is used to endotype both asthma and COPD. This is very important as it will help identify patients who are candidates for LAMA and LABA/ICS. An evidence-based approach allows healthcare professionals to take the appropriate steps to slow symptomatic and physiologic disease progression. The consideration for biologic therapy in this group of patients will definitely need further clarification.
B.E.C.

Food and Drug Allergy/Hypersensitivity Reactions

Santos AF, Brough HA: Making the most of in vitro tests to diagnose food allergy. J Allergy Clin Immunol Pract. 2017;5:237-248.

Together with the clinical history, in vitro tests can be used to make the diagnosis of IgE-mediated food allergy, or to avoid or defer the need for oral food challenge (OFC). The authors review the major in vitro tests for food allergy and their role in deciding whether OFC is needed to make the correct diagnosis.

Specific IgE testing has long been used for diagnosis of food allergy, offering high sensitivity but low specificity. Diagnostic cutoff values vary widely between studies; validated cutoffs are useful when applied to similar patient populations. Tests measuring specific IgE to component allergens are available for single and multiple allergens. To date, these tests have been best studied for peanut, but clinically relevant findings have also been reported for tree nuts and cow's milk, among others. Allergen-specific/total IgE and allergen-specific IgG4/IgE ratios have been evaluated to improve on the diagnostic performance of food-specific IgE testing.

Basophil activation tests assess the ability of IgE to mediate basophil activation after allergen stimulation. Expression of activation markers such as CD63 or CD203c can differentiate allergic from sensitized-tolerant patients, improving on the specificity of specific IgE or skin prick tests. This test requires special equipment and personnel, and is reserved for situations where routine tests can't make a precise diagnosis. Tests of the allergen peptides to which IgE binds can further enhance IgE specificity.

The authors discuss the interpretation of allergy test results in determining the likelihood of clinical allergy, and thus in deciding whether OFC is needed. Several factors can affect the probability of allergy at a given level of specific IgE, including history of immediate allergic reaction, age, ethnicity, and clinical setting. Key factors affecting the decision to perform OFC include previous history of reactions and recent exposure to the implicated food. Further studies are needed to optimize diagnostic accuracy so as to minimize the number of OFCs.

COMMENT: This review of lab results for food allergy outlines the clinical correlation with various in vitro tests for food allergy, since using the cutoff of 0.35 kU/L for sIgE has high sensitivity but poor specificity. Relevant points include the fact that for cow's milk allergy, elevated casein (Bos d 8) was the best predictor of even baked-milk challenge failure. The basophil activation test is logistically difficult but may be clinically helpful, since basophils of truly allergic patients express CD63 and CD203c whereas patients who are just sensitized have much lower activation markers. If further validation studies find similar results, BAT has the potential to reduce the need for oral food challenge.
S.M.F.

Sampson HA, Shreffler WG, Yang WH, et al: Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. JAMA. 2017;318:1798-1809.

Based on studies in animals and initial trials in humans, epicutaneous therapy using an allergen-adsorbed patch is a potentially effective treatment for peanut allergy. Participants from a recent phase 2b trial were enrolled in an open-label extension phase.

The study included 222 patients, median age 11 years, who were sensitized to peanut and had a positive response to challenge with peanut protein at an eliciting dose of 300 mg or less. They were randomly assigned to receive an epicutaneous patch containing 50, 100, or 250 μg of peanut protein or placebo. After 1 year of daily treatment, change in eliciting dose was assessed by double-blind, placebo-controlled food challenge. Treatment response was defined as at least a tenfold increase in eliciting dose, and/or an eliciting dose of 1,000 mg or higher. Ninety-four percent of patients completed the study.

At 12 months, the response rate was 50% in patients receiving the 250 μg peanut patch versus 25% in those receiving the placebo patch. There was no significant difference between the 100 μg and placebo patches. The difference in response rate was significant only in the 6- to 11-year age group – 53.6% with the 250 μg peanut patch versus 19.4% with placebo – not in adolescents/adults.

There were no serious dose-related adverse events. Nearly all patients in all groups had local skin reactions or other treatment-emergent adverse events. Median treatment adherence was 97.6%, while the dropout rate due to adverse events was 0.9%.

An epicutaneous peanut patch containing 250 μg of peanut protein yields a significant treatment response in patients with peanut allergy. There is evidence of an interaction by age group, with a significant difference in treatment response only in children aged 6 to 11. A phase 3 trial evaluating this dose of epicutaneous peanut immunotherapy in children is underway.

COMMENT: The dilemma of patients with food allergy is in the current lack of curative treatment. Patients are advised to avoid the food and be prepared to treat with epinephrine in case of exposure. Patients and their families live with fear and concern regarding the potential for accidental exposure, which negatively affects their quality of life. This study of an epicutaneous patch for peanut shows promising results regarding safety and tolerability. While further studies are needed, the peanut patch may be a treatment option, as seen in the response of children between the ages of 6 and 11 years who tolerated increases in eliciting dose during oral food challenge after 1 year of treatment. The high compliance and lack of dose-related adverse reactions are also reassuring. From the perspective of a pediatric allergist caring for patients with food allergy, the hope offered by any treatment option, even in the case of accidental exposure, is valuable.
V.H.-T.

Ierodiakonou D, Garcia-Larsen V, Logan A, et al: Timing of allergenic food introduction to the infant diet and risk of allergic or autoimmune disease: a systematic review and meta-analysis. JAMA. 2016;316:1181-1192.

Recent evidence suggests that earlier introduction of potentially allergenic foods to the infant diet may reduce the risk of developing food allergy. This is in contrast to previous advice to delay introduction of these foods. The authors present a systematic review and meta-analysis of evidence on the timing of allergenic food introduction during infancy.

Data from 204 papers reporting on 146 studies were extracted for analysis. Five studies including 1,915 participants provided moderate-certainty evidence that introducing egg at 4 to 6 months reduced the development of egg allergy: risk ratio (RR) 0.56. In a population with a 5.4% incidence of egg allergy, this would translate into an absolute risk reduction of 24 cases per 1,000 population.

Two studies totaling 1,550 participants suggested that introducing peanut at 4 to 11 months reduced the risk of peanut allergy: RR 0.29. Given a 2.5% incidence of peanut allergy, absolute risk reduction would be 18 cases per 1,000 population. Age at introduction of egg or peanut did not affect the risk of other food allergies. There was low-certainty evidence for benefits of early introduction of fish, and high-certainty evidence that age at gluten introduction did not affect the risk of celiac disease.

This 2016 review and meta-analysis supports the benefits of early introduction of egg and peanut in reducing the risk of allergy to these foods. The authors point out the limitations of the evidence base on early introduction of allergenic foods. Further studies are needed to confirm the findings and assess the magnitude of the treatment effect.

COMMENT: In this systematic review and meta-analysis, early egg/peanut introduction was associated with significantly lower risk for developing egg/peanut allergy. The strength of evidence was downgraded based on imprecision and indirectness. The latter refers to differences in study populations, interventions, and/or outcome measures, which are not uncommon in systematic reviews. The findings provide further support for recommendations to not delay introduction of allergenic foods during infancy.
D.M.L.

Anaphylaxis

Lieberman PL, Jones I, Rajwansi R, et al: Anaphylaxis associated with omalizumab administration: risk factors and patient characteristics. J Allergy Clin Immunol. 2017;140:1734-1736.

Since its first studies in humans, omalizumab has been associated with episodes of anaphylaxis. The authors analyze the patient characteristics and risk factors for omalizumab-related anaphylaxis.

Of 132 potential cases reported to a pharmacosurveillance database, 96 were independently adjudicated as omalizumab-related anaphylaxis. The mean age was 40.5 years and 84% of patients were female; the indication for omalizumab was asthma in 80% of patients. Previous anaphylactic events were documented for 43% of patients.

Respiratory symptoms were the most common manifestation, followed by cutaneous symptoms or angioedema. About 70% of reactions occurred within the first two or three doses of omalizumab; median time to anaphylaxis was 60 minutes. Treatment included epinephrine in 60% of cases, and 17% of patients were hospitalized. None of the patients died.

The study presents the largest number of adjudicated cases of omalizumab-related anaphylaxis reported to date. Previous anaphylaxis unrelated to omalizumab appears to be an important risk factor; the mechanism of this association is unclear. Most anaphylactic reactions to omalizumab occur within the first two or three doses, usually within 60 minutes.

COMMENT: This letter to the editor reviews the characteristics of reported cases of anaphylaxis associated with omalizumab. Important findings include the facts that 84% of patients were female, 43% had prior anaphylactic events, and 64% of reactions occurred within 60 minutes. Anaphylaxis occurred within the first two doses in 69% of cases and first three doses in 72%. The authors suggest that a certain subset of patients, particularly those with prior anaphylaxis, may be at increased risk for anaphylaxis with omalizumab.
S.M.F.

Lee S, Hess EP, Lohse C, et al: Trends, characteristics and incidence of anaphylaxis in 2001-2010: a population-based study. J Allergy Clin Immunol. 2017;139:182-188.

Studies suggest that the incidence of anaphylaxis may be rising. Data from the Rochester Epidemiology

Project were used to study temporal trends in the incidence of anaphylaxis.

The analysis included 631 residents of Olmsted County, Minn., median age 31 years, with incident anaphylaxis between 2001 and 2010. About three-fourths of patients were treated in the emergency department; 15 percent were hospitalized and none died.

After adjustment for age and sex, the incidence of anaphylaxis was 42 per 100,000 person-years. During the period studied, the overall incidence of anaphylaxis increased by 4.3% per year, while the incidence of food-related anaphylaxis increased by 9.8% per year. Children up to age 9 had the highest incidence of anaphylaxis triggered by foods. Venom-related anaphylaxis was most common in adults aged 20 to 39 and medication-related anaphylaxis was most common in those aged 30 to 39. Incidence rates were similar for males and females, with some differences between age groups. Use of epinephrine for anaphylaxis treatment increased during the period studied.

These population-based data suggest that the incidence of anaphylaxis increased from 2000 to 2010. Anaphylaxis triggered by foods showed the sharpest increase and was most common in children. However, the highest incidence of anaphylaxis was in the 30 to 39 age group, while the overall increase in incidence was limited to residents aged 20 to 49.

COMMENT: These Mayo Clinic researchers analyzed all patients presenting with anaphylaxis over a 10-year period in Olmstead County, Minn. There was an average increase in the incidence of anaphylaxis of 4.3% per year overall, but food-related anaphylaxis increased 9.8% per year. Food-related anaphylaxis was most common in children aged 0 to 9 years, whereas venom-related anaphylaxis was most common in adults aged 20 to 39. Medication-related anaphylaxis was most common in the 30 to 39 age group. The finding of an overall increase in epinephrine use over time suggests that more patients are following our recommendations for acute treatment of anaphylaxis.

S.M.F.

Buka RJ, Knibb RC, Crossman RJ, et al: Anaphylaxis and clinical utility of real-world measurement of acute serum tryptase in UK emergency departments (ED).
J Allergy Clin Immunol Pract. 2017;5:1280-1287.

Patients with anaphylaxis may have acute elevation of serum tryptase. Current UK guidelines call for serial measurement of serum tryptase, but these results are not immediately available in the emergency department (ED). This study evaluated the clinical utility of acute serum tryptase for anaphylaxis in a "real world" ED setting.

The retrospective study included 426 cases of anaphylaxis seen at three British EDs in 2012. All cases met World Allergy Organization diagnostic criteria for anaphylaxis. Available data on acute serum tryptase levels were analyzed and the sensitivity, specificity, and negative and positive predictive value (NPV and PPV) were calculated.

Acute serum tryptase was measured in 33.1% of cases. Tryptase was measured a mean of 4 hours, 42 minutes after symptom onset; in no case were serial tryptase measurements obtained. Acute serum tryptase level greater than 12.4 ng/mL – corresponding to the 75th percentile – was 28% sensitive and 88% specific for anaphylaxis, with a PPV of 0.93 and NPV of 0.17. Male sex and especially hypotension were significant predictors of a higher acute serum tryptase level: odds ratio 2.66 and 7.08, respectively.

In this study of anaphylaxis in British EDs, acute serum tryptase has high specificity and PPV, but low sensitivity and NPV, for anaphylaxis. Compliance with UK recommendations for serial tryptase levels is very low, perhaps reflecting the impracticality of following this guideline. There is evidence to suggest that using an epinephrine autoinjector may prevent an increase in serum tryptase.

COMMENT: In this retrospective analysis of patients presenting to three hospital EDs with anaphylaxis, 28.9% had acute serum tryptase levels of 11.4 ng/ml or more with 19% having levels of 20 ng/ml of more. Hypotension and male sex predicted higher serum tryptase levels; patients with hypotension were seven times more likely to have elevated levels. The frequency of elevated serum tryptase was similar in food-induced anaphylaxis compared to other causes. The bottom line is that acute serum tryptase levels greater than or equal to 11.4 ng/ml have a high PPV and specificity but a low sensitivity and NPV for the diagnosis of anaphylaxis in the ED.

S.M.F.

Immune Hypersensitivity Disorders

Steri M, Orr ù V, Idda ML, et al: Overexpression of the cytokine BAFF and autoimmunity risk. N Engl J Med. 2017;376:1615-1626.

Previous genomewide association studies (GWAS) have identified many independent signals for multiple sclerosis (MS) and systemic lupus erythematosus (SLE), although little is known about the causal variants and effector mechanisms. This GWAS reports a gene variant associated with an increased risk of autoimmunity in a Sardinian population with high prevalences of MS and SLE.

Including 2,273 patients with MS and 2,148 controls, the study was performed in Sardinia, which has high prevalences of MS and SLE. Both diseases were associated with a variant in *TNFSF13B,* which encodes tumor necrosis factor superfamily member 13B, also known as B-cell activating factor (BAFF). On analysis of quantitative immune variables, the risk allele linked to upregulated humoral immunity, including increased levels of soluble BAFF, B lymphocytes, and immunoglobulins.

Increased risk of autoimmunity resulted from an insertion-deletion variant, GCTGA, leading a shorter transcript

with no microRNA binding site, and thus to increased soluble BAFF production and up-regulated humoral immunity. Population genetic studies suggested that the risk allele may have conferred an evolutionary advantage in resistance to malaria, which historically was highly prevalent in Sardinia.

The study identifies a *TNFSF13B* variant associated with high risk of the autoimmune disorders MS and SLE. The mechanism of the association involves the cytokine and drug target BAFF. The researchers "infer that the increased risk of MS and SLE associated with BAFF overexpression mainly involves humoral immunity, consistent with the efficacy of B-cell-depleting therapies."

COMMENT: This elegant and complex study used a GWAS approach in a Sardinian population who are at higher risk for multiple sclerosis and SLE. It identified a single-nucleotide polymorphism whose pattern of linkage dysequilibrium differed from that in Sardinia and mainland Europe. This led the authors in search of an indel, which they identified and named BAFF-var. This variant was most strongly associated with multiple sclerosis and was also associated with SLE. The researchers hypothesize that BAFF-var may have been positively selected in Sardinia because it provides resistance to malaria. The variant leads to higher soluble BAFF and thus to higher B cells and antibody production and increased risk of autoimmunity (just like in mice). If you are unfamiliar with terms such as GWAS, indel, miRNA, and random genetic drift, this article may not be your top pick for the MOC test.
D.A.K.

Cunningham AL, Lal H, Kovac M, et al: Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older.
N Engl J Med. 375:1019-1032, 2016.

In a previous trial, the herpes zoster subunit (HZ/su) vaccine was highly effective in reducing the risk of herpes zoster in adults aged 50 or older. This paper reports findings from a concurrent study of the HZ/su vaccine in adults 70 or older.

The phase 3 randomized trial included 13,900 participants, mean age 75.6 years, in 18 countries. Participants received two intramuscular doses of HZ/su or placebo, given 2 months apart. Vaccine efficacy against herpes zoster and postherpetic neuralgia were analyzed, along with safety and reactogenicity.

At a mean follow-up of 3.7 years, the incidence of herpes zoster was 0.9 cases per 1,000 person-years in the HZ/su group versus 9.2 per 1,000 in the placebo group. Vaccine efficacy was 89.8%, with similar outcomes for participants in their seventies and eighties. On pooled analysis of the two trials, overall vaccine efficacy was 91.3% against herpes zoster and 88.8% against postherpetic neuralgia.

Participants receiving HZ/su were more likely to report injection-site and systemic reactions: 79.0%, compared to 29.5% in the placebo group. Serious adverse events, possible immune-mediated diseases, and deaths were similar between groups. There was no increase in events after the second dose.

The HZ/su vaccine greatly reduces the risk of herpes zoster in adults aged 70 and older, as in those aged 50 or older. Adjuvants such as the $AS01_B$ system used in this product may improve the efficacy of vaccines in older adults and other groups with lower responses to vaccination.

COMMENT: The newest vaccine to prevent herpes (Shingrix) was approved by the FDA in 2017. It is a recombinant subunit vaccine, not a live-attenuated virus. This study, published in 2016, presented safety and efficacy data on both individuals aged 70 or older and also pooled data with another study including patients aged 50 or older. Regardless of age, the HZ/su vaccine was 90% effective in reducing risk of shingles and thereby reduced the likelihood of postherpetic neuralgia (higher than prior studies with the live-attenuated vaccine). As allergists/immunologists, we could consider this vaccine for certain patients with immunodeficiencies that are contraindications to the live-attenuated virus, but data are currently lacking on this approach. Many of my patients have asked about HZ/su. The present article is a good one to understand the efficacy and common side effects of this new vaccine.
D.A.K.

Johnson DB, Balko JM, Compton ML, et al: Fulminant myocarditis with combination immune checkpoint blockade.
N Engl J Med. 2016;375:1749-1755.

Immune checkpoint inhibitors such as ipilimumab and nivolumab have led to improved survival for patients with melanoma and other cancers. However, these agents carry a risk of severe, immune-related adverse events, especially with combination immunotherapy. Two cases of fatal myocarditis in patients receiving combination therapy with ipilimumab and nivolumab are reported.

The patients were a 65-year-old man and a 63-year-old woman receiving the two immune checkpoint inhibitors for treatment of metastatic melanoma. After the initial doses, both patients developed myositis with rhabdomyolysis with cardiac electrical instability that did not respond to treatment. Both died as a result of fulminant myocarditis.

Postmortem studies showed myocardial T-cell and macrophage infiltrates of the myocardium, with clonal T-cell populations identical to those found in tumors and skeletal muscle. Cardiac and skeletal striated muscle, along with tumor, were the only affected tissues. A pharmacosurveillance database showed a 0.27% rate of myocarditis in patients treated with the combination of ipilimumab and nivolumab. The two patients shared a single common HLA class II allele, HLA-DQB1*03:01.

These cases show the possibility of a rare, potentially fatal myocarditis resulting from a T-cell driven reaction to the combination of two immune checkpoint inhibitors. Further study of the mechanisms of this reaction might provide insights into the development of myocarditis in

patients without cancer, as well as the interactions between the immune system and the myocardium.

COMMENT: Immune checkpoint inhibitors are revolutionizing cancer immunotherapy by allowing T cells to target cancer cells more effectively. This release of the "brakes" on the immune system comes at a cost, with the emergence of a number of adverse effects related to aberrant activation of autoreactive T cells. This case report describes two patients with myeloma treated with the combination of an antibody against CTLA-4 and PD-1. Within 12 to 15 days of treatment, they were hospitalized with fatigue, and chest pain/myalgias. Labs were consistent with myositis. Despite early treatment with high-dose glucocorticoids, along with infliximab in one case, both patients died of fulminant myocarditis. Optimal surveillance for these immune-mediated problems, as well as their treatment, remains unclear. But as allergists, we should expect to be seeing more such patients.

D.A.K.

Immunodeficiencies

Banerji A, Busse P, Shennak M, et al: Inhibiting plasma kallikrein for hereditary angioedema prophylaxis.
N Engl J Med. 2017;376:717-728.

Uncontrolled plasma kallikrein generation plays a central role in the pathogenesis of hereditary angioedema (HAE) with C1 inhibitor deficiency. Lanadelumab (DX-2930) is a recombinant, fully human monoclonal antibody inhibitor of kallikrein. This phase 1b trial evaluated lanadelumab for long-term prevention of angioedema attacks in HAE patients.

Thirty-seven adult patients with type I or II HAE with C1 inhibitor deficiency were randomly assigned to treatment with lanadelumab (24 patients) or placebo (13 patients), two treatments given subcutaneously 14 days apart. Lanadelumab was given in ascending doses of 30, 100, 300, or 400 mg. The analysis focused on the rate of angioedema attacks in the lanadelumab 300 or 400 mg groups, compared to placebo.

In both of the two higher-dose lanadelumab groups, cleavage of high-molecular-weight kininogen was reduced to levels observed in subjects without HAE. All 5 patients in the 300 mg group and 2 of 11 patients in the 400 mg group were free of attacks from day 8 to 50, compared to 3 of 11 patients in the placebo group. In the combined 300 and 400 mg groups, lanadelumab was associated with a 91% reduction in the attack rate.

No patient discontinued lanadelumab due to adverse events, and no important safety issues emerged during treatment. Angioedema, injection-site pain, and headache were the most frequent adverse events.

The kallikrein inhibitor lanadelumab is a promising agent for prophylactic treatment of HAE with C1 inhibitor deficiency. At the higher doses studied, it eliminates or significantly reduces the rate of angioedema attacks, compared to placebo.

COMMENT: Living with any chronic disease is difficult. Patients with HAE may have recurrent and life-threatening exacerbations and live with the uncertainty of when they will occur. Many patients not only need treatment options, but would also benefit from prophylaxis. This double-blind, placebo-controlled trial demonstrates that a new kallikrein inhibitor is a well-tolerated option for subcutaneous prophylaxis in HAE. All 5 patients receiving the 300 mg sc dose every 2 weeks were attack-free. This is the dose that is now approved by the FDA and available as an additional option to improve the lives of HAE patients.

V.H.-T.

Monach PA, Stone JH, Sharma A, Nazarian RM: Case 6-2017: A 57-year-old woman with fatigue, sweats, weight loss, headache, and skin lesions. N Engl J Med. 2017;367:775-786.

Patients with IgG4-related disease have plasmacytosis and variable fibrosis. Sclerosing cholangitis of large bile ducts is the most common clinical manifestation; skin involvement and arteritis or periarteritis have also been described. An atypical case of IgG4-related disease leading to a complex diagnostic process is reported.

The patient was a 57-year-old woman seen at a rheumatology clinic with fatigue, night sweats, headache, abdominal pain. Over two years, she been evaluated by a wide range of specialists, with extensive laboratory tests and imaging studies. She had prominent upper eyelids with swelling of the lacrimal gland, swelling and nodular temporal arteries, hypertrophic sublingual glands, and purpuric skin lesions of the legs. Laboratory findings included polyclonal hypergammaglobulinemia, hypocomplementemia, and plasmacytosis in biopsy specimens of multiple organs.

Differential diagnosis included giant-cell arteritis, sarcoidosis, and Sjögren's syndrome, among other possibilities. The findings were deemed most consistent with IgG4-related disease, despite atypical features including dramatic constitutional symptoms and arthritis. The patient's serum IgG4 was normal, attributed to the "prozone effect": a false-negative effect in conditions of antigen excess.

Pathologic examination of a temporal biopsy specimen was consistent with IgG4-related vasculitis. This diagnosis was supported by subsequent skin biopsy, as well as analysis of previous lymph node and liver biopsies. The patient's condition improved with two doses of rituximab and a course of prednisone. IgG1, IgG4, and serum complement levels normalized as well.

COMMENT: Rare diseases pose a diagnostic dilemma for clinicians. This is an interesting case presentation of a patient with IgG4-related disease. The authors remind us that while some patients present with typical features, such as • • •

sclerosing cholangitis and prominent salivary and lacrimal glands, others do not. Interestingly, IgG4 levels can be artificially low levels in one-fourth of patients, as in this case. Medium-size artery vasculitis in the temporal artery and skin were also features seen in this patient. The skin lesions (purpura) persisted even after treatment with glucocorticoids. The value of multispecialty collaboration and the need to continue to pursue necessary diagnostic modalities to confirm the diagnosis of rare diseases are evident through this case presentation.
V.H.-T.

de la Morena MT, Leonard D, Torgerson TR, et al: Long-term outcomes of 176 patients with X-linked hyper-IgM syndrome treated with or without hematopoietic cell transplantation.
J Allergy Clin Immunol. 2017;139:1282-1292.

X-linked hyper-IgM syndrome (XHIGM) is a rare primary immunodeficiency disorder with high morbidity and mortality. Hematopoietic cell transplantation (HCT) is potentially curative, but carries substantial complications and is not always an option. This study compared long-term survival and well-being outcomes for patients with XHIGM who did and did not undergo HCT.

The researchers identified 189 patients diagnosed with XHIGM at 28 centers between 1964 and 2013. Of these, 176 had valid follow-up data. Treatment included HCT for 38% of patients. Survival and general well-being were compared for HCT and non-HCT patients at an average follow-up of 8.5 years.

Overall mortality was not significantly different for the HCT and non-HCT groups; for all patients, median survival time from diagnosis was 25 years. The risks associated with HCT decreased for patients diagnosed with XHIGM between 1987 and 1995, with hazard ratios becoming significant for those diagnosed between 1995 and 1999. Liver disease was an independent risk factor for mortality: hazard ratio 4.9.

Survivors who underwent HCT had higher median Karnofsky/Lansky scores, compared to survivors in the non-HCT group. Graft-versus-host disease developed in 40% of HCT recipients, with most deaths occurring within 1 year after HCT. Preventive measures including gamma-globulin and antibiotics were widely used across geographic locations.

For all patients diagnosed with XHIGM over the past five decades, survival is similar for those treated with or without HCT. Survivors who receive HCT show some improvement in well-being; reductions in the hazards associated with HCT became significant in the late 1990s. For patients undergoing HCT, early diagnosis of XHIGM is associated with better survival.

COMMENT: Treatment options for primary immunodeficiency can be overwhelming and difficult to consider. This retrospective study compared outcomes of patients with XHIGM who were treated with and without HCT. As in other primary immunodeficiency diseases, early age at diagnosis was associated with improved survival. The HCT patients had "somewhat" greater well-being, as measures of activity of daily living favored transplantation. The study found no difference in survival between patients who did and did not receive HCT. This is valuable information for practicing immunologists to be able to share with patients and families, as they consider their treatment options for this life-threatening primary immunodeficiency.
V.H.-T.

Eosinophilic or Gastrointestinal Disorders

O'Sullivan JA, Bochner BS: Eosinophils and eosinophil-associated diseases: an update. J Allergy Clin Immunol. 2018;141:505-517.

The recent approval of two biologic agents targeting interleukin-5 (IL-5) draws renewed attention to the importance of eosinophils in human health and disease. This review presents an update on advances in understanding of basic eosinophil biology and clinical advances related to eosinophils and associated diseases.

Scientific studies have provided new insights into the development of eosinophils and their basic biology, including the role of the IL-1 family cytokine IL-33 in promoting eosinophilopoiesis. Other studies have clarified the intrinsic and extrinsic pathways regulating eosinophil longevity. Molecular profiling studies have recognized distinctions between eosinophils in different patients and diseases, while several recent studies have recognized the phenotypic diversity of eosinophils within organisms. Preclinical models have demonstrated eosinophils' involvement in the pathogenesis of cutaneous and airways diseases, digestive tract diseases, and cancer.

Studies have investigated the roles of eosinophils in upper and lower airway diseases, including the finding that increased eosinophil counts are related to exacerbation risk in asthma and chronic obstructive pulmonary disease. Therapeutic studies have reported the efficacy of anti-IL-5 agents in patients with eosinophilic granulomatosis with polyangiitis, agents targeting IL-5 receptor α in some groups of asthma patients, and treatments targeting IL-4 receptor α in chronic rhinosinusitis with nasal polyps and atopic dermatitis. There are also promising results of treatments for eosinophilic gastrointestinal disorders, such as proton pump inhibitors, dexpramipexole, the antisense DNA agent SB010, and the CRTH2 antagonist fevipripant. The authors prioritize areas for further scientific and clinical studies of eosinophils and related diseases.

COMMENT: This update highlights recent advances in our understanding of the basic science and clinical impact of eosinophils. From a basic science perspective, impor-

tant themes include the role of IL-33 in eosinophilopoiesis, the homeostatic and regulatory roles of eosinophils, and the pathways responsible for eosinophil longevity. From a clinical perspective, the authors discuss the association between increased eosinophil counts and exacerbations of asthma and COPD; the use of biologics including anti-IL-5 agents for treatment of EGPA and Th2-high asthma; and IL-4 receptor α antagonist in the treatment of CRSwNP and atopic dermatitis. This is truly an encyclopedic review of the topic.
J.J.O.

Spergel J, Aceves SS: Allergic components of eosinophilic esophagitis. J Allergy Clin Immunol. 2018;142:1-8.

The prevalence of eosinophilic esophagitis (EoE) is rising, with up to 1 in 1,000 adults and children affected worldwide. A growing body of evidence suggests that EoE is an allergic disorder. The authors present an update on the role of antigens in provoking the Th2-mediated esophageal immune response in patients with EoE.

It has been established that EoE is an antigen-driven disease; milk, egg, soy, and wheat are the most common triggers. On molecular profiling studies, EoE is an eosinophil-predominant condition with a Th2 profile, similar to asthma and other allergic diseases. Aeroallergens can also act as triggers for EoE, including dust mite, pollen, and mold. One referral-center study reported symptomatic oral allergy syndrome in 50% of patients with EoE. Antigens induce eosinophil, basophil, mast cell, and T-cell infiltration. The pathogenesis of EoE reportedly involves local epithelial immune activation with production of thymic stromal lymphopoietin and eotaxin-3.

For most patients, EoE is a chronic condition requiring long-term avoidance of the implicated food. Antigen sensitization may be one factor predisposing to persistent disease. A combination of skin prick and patch testing may have diagnostic utility in identifying triggering food antigens in children, but not necessarily in adults. Some reports have described oral immunotherapy to foods and pollens triggering EoE. The authors highlight key areas for further study, including the identification of antigen-specific esophageal T cells and allergen immunotherapy regimens that may be effective in treating EoE.

COMMENT: This is an excellent review by two leading experts in EoE, focusing on the role of allergens in provoking Th2 inflammation, including inhalant allergens. Oral allergy syndrome occurs in 50% of patients and pollen may trigger seasonal flares of EoE. Food IgE testing is not useful in adults. and no tests (skin test, atopy patch, etc) appear very helpful in guiding dietary management versus empiric elimination. This is a great article to get up-to-date on the current theories of immunopathogenesis, diagnosis, and role of other atopic conditions in EoE.
D.A.K.

Kuang FL, Klion AD. Biologic agents for the treatment of hypereosinophilic syndromes.
J Allergy Clin Immunol Pract. 2017;5:1502-1509.

Patients with hypereosinophilic syndromes (HES) have peripheral eosinophilia greater than 1.5 × 10^9/L or increased tissue eosinophilia leading to end-organ damage. Conventional treatments such as glucocorticoids, hydroxyurea, and interferon-α are helpful for most patients, but treatment resistance and toxicity are common. The authors discuss the growing role of biologic agents targeting eosinophils in the treatment of HES.

The authors outline the general approach to conventional therapy for HES according to clinical subtype. Despite a number of available immunomodulatory and cytotoxic agents, many patients are treatment-refractory or develop treatment-related toxicity. Several monoclonal antibodies targeting eosinophils may provide promising treatment alternatives, although none is yet approved for use in HES.

A growing body of evidence supports the effectiveness of anti-IL-5 therapy with high-dose mepolizumab for patients with some HES subtypes, including glucocorticoid-sensitive HES. Reslizumab is likely to be effective as well. Benefits of mepolizumab include a glucocorticoid-sparing effect. Studies in patients with eosinophilic gastrointestinal disorder have suggested the effectiveness is lower in EoE than in other forms of HES. Other biotherapeutic agents under development may offer advantages over anti-IL-5 therapy. These include the anti-il-5Rα agent benralizumab and agents directed against the eosinophil receptor sialic acid-binding immunoglobulin-like lectin 8 (Siglec-8).

New and emerging antieosinophil biologic agents have the potential to improve treatment for HES, without off-target effects. The article addresses the classification and diagnostic approach to HES, and includes a summary of clinical trials of biologics for HES according to clinical subtype.

COMMENT: Hypereosinophilic syndromes can be confusing. Now, with increased interest in eosinophils with anti-IL5 drugs, these cells are being measured more often. This article helps us understand the importance of the diagnostic workup and options for therapy in HES. It is important to place rational expectations on response to treatment and to outline follow-up care. Careful attention to comorbid conditions and evaluation of the treatment plan are important.
B.E.C.