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American College of Allergy, Asthma & Immunology

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Head and Neck

Weinstein SF, Katial R, Jayawardena S, et al: Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma.
J Allergy Clin Immunol. 2018;142:171-177.

In previous trials, the interleukin (IL)-4/IL-13 inhibitor dupilumab has reduced exacerbations and improved lung function in patients with uncontrolled, persistent asthma. Many patients have comorbid type 2 immune diseases, including perennial allergic rhinitis (PAR). Pivotal trial data were analyzed to assess dupilumab's impact on allergic rhinitis (AR) symptoms in patients with comorbid asthma and PAR.

The post hoc analysis used data from a phase 2b trial of dupilumab, 200 or 300 mg every 2 weeks, versus placebo in patients with persistent asthma symptoms despite medium- to high-dose inhaled corticosteroids plus long-acting β2-agonists. Based on specific IgE response (0.35 kU/L or higher) to typical perennial allergens, 241 patients (61.5% of the sample) were classified as having PAR. The study assessed dupilumab's effects on PAR outcomes, based on the 22-item Sino-Nasal Outcome Test (SNOT-22).

At the 300 mg dose, dupilumab was associated with significant improvement in PAR outcomes: least-squares mean difference in the total SNOT-22 score was –5.98, compared to placebo. Patients receiving dupilumab 300 mg also had lower scores for AR-associated symptoms of nasal blockage, runny nose, sneezing, and postnasal discharge. Total and AR-specific symptom scores were numerically but not statistically lower with the 200 mg dose of dupilumab. As in the overall sample, dupilumab was safe and generally well tolerated in patients with comorbid PAR.

Add-on therapy with dupilumab 300 mg every 2 weeks is associated with improvement in nasal symptoms for patients with uncontrolled persistent asthma and comorbid PAR. While calling for further studies in this patient subgroup, the investigators conclude: "A systemic therapy with a selective immunomodulator that treats both AR and uncontrolled persistent asthma may improve outcome in patients with comorbid AR and asthma."

COMMENT: The role of dupilumab in patients with PAR adds to the other indications: atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps. The results support the unified airway hypothesis, showing benefits with dupilumab in patients with asthma and PAR. The cost of the drug would make dupilumab a difficult cost-effective sale in patients without asthma as a comorbidity.
B.E.C.

Niederberger V, Neubauer A, Gevaert P, et al: Safety and efficacy of immunotherapy with the recombinant B-cell epitope-based grass pollen vaccine BM32.
J Allergy Clin Immunol 2018;142:497-509.

BM32 is a new grass pollen allergy vaccine based on recombinant fusion proteins of nonallergenic peptides • • •

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'MOC' ARTICLES

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from the IgE-binding sites of the four major timothy grass allergens, plus the preS protein from the large surface antigen of the hepatitis B virus. Previous studies have shown reduced symptom scores in grass pollen-allergic patients treated with BM32, with induction of allergen-specific IgE and reduced allergen-specific T-cell proliferation. The authors report a multicenter, placebo-controlled field trial of BM32 vaccine for grass pollen allergy.

The trial included 181 patients with grass pollen allergy and allergic rhinitis and/or mild asthma, enrolled at 11 European centers. After a baseline season, patients were randomly assigned to three preseasonal injections of low- or high-dose (80 or 160 μg) BM32 vaccine or placebo, plus a booster injection in the fall. In the second season, all BM32 patients received the low-dose vaccine, while placebo patients continued on placebo.

On double-blind analysis, patients in the BM32 group had a nonsignificant reduction (about 20%) in mean daily combined symptom medication scores, calculated for the peak of grass pollen season (primary endpoint). There were accompanying improvements in visual analog scale score, rhinoconjunctivitis-related quality of life, and asthma symptom scores. The BM32 vaccine induced allergen-specific IgG but not IgE and prevented the seasonal increase in allergen-specific IgE during the second year. Six grade 2 reactions occurred during the first year in the BM32 group, compared to one in the placebo group. In the second year, systemic events were infrequent in both groups.

The recombinant B cell epitope-based BM32 vaccine produces some improvement in symptoms of grass pollen allergy over two seasons. The vaccine is safe, requires only a few injections, and is very well tolerated, supporting progression to phase 3 clinical trials. Since it doesn't increase allergen-specific IgE, BM32 might also be used in preventive vaccination studies.

COMMENT: These researchers used a novel BM32 allergy vaccine based on recombinant fusion proteins to provide allergen immunotherapy for grass pollen allergy. Although the primary endpoint was not reached, there was clinical improvement, particularly in the second year of treatment. Not only was there a dramatic increase in allergen-specific IgG, the vaccine also induced increases in Th1 but not Th2 responses. Since there was minimal IgE response to BM32, high doses could be used safely. The authors suggest that these types of vaccines, which require fewer injections, could be used safely to induce blocking IgG in patients with pollen allergy.
S.M.F.

Ta LDH, Yap GC, Tay CJX, et al: Establishment of the nasal microbiota in the first 18 months of life: correlation with early-onset rhinitis and wheezing.
J Allergy Clin Immunol 2018;142:86-95.

Development of the nasal microbiome during infancy may affect local immune responses and susceptibility to upper respiratory infections, but its relationship to allergic disease risk remains unclear. This longitudinal study compared the development of the microbiota in infants who did and did not develop rhinitis and wheeze in the first 18 months of life.

The case-cohort study included 122 infants enrolled in a birth cohort study in Singapore. At seven times during the first 18 • • •

months, nasal microbiota samples were analyzed using 16S rRNA multiplexed pair-end sequencing. Findings were compared for 28 infants who developed rhinitis alone, 34 who developed rhinitis plus wheeze, and 60 healthy controls.

Through 18 months, bacterial diversity decreased in the two groups of infants with rhinitis, compared to increasing diversity in healthy controls. Infants with rhinitis, with or without wheezing, showed decreased abundance of the Corynebacteriaceae family (Actinobacteria phylum) compared to those with neither condition. Infants with rhinitis plus wheeze also had greater abundance of Proteobacteria, Oxalobacteraceae, and Aerococcaceae family (Firmicutes phylum), compared to controls. The Staphylococcaceae family differed until 9 months, being more abundant at early times in controls than in the rhinitis groups. Factors affecting the nasal microbiome development included male sex, presence of siblings, cesarean delivery, and attending infant care.

The study shows distinct differences in the nasal microbiota through 18 months in infants who do and do not develop rhinitis, alone or with wheezing. The authors call for further study to evaluate the impact of the nasal microbiome on the risk of allergic rhinitis and asthma later in childhood.

COMMENT: In this case-control study, nasal swabs obtained in the first 18 months of life confirmed the hypothesis that nasal microbiome influences the development of rhinitis and wheezing. Interestingly male sex, presence of older siblings, cesarean delivery, and infant daycare were significant factors in the establishment of the nasal microbiome. The same factors influenced the presence of Corynebacteriaceae, which had a protective effect against development of respiratory symptoms. Follow-up data found that 20% of infants with rhinitis at 18 months continued to have symptoms at 5 years. Controls remained rhinitis-free, suggesting that rhinitis status at 18 months is a predictor for childhood rhinitis.
S.M.F.

Dermatologic

Maurer M, Fluor J, Khan D: How to approach chronic inducible urticaria.
J Allergy Clin Immunol Pract. 2018;6:1119-1130.

Chronic inducible urticaria (CIndU) refers to a group of chronic urticarias with physical or nonphysical triggers, leading to recurrent wheals and/or angioedemas. This article reviews the clinical features, diagnosis, and treatment of CIndU.

Compared to chronic spontaneous urticaria, CIndU has a longer duration and lower remission rate, sometimes with systemic symptoms of mast cell activation. The pathophysiology of CIndU is unclear, but involves mast cell activation and degranulation and release of proinflammatory mediators. Management focuses on controlling symptoms by avoiding triggers, desensitization, blocking mast cell mediators, and preventing mast cell degranulation.

The review focuses on four types of CIndU. Patients with symptomatic dermographism (SD), the most common physical CIndU, develop itchy wheals in response to rubbing, scratching or scrubbing. Those with cold urticaria (ColdU) develop wheals after contact with cold, or after skin cooling and rewarming. Primary acquired ColdU is the most common type; secondary, atypical, and hereditary forms have been described.

Patients with cholinergic urticaria (CholU) develop itching, redness, and popular wheals in response to exercise or passive warming, or sometimes emotional stress or spicy foods. This form of CIndU must be differentiated from exercise-induced anaphylaxis. Delayed pressure urticaria is associated with delayed erythema and edema, typically 4 to 6 hours after pressure stimuli. Swelling of the hands and feet may closely resemble angioedema.

The review addresses clinical management of each form of CIndU, including provocation tests and treatment. Although some new tests and treatments have become available, more research is needed to explore the causes and possible cures for these conditions.

COMMENT: In this detailed, well-referenced review article, the authors explain the evaluation and therapy for various forms of CIndU, including physical and nonphysical triggers. Interesting points include that SD affects 25% of patients with chronic spontaneous urticaria. Antihistamine therapy results in complete control in only 25% of patients with SD but marked improvement in 49%. The ice cube test is helpful for patients with ColdU. Antihistamines are the treatment of choice for CIndU, but the authors suggest considering off-label omalizumab therapy for patients with ColdU or SD.
S.M.F.

Aygören–Pürsün E, Bygum A, Grivcheva–Panovska V, et al: Oral plasma kallikrein inhibitor for prophylaxis in hereditary angioedema.
N Engl J Med. 2018;379:352-362.

Hereditary angioedema (HAE) is caused by C1 esterase inhibitor gene mutations, leading to over-activation of the kallikrein-bradykinin cascade. A phase 2 trial evaluated the oral small-molecule plasma kallikrein inhibitor BCX7353 for prevention of HAE attacks.

The three-part Angioedema Prophylaxis 1 (APeX-1) trial included 77 patients with a clinical diagnosis of type I or II HAE and a documented history of two or more attacks per month for 3 consecutive months. Patients were randomly assigned to treatment with oral BCX7353, daily dose 62.5, 125, 250, or 350 mg, or placebo.

Patients receiving BCX7353 125, 250, or 350 mg/d had a significant reduction in the rate of confirmed angioedema attacks: 73.8% lower than in the placebo group. The 125 mg dose eliminated attacks in 43% of patients, while those receiving BCX7353 125 or 250 mg had significant

improvement in quality of life. Gastrointestinal adverse events occurred in 44% of patients at the 350 mg dose and 50% at the 250 mg dose, compared to 29% at the 125 mg dose. Across the dose range studied, BCX7353 produced dose-dependent kallikrein inhibition.

The APeX-1 trial supports the effectiveness of BCX7353 as a once-daily oral kallikrein inhibitor for prevention of HAE attacks. The 125 mg/d dose reduces angioedema attacks and improves quality of life with fewer adverse effects than higher doses. Further studies are needed to establish the long-term safety profile of BCX7353.

COMMENT: The APeX-1 trial used a unique oral kallikrein inhibitor (BCX7352) in various doses to block attacks of HAE. Patients receiving the 125 mg dose had a 73.8% difference in the prevention of attacks, with 43% achieving attack-free status compared to the placebo group. Interestingly, there was an apparent U-shaped therapeutic response, since patients receiving higher doses had increased gastrointestinal adverse events that may have been interpreted as early HAE attacks. A safe, nonhormonal oral medication for HAE prophylaxis would be a "game-changer" for these patients.

S.M.F.

Fonacier L, Noor I: Contact dermatitis and patch testing for the allergist.
Ann Allergy Asthma Immunol. 2018;120:592-598.

Contact dermatitis (CD) should be suspected in patients with chronic eczematous or noneczematous dermatitis. Irritant contact dermatitis (ICD) accounts for 80% of cases and allergic contact dermatitis (ACD) for 20%. The authors review current knowledge of CD, focusing on irritant and allergic causes and the role of patch testing (PT).

Allergic CD is typically localized to the skin area that comes into contact with the involved allergen, although some allergens may cause patchy or diffuse distributions. Systemic CD may result from allergen inhalation, ingestion, or infusion. Irritant CD is caused by repeated weak chemical exposure; occupational cases most often involve the hands. The diagnosis of occupational CD can be difficult to make, relying on careful history and examination.

Patch testing can play an important role in identifying the causative allergen and is the gold standard for diagnosis of ACD. Concentrations of standard allergens for patch testing are known for the skin of the back only. The authors highlight the importance of determining the clinical relevance of positive patch test results. They also present some allergen "pearls," including nickel, the most common positive patch test allergen; as well as topical medications, cosmetics, and preservatives.

Once the causative allergen or irritant is identified, the patient is counseled regarding avoidance and possible cross-reactivity. Workers should be advised that CD may be a persistent problem requiring long-term management, even after treatment and workplace modification. The authors note that "the outlook for occupational CD is poor," with high rates of continued disease at follow-up.

COMMENT: This review of CD points out that 80% of cases are due to ICD and 20% due to ACD. Bakers have the highest rate of occupational CD due to flour, grains, foodstuffs, and baking-associated enzymes. Agricultural workers have the second-highest rate, usually due to cow dander. Nickel is positive in 19% of patients having PT. Patients with nickel sensitivity are at risk of systemic CD after eating nickel-containing foods, including chocolate, soy, legumes oats, almonds, cashews, shellfish and certain seafood.

S.M.F.

Lung

Dekhuijzen R, Lavorini F, Usmani OS, et al: Addressing the impact and unmet needs of nonadherence in asthma and chronic obstructive pulmonary disease: where do we go from here?
J Allergy Clin Immunol Pract. 2018;6:785-793.

Treatment nonadherence is a major problem in management of asthma and chronic obstructive pulmonary disease (COPD). The new Ascertaining Barriers to Compliance taxonomy defines three phases of adherence: initiation; implementation, with inhaler technique being of prime importance; and discontinuation. The issue of nonadherence in asthma and COPD is reviewed, including recommendations to improve disease control and reduce healthcare spending.

Nonadherence to inhaler use is a key contributor to suboptimal adherence, with causes including intentional and unintentional factors. Suboptimal inhaler technique consistently leads to poor clinical outcomes, and thus to increased direct and indirect costs. Reports suggest that nonadherence in asthma and COPD is a "treatable trait" – a 25% increase in adherence has been linked to a 10% reduction in severe exacerbations. The authors highlight the importance of choosing the best inhaler for the individual patient.

The review highlights strategies to improve inhaler adherence, including patient empowerment and education/training approaches, such as improved clinician-patient communication, adherence counseling, and information feedback. Electronic dose monitoring is increasing in popularity, with studies suggesting positive effects on adherence in both asthma and COPD. Digital technology and telehealth approaches, such as text messaging and smartphone apps, are promising strategies. The authors believe that improved adherence in asthma and COPD is "eminently achievable" through the use of appropriate strategies.

COMMENT: Healthcare practitioners believe that poor adherence to controller therapy is a major reason for exacerbations. The three phases of adherence are described in the manuscript. The causes of and the approach to • • •

improving adherence are outlined in detail. Exploring adherence in patients is vitally important, and this manuscript gives practical advice to improve adherence. Electronic monitoring and digital technology are becoming rapidly available and may prove to be major adjuncts in patient care.
B.E.C.

Chipps BE, Bacharier LB, Farrar JR, et al: The Pediatric Asthma Yardstick: practical recommendations for a sustained step-up in asthma therapy for children with inadequately controlled asthma.
Ann Allergy Asthma Immunol. 2018;120:559-579.

Even with individualized treatment, disease control in pediatric asthma can be difficult to achieve. The authors describe the Pediatric Asthma Yardstick as a new tool to inform assessment and step-up therapy for children and adolescents with inadequately controlled asthma.

The Pediatric Asthma Yardstick presents patient profiles and recommendations for step-up therapy for poorly or not well controlled asthma in adolescents (age 12 to 18), school-aged children (aged 6 to 11), and preschool children (age 5 or younger). Recommended strategies are informed by current step-based strategies, including the National Asthma Education and Prevention Program (NAEPP) guidelines and the Global Initiative for Asthma (GINA) management strategy, with modifications based on newer information and expert clinical experience. Strategies seek to achieve good symptom control, including little or no sleep disturbance and normal activity; and to minimize risk of exacerbations, impaired lung function, and medication side effects.

The article includes patient profiles of adolescents, school-aged children, and preschool children with intermittent, mild to moderate, and moderate to severe persistent asthma. For each profile, recommended treatments are presented along with other options, including targeted biologic therapies. The recommendations also include steps at which referral to a pediatric asthma specialist should be considered or obtained.

The authors discuss the ongoing evolution of pediatric asthma management, including the "new care model" of treatment based on phenotype. They suggest periodic monitoring of lung function in children with persistent asthma and strategies to identify those with or at risk of loss of asthma control.

COMMENT: This review updates the NAEPP 2007 guidelines and is consistent with GINA 2017. It lays the groundwork for discussion with patients about diagnosis, natural history and treatment of pediatric asthma. The five steps of care for pediatric asthma are evaluated in detail with therapeutic options given at each level of care. Updates are available in *Annals* in January and June of each year, and the article and updates are available as open access.
B.E.C.

Jackson DJ, Bacharier LB, Mauger DT, et al: Quintupling inhaled corticosteroids to prevent childhood asthma exacerbations. N Engl J Med. 2018;378:891-901.

Increasing the inhaled corticosteroid dose is a common strategy in patients with early signs of loss of asthma control. There is little evidence on the safety and efficacy of this approach in childhood asthma. The randomized "Step Up Yellow Zone Inhaled Corticosteroids to Prevent Exacerbations" (STICS) trial evaluated the strategy of quintupling ICS dose to prevent pediatric asthma exacerbations.

The study included 254 children, aged 5 to 11, with mild-to-moderate persistent asthma and at least one exacerbation requiring systemic glucocorticoids during the past year. Over 52 weeks, all received open-label low-dose maintenance ("green zone") therapy with fluticasone: 44 μg 2 puffs bid. When signs of loss of asthma control appeared ("yellow zone"), patients either continued low-dose ICS or received quintuple-dose therapy with fluticasone, 220 μg 2 puffs bid for 7 days.

There was no significant difference in severe exacerbations requiring systemic glucocorticoids during blinded treatment with low-dose versus high-dose ICS: at least one severe exacerbation occurred in 38 children in the high-dose group and 30 in the low-dose group. Other outcomes were similar as well, including time to first severe exacerbation, emergency or urgent care visits for asthma, and symptom burden during yellow-zone episodes. Reflecting higher inhaled and total glucocorticoid exposure, children in the high-dose ICS group had reduced linear growth: –0.23 cm per year. Electronic diaries suggested that both groups had about two yellow-zone episodes per year.

For school-age children with persistent asthma, quintupling the dose of ICS in response to early signs of loss of asthma control does not reduce severe exacerbations. Other clinical outcomes are also similar to those of children who remain on low-dose ICS during yellow-zone periods.

COMMENT: Loss of control in childhood asthma often leads to frank exacerbations. The STIC trial examines the utility of increasing ICS from low-dose to five times higher at the first sign of loss of control. There was no change in any outcome. An electronic diary compiled approximately 72% of the days, with 98% adherence to ICS on days that the diaries were recorded. This verifies that low-dose ICS is of value in preventing exacerbations. The findings reinforce the value of fixed and reliever ICS/LABA as an important intervention strategy, and support ongoing study of ICS/SABA as a potentially effective intervention for loss of asthma control.
B.E.C.

Food and Drug

Kuyucu S, Caubet J-C: Hypersensitivity reactions to antiepileptic drugs in children: epidemiologic, pathogenetic, clinical, and diagnostic aspects.
J Allergy Clin Immunol Pract. 2018;6:1879-1891.

Anti-epileptic drugs (AEDs) are one of the most common causes of drug hypersensitivity reactions (DHRs), and severe reactions in particular, Pediatric AED use has become dramatically more prevalent in recent years. The authors report a clinical management review of drug hypersensitivity reactions to AEDs in children.

Based on review of the literature since the 1990s, aromatic AEDs such as phenytoin, phenobarbital, and carbamazepine are mainly implicated in reports of DHRs, and are still the main AEDs prescribed in both developed and developing countries. Newer AEDs are assumed to have lower toxicity, but severe reactions have been described. The pathogenesis of DHRs to AEDs is complex, involving metabolic, genetic, and immunologic factors. Recent studies have linked AED-related DHRs in both adults and children to HLAs and/or polymorphisms of AED metabolic enzymes.

Risk factors for DHRs to AEDs in children include young ages, concurrent medications, high starting doses and rapid escalation, and certain HLA genotypes. Reactions may range from minor skin rashes to severe reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms (DRESS). Very few studies have evaluated the role of available diagnostic tests for pediatric DHRs to AEDs. Based mainly on adult studies, patch testing has relatively high value in identifying the causative drug.

Identification and elimination of the culprit drug is the mainstay of management, including evaluation of the initial indication and prescription of alternative medications. Substantial rates of cross-reactivity have been reported, mainly involving aromatic AEDs. Desensitization may be considered if other alternatives fail, but there are few data on this approach, particularly in children.

COMMENT: Few studies have investigated diagnostic tools in pediatric epilepsy patients with hypersensitivity to their AEDs. This review describes AEDs, particularly aromatic AEDs, as a frequent cause of DHRs. Severe reactions have also been described. Factors including young age and viral infections, as well as some genetic markers, may help us identify patients at increased risk of hypersensitivity reactions. Further pediatric studies of the utility of diagnostic tools, such as drug patch tests, are needed. Allergists have the opportunity to make a difference for children with epilepsy by collaborating with pediatricians and pediatric neurologists to properly identify patients at risk of AEDs and aiding in management.
V.H.-T.

Macy E, Vyles D: Who needs penicillin allergy testing? Ann Allergy Asthma Immunol. 2018;121:523-529.

While it may seem reasonable to avoid penicillin in patients with a recorded history of "penicillin allergy," unnecessary penicillin avoidance carries certain harms. This review focuses on the issue of penicillin allergy, including current recommendations for penicillin hypersensitivity testing.

Penicillin allergy is frequently recorded, but most reported reactions are not consistent with clinically significant, immunologically mediated hypersensitivity. Penicillin-associated anaphylaxis is the most-feared consequence of penicillin re-exposure, but is "extremely rare." In a recent audit, the authors found that 0.5% to 1% of penicillin exposures led to a new allergy report, with less than 1 in 1,000 episodes involving anaphylaxis. Severe cutaneous adverse reactions to penicillin are "much rarer" than anaphylaxis.

The authors suggest that all patients with unconfirmed penicillin allergy should be evaluated and, if appropriate, undergo confirmatory testing. The standard test to confirm penicillin-class antibiotic hypersensitivity is oral challenge with a therapeutic dose. Patients are observed for 1 hour and followed up for 5 days to confirm the absence of acute or delayed, clinically significant T cell-mediated hypersensitivity.

Low-risk patients with a history of reactions unlikely to be IgE-mediated can undergo direct challenge with oral amoxicillin. For higher-risk patients, puncture and intradermal skin testing with penicilloyl-polylysine can be considered: at least 5 mm of wheal and flare greater than wheal is considered a positive test result. If skin tests are positive, the patient should not have oral challenge. Oral penicillin desensitization is indicated for patients with positive skin tests or immediately positive oral challenge, if they have a confirmed infection for which penicillin is the antibiotic of choice.

COMMENT: Allergists are charged with initiatives to correctly diagnose patients with penicillin allergy. Patients with penicillin allergy are treated with broader-spectrum antibiotics that are associated with increased morbidity, as well as more time in the hospital resulting in increased healthcare costs. The authors remind us that most patients with "penicillin allergy" are able to tolerate penicillin. Low-risk patients may safely tolerate a direct oral amoxicillin challenge. Others with reactions within the past 12 months or a history of anaphylaxis would benefit from penicillin skin testing.
V.H.-T.

**Schuyler AJ, Wilson JM, Tripathi A, et al: Specific IgG_4 antibodies to cow's milk proteins in pediatric patients with eosinophilic esophagitis.
J Allergy Clin Immunol. 2018;142:139-148.**

Studies in adults with eosinophilic esophagitis (EoE) have reported specific IgE antibodies to implicated foods, including cow's milk (CM) and wheat. The clinical significance of this finding is unclear, and it has not been studied in children. This study measured serum food-specific IgG_4($sIgG_4$) levels in children with EoE.

The study used serum samples from 71 children with biopsy-confirmed EoE, and from an unselected birth cohort of 210 early-adolescent children. Component diagnostics were used to measure $sIgG_4$ and IgE to major CM proteins along with other food allergen proteins. The effects of sex, age, and milk consumption were analyzed as well.

Children with EoE were more likely to have high titers (over 10 mg/mL) of $sIgG_4$ to CM proteins, compared to controls. Odds ratios for EoE associated with high-titer $sIgG_4$ CM proteins ranged from 5.5 for Bos d 5 and 8.8 for Bos d 8. Generally, specific IgE levels of CM proteins in EoE patients were 4 IU/mL or less, leading to $sIgG_4$/IgE ratios of 10,000 or higher.

After adjustment for age and milk consumption, high titers of $sIgG_4$ to CM proteins were strongly associated with EoE. The associations were strongest in boys, with odds ratios over 20 for all three CM proteins studied. Monitoring of EoE patients undergoing an elimination diet showed decreased levels of $sIgG_4$ to CM proteins, with or without remission.

Children with EoE commonly have high titers of $sIgG_4$ to CM proteins, compared to unselected controls. The differences appear of greater magnitude in boys than girls. The investigators conclude: "Although it is not clear that this response is pathogenic, $sIgG_4$ levels imply that these antibodies are an important feature of the local immune response that gives rise to EoE."

COMMENT: There is interest in biomarkers that may help diagnose or manage our patients with EoE. In particular, pediatric EoE patients have high-titer $sIgG_4$ levels to food allergens. In contrast to other diseases where the presence of $sIgG_4$ may correlate with tolerance, high $sIgG_4$ to CM is not associated with CM tolerance. Since 10% of controls had high $sIgG_4$ titers to CM, this marker alone doesn't appear to explain pathology of EoE. Interestingly, both EoE and IgG_4-related disease are steroid responsive and more common in males. Biomarkers of IgG_4-related disease are also present in patients with EoE. Further studies are needed to determine whether $sIgG_4$ levels to CM could be used to diagnose or monitor disease.

V.H.-T.

Anaphylaxis

Carter MC, Desai A, Komarow HD, et al: A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis.
J Allergy Clin Immunol. 2018;141:180-188.

Some patients with idiopathic anaphylaxis (IA) are found to have an underlying clonal disorder, such as systemic mastocytosis. This prospective study evaluated the prevalence of clonal mast cell disorders in patients with IA, including an approach to identifying patients with recurrent IA who are candidates for bone marrow biopsy.

The study included 56 patients with IA, aged 13 to 69, enrolled over 6 years in a National Institutes of Health (NIH) protocol. Evaluation included bone marrow examination with flow cytometry and *KIT* mutational analysis to assess the presence of clonal mast cell disorders.

Clonal mast cell disease was diagnosed in 14 percent of patients. Four patients were diagnosed with indolent systemic mastocytosis (ISM) and four with monoclonal mast cell activation syndrome (MMAS). Allele-specific quantitative polymerase chain reaction (ASqPCR) for the *KIT* D816V mutation contributed to the identification of ISM, but not MMAS. Based on clinical findings, serum tryptase measurement, and ASqPCR, the investigators developed a modified score for identifying candidates for bone marrow biopsy, with a sensitivity of 75% and specificity of 100%. Patients who had IA without a clonal mast cell disorder showed no evidence of a hyperresponsive mast cell phenotype.

About 1 in 7 patients with IA can be diagnosed with a clonal mast cell disorder. The modified NIH Idiopathic Clonal Anaphylaxis Score can reliably screen out IA patients who do not have a clonal disorder.

COMMENT: Idiopathic anaphylaxis is a particularly vexing condition that has frustrated clinicians for decades. In this important prospective study from the NIH, the investigators studied the potential associations of IA with clonal mast cell disorders. Their finding that 14% of patients with IA demonstrate clonal mast cell disease is very significant. This is similar to studies of patients with venom anaphylaxis. The report should remind us that IA is commonly associated with monoclonal mast cells disorders and requires evaluation beyond serum tryptase, including bone marrow and genetic testing.

A.M.

Wright CD, Longjohn M, Lieberman PL, Lieberman JA: An analysis of anaphylaxis cases at a single pediatric emergency department during a 1-year period.
Ann Allergy Asthma Immunol. 2017;118:461-464.

Rates of emergency department (ED) visits and hospitalizations for anaphylaxis are increasing, especially for reactions to foods. Few studies have focused on anaphylaxis in children. The authors review a one-year experience with anaphylaxis at a pediatric ED.

Of 917 unique ED visits, 40 definitively met National Institutes of Health/National Institute of Allergy and Infectious Diseases criteria for true anaphylaxis. Median age was 6.5 years; 70% of the children were boys and 80% were African American. Foods, most commonly peanut, accounted for 65% of cases of anaphylaxis. Venom or insect sting was the cause in 12.5% of cases and medications in 5%; the remaining 17.5% were idiopathic.

Multiorgan involvement was present in all cases: skin in 98% of patents, lower respiratory tract in 78%, and gastrointestinal tract in 40%. Only 32.5% of patients received epinephrine, while 62.5% received H_1 antihistamines and 52.5% received systemic glucocorticoids. There were no hospitalizations and no deaths. Of 12 patients referred to an allergist, only 4 made an outpatient allergy visit.

This experience supports the importance of food reactions as a cause of anaphylaxis in children. Despite guideline recommendations, most children with anaphylaxis do not

receive epinephrine. Efforts to increase the rates of allergist referral and follow-up are needed.

COMMENT: There is little question that food allergy and food-induced anaphylaxis in children are on the rise. In this analysis of data from a single pediatric ED, foods were clearly the most common inciting agent. Fortunately, no deaths were reported, but almost 80% of the children had lower respiratory involvement. Sadly, only 12% of these severely affected children were referred to allergists. This should be unacceptable to our patients and the medical community!

A.M.

Bonadonna P, Zanotti R, Pagani M, et al: Anaphylactic reactions after discontinuation of Hymenoptera venom immunotherapy: a clonal mast cell disorder should be suspected.
J Allergy Clinical Immunol Pract. 2018;6:1368-1372.

For patients with Hymenoptera venom allergy and a history of severe reactions, venom immunotherapy (VIT) protects against future reactions in most cases. Case reports have described severe and even fatal reactions after completion of VIT in venom-allergic patients with mastocytosis. This study evaluated the presence of clonal mast cell disorders in patients who had anaphylactic reactions after completing Hymenoptera VIT.

The study included 19 patients at an Italian center who had severe reactions to Hymenoptera stings after completing at least 4 years of VIT. The patients were 17 men and 2 women, mean age 56 years; none had a previous diagnosis of mastocytosis. Based on the presence of a Red Espanola de Mastocitosis score of 2 or higher or a serum basal tryptase level of greater than 25 ng/mL, patients underwent a hematologic workup and/or skin biopsy.

A clonal mast cell disorder was diagnosed in 18 of 19 patients. The diagnosis was bone marrow mastocytosis in 14 patients, mastocytosis of the skin in 2, monoclonal mast cell activation syndrome in 1. Another patient was classified as having nonclonal mast cell activation syndrome. At the time of bone marrow biopsy, 8 of the patients with clonal mast cell disorders had normal serum basal tryptase.

In this series, 95% of patients with anaphylactic reactions after a full course of Hymenoptera were found to have a clonal mast cell disorder. The results suggest that patients who lose protection after VIT should be evaluated for possible mastocytosis. For those diagnosed with mastocytosis, lifelong VIT is indicated.

COMMENT: Hymenoptera anaphylaxis is an unsettling condition for patient and allergist. Most patients are adequately protected by a 3- to 5-year course of VIT. Unfortunately, a minority of patients who are adequately treated will react to either sting challenges or field stings. In this series of patients with severe anaphylactic reactions following VIT discontinuation, 95% were found to have clonal mast cell disorders! We must be on the lookout for these patients and remember that they can have normal serum tryptase levels.

A.M.

Motosue M, Bellolio MF, Van Houten HK, et al: Outcomes of emergency department anaphylaxis visits from 2005 to 2014.
J Allergy Clin Immunol Pract. 2018;6:1002-1009.

Studies have suggested a rising incidence of anaphylaxis in the United States, but there are few data on trends in anaphylaxis-related healthcare burden. The authors analyzed nationwide data on the outcomes of emergency department (ED) visits for anaphylaxis from 2005 through 2014.

The analysis included data on more than 100 million Medicare Advantage or privately insured individuals in the United States. Using validated methods, the researchers identified 56,212 anaphylaxis-related ED visits over the 10-year period studied. Trends in ED discharges, observation stays, hospital and ICU admission, and endotracheal intubations were analyzed.

Patients with ED-related hospitalizations had a mean age of 36 years; about one-fourth were younger than 18. Females accounted for 57.5% of patients, while 51.3% were white. The proportion of patients observed or admitted to the hospital rose from 13.2% in 2005 to 18.2% in 2014 – an increase of 37.6%. Admissions to the ICU increased by 27.4%, from 4.5% to 5.8%. Endotracheal intubations increased by 145.2%, from 0.8% to 1.9%. The increases in ICU admissions and intubations were especially pronounced in patients aged 65 years or older and in those with unspecified or medication triggers.

The findings of this analysis of anaphylaxis-related ED visits are consistent with an increase in anaphylaxis severity. The investigators conclude: "Enhanced awareness of these trends among patients, practitioners, and the community is necessary to create effective strategies to prevent anaphylaxis and decrease associated adverse consequences."

COMMENT: This observational study of over 100 million patients over a 10-year period yields sobering results for allergists as well as the general medical community. The data clearly show increases in the incidence and severity of anaphylaxis presenting to the ED. The findings of increasing ICU admissions and need for intubation should serve as a call for action for all of us to be involved in educational initiatives for patients and providers.

A.M.

Immune Hypersensitivity Disorders

De Benedetti F, Gattorno M, Anton J, et al: Canakinumab for the treatment of autoinflammatory recurrent fever syndromes.
N Engl J Med. 2018:378;1908-1919.

Previous studies have suggested that excessive interleukin (IL)-1β production may be a common mediator in three monogenic autoinflammatory recurrent fever syndromes: familial Mediterranean fever (FMF), mevalonate kinase deficiency (MVD), and tumor necrosis factor receptor-associated periodic syndrome (TRAPS). This phase 3 trial evaluated the anti-IL-1β monoclonal antibody canakinumab for treatment of these disorders.

The Canakinumab Pivotal Umbrella Study in Three Hereditary Periodic Fevers (CLUSTER) trial included 63 patients with colchicine-resistant familial Mediterranean fever, 72 with mevalonate kinase deficiency, and 46 with TRAPS. At the time of a disease flare, patients were randomly assigned to canakinumab, 150 mg sc every 4 weeks, or placebo.

Through 16 weeks, canakinumab yielded higher complete response rates (resolution of flare or no flare) in all three groups: 61% versus 6% in FMF, 35% versus 6% in MVD, and 45% versus 8% in TRAPS. In a subgroup of patients, canakinumab dose was increased to 300 mg: response rates were 71% in FMF, 57% in MVD, and 73% in TRAPS.

After 16 weeks, extended treatment with canakinumab every 8 weeks achieved disease control in 46% of patients with FMF, 23% with MVD, and 53% with TRAPS. Infections were the most frequent adverse event in patients receiving canakinumab dose, but few were serious.

Anti-IL-1β therapy with canakinumab is effective in preventing and controlling flares in patients with FMF, MVD, or TRAPS. The authors note that canakinumab had benefits (fewer fever days and flares) even in patients who did not have a complete response. The study design addressed the rarity of these autoinflammatory recurrent fever syndromes, based on the hypothesis of a common mediator.

COMMENT: Autoinflammatory syndromes are relatively rare conditions, making them a challenge to study. This clinical trial used a very innovative study design involving randomization to drug or placebo, dose escalation, drug withdrawal, and longer-term open-label treatment to study three separate monogenic autoinflammatory syndromes. The trial clearly showed marked benefits with canakinumab in resolving acute flares and preventing additional flares. Although canakinumab was associated with increased infections, these were similar to what is known for cryopyrinopathies.

D.A.K.

Wechsler ME, Akuthota P, Jayne D, et al:
Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis.
N Engl J Med. 2018;376:1921-1932.

Patients with eosinophilic granulomatosis with polyangiitis (EGPA), previously known as Churg-Strauss syndrome, have asthma and eosinophilic vasculitis involving one or more organ systems. Preliminary studies have shown clinical improvement with interleukin-5 (IL-5) blockade using mepolizumab for EGPA. This phase 3 trial evaluated add-on therapy with mepolizumab in patients with EGPA.

The study included 136 patients with relapsing or refractory EGPA who had been on a stable dose of prednisolone or prednisone for at least 4 weeks. They were randomly assigned to 52 weeks of treatment with mepolizumab, 300 mg every 4 weeks, or placebo plus standard care. Efficacy and safety outcomes were analyzed.

In the mepolizumab group, 28% of patients accrued at least 24 weeks of remission, compared to 3% in the placebo group: odds ratio (OR) 5.91. Patients receiving mepolizumab were more likely to be in remission at both 36 and 48 weeks: 32% versus 3%, OR 16.74. There was no remission for 47% of patients in the mepolizumab versus 81% with placebo. Annualized relapse rates were 1.14 versus 2.27.

In the last 4 weeks of the study, average daily glucocorticoid dose was 4.0 mg or less in 44% of the mepolizumab group versus 7% of the placebo group: OR 0.20. Safety outcomes were consistent with other mepolizumab studies.

In patients with EGPA, anti-IL-5 therapy with mepolizumab increases remission rate and weeks in remission, leading to a reduced glucocorticoid dose. Although this represents a treatment advance for patients with a rare condition, it is unclear why nearly half of patients did not achieve protocol-defined remission.

COMMENT: Patients with EGPA often remain steroid-dependent; immunosuppressive agents are frequently used despite a paucity of evidence. This multicenter study evaluated mepolizumab for EGPA at a higher dose (300 mg) than used for eosinophilic asthma. Remission was achieved in 44% of patients, while relapses were prevented in about 50%. Why the other half of patients failed to respond may be due to permanent vasculitic damage, insufficient dosing, or adrenal insufficiency limiting steroid tapering. As experts in biologic therapy, allergists will likely be called upon to treat more patients with EGPA.

D.A.K.

Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, et al: Hypersensitivity reactions to therapeutic monoclonal antibodies: phenotypes and endotypes.
J Allergy Clin Immunol. 2018;142:159-170.

Hypersensitivity reactions (HSRs) have emerged as a limiting factor on the use of monoclonal antibodies (mAbs) for treatment of cancer and inflammatory diseases. There are limited data on the diagnosis and clinical management of these reactions, including the use of desensitization. The authors analyzed the phenotypes and endotypes of HSRs to mAbs, including a new classification and an approach to desensitization.

The retrospective study included HSRs to 16 mAbs in 104 patients treated at the authors' center from 2014 through 2016. Fifty-six percent of patients had an oncologic diagnosis; 37% had evidence of atopy and 27% had adverse reactions to other medications. On analysis of initial reactions, 63% of patients had a type I-like reaction, 13% had cytokine-release reactions. 21% had mixed reactions,

and 3% had delayed type IV reactions. The severity of the initial reactions was grade II in 48% and grade III in 29%.

The analysis included 526 desensitizations, 80% of which used a three-bag, 12-step protocol. Only 23% of patients had breakthrough HSRs during desensitization. Of these, 52% were cytokine-release reactions, 32% were type I, 12% were mixed, and 4% were type I with delayed type IV.

Skin testing to ten mAbs was performed in 58 patients, 41% of whom had positive results. During desensitization, 1 patient had elevated serum tryptase. Eight patients had elevated interleukin-6 (IL-6), which was consistently related to cytokine-release symptoms. Ninety-nine percent of desensitizations were successfully completed; intravenous fluids and dose reduction were useful strategies in difficult cases.

Based on their analysis of phenotypes and endotypes, the authors propose a new classification for HSRs to mAbs. Their experience supports the safety and efficacy of desensitization in this group of patients. The authors conclude, "Precision and personalized medicine should be applied to patients with HSR to biologicals."

COMMENT: Prior studies have shown that rapid desensitization protocols can be used successfully in patients with reactions to mAbs. The present study in a larger group of patients with additional biologic agents extends this work. The authors propose that patients may be subclassified into phenotypes and endotypes. However, the latter is less clear, particularly for cytokine release syndromes, as biomarker data (IL-6 levels) were limited. Whether these protocols truly induce tolerance for non-IgE-mediated mechanisms remains unclear. Regardless, this study provides an approach to managing these complex patients with excellent safety outcomes.
D.A.K.

Immunodeficiencies

Hajjar J, Al-Kaabi A, Kutac C, et al: Questioning the accuracy of currently available pneumococcal antibody testing. J Allergy Clin Immunol. 2018;142:1358-1360.

Pneumococcal antibody testing plays an important role in the diagnosis of humoral immunodeficiency syndromes. This study compared *Streptococcus pneumoniae* serotype antibody responses to pneumococcal vaccination in 45 patients, analyzed by different laboratories.

Split serum samples were sent to two commercial laboratories. The patients' mean age was 7 years; 26 had a documented history of recurrent infections. The laboratories measured 14 *S. pneumoniae* serotypes. Based on a cutoff point of 1.3 μg/mL or higher, one laboratory reported protective antibody levels for a median 2 out of 14 serotypes by one laboratory and 11 of 14 by the other. On patient-level analysis, one of the laboratories consistently reported a higher number of protective antibody levels for 14 of the 45 patients. The differences in reporting were similar for patients with recurrent infections versus a history of pneumonia.

The findings suggest a "clinically relevant discrepancy" in *S. pneumoniae* antibody levels reported by different laboratories for patients being investigated for possible immunodeficiency. The researchers write, "These discordant levels could lead to different diagnoses for patients, which could affect medical management and ultimately clinical outcomes."

COMMENT: Immunologists use pneumococcal antibody testing after vaccination to assess humoral immune function and to decide whether antibiotic prophylaxis or immune globulin replacement should be considered. This study used the definitions of a "normal" response from the 2012 AAAAI Basic and Clinical Immunology working group report. The results from two commercial labs on the same serum sample would have led to different conclusions for 14 of the 45 patients studied. This study highlights the need for better tests to evaluate for humoral immunodeficiency.
G.B.L.

**Mayor P, et al. Cancer in primary immunodeficiency diseases: Cancer incidence in the United States Immune Deficiency Network Registry.
J Allergy Clin Immunol. 2018;141:1028-1035.**

It has long been recognized that primary immunodeficiency diseases (PIDD) are associated with an increased risk of cancer. Most studies of this issue were performed decades ago and had important limitations. The United States Immune Deficiency Network (USIDNET) was analyzed to assess cancer rates among patients with PIDD.

The study included 3,658 patients enrolled in the USIDNET registry from 2003 to 2015. Overall and site-specific cancer incidence were analyzed, compared to age-adjusted rates in the Surveillance, Epidemiology and End Results (SEER) program database.

Overall, patients with PID had a 1.42 excess relative risk of cancer, compared to the age-adjusted general population. Cancer incidence was 1.91-fold higher in men with PIDD, but similar to the general population for women. The most common cancers in the SEER database – breast, prostate, lung, and colorectal cancer – did not have a higher incidence among patients with PIDD. However, PIDD was associated with a significant increase in lymphoma: a 10-fold increase in men and an 8.34-fold increase in women. Skin cancer and leukemia were also increased in PIDD patients. Seventy percent of cancers associated with PIDD occurred in patients with common variable immunodeficiency, who accounted for just 35% of patients in the USIDNET registry. Lymphoma and skin cancer were the highest-incidence cancers in CVID patients.

The updated analysis shows an increased incidence of cancer among patients with PIDD, compared to the

general population. The PIDD-associated increase is mainly driven by an increase in lymphoma, whereas the risk of common solid malignancies is not significantly increased. The authors discuss the implications for evidence-based approaches to surveillance and early detection of cancers in patients with PIDD.

COMMENT: This analysis of the USIDNET registry alerts immunologists to the increased risk of certain malignancies in patients with PIDD. The most common malignancies in men and women (lung, colon, breast, and prostate) were similar between patients with PIDD and age-adjusted controls. However, men and women with PIDD, particularly CVID, had an eight- to ten-fold excess relative risk of lymphoma. Patients with CVID were also more likely to develop skin and gastric cancer. We await the development of screening recommendations for these PIDD-specific malignancies.

G.B.L.

Bonilla FA: Update: vaccines in primary immunodeficiency. J Allergy Clin Immunol. 2018;141:474-481.

Assessing clinical responses to vaccines can play a useful role in diagnosis of primary immunodeficiencies (PIDs). Some vaccines, particularly those containing viable organisms, have the potential to cause infections in immunodeficient patients. The author reviews the diagnostic and therapeutic uses of vaccines in patients with PIDs.

The use of vaccines for diagnosing immunodeficiency depends on knowing the normal seroconversion rate; threshold protective levels have been established for many vaccines. The article addresses the diagnostic use of tetanus and diphtheria toxoid vaccines, pneumococcal conjugate and polysaccharide vaccines, and typhoid vaccine. Little is known about the role of vaccine failure – development of a disease against which the patient was fully immunized – in diagnosing immunodeficiency. The uses of and options for measuring antibody responses in patients receiving immunoglobulin therapy are discussed.

Therapeutic uses of human papillomavirus vaccine and influenza virus vaccine in patients with PIDs are discussed; there are few data on vaccine responses in patients receiving immunoglobulin therapy. Most reports of adverse events related to immunization in patients with PIDs involve viable vaccines, including MMR and varicella vaccines, oral polio vaccine, and the more recently introduced rotavirus vaccine.

Screening and early diagnosis of immunodeficiency will reduce the risk of harm from viable vaccines. Systematic collection of data on vaccine complications and failures will provide valuable information on the diagnosis and cost-effective use of vaccines in patients with PID.

COMMENT: This review provides multiple pearls in the use of vaccination in the diagnosis and treatment of PIDs. Table II provides a quick reference to the normal responses to common vaccinations, but also highlights the problems with diagnostic use of pneumococcal vaccination. For patients on immune globulin replacement, the rabies, typhoid, and tick-borne encephalitis virus vaccines can be used to assess humoral immunity. The HPV vaccine is recommended for PID patients susceptible to HPV infection; the influenza vaccine is recommended for all patients, unless they are incapable of a response. Live vaccines are contraindicated in patients on immune globulin and patients with significant T-cell defects.

G.B.L.

Eosinophilic or Gastrointestinal Disorders

Khoury P, Abiodun AO, Holland-Thomas N, et al: Hypereosinophilic syndrome subtype predicts responsiveness to glucocorticoids.
J Allergy Clin Immunol Pract. 2018;6:190-195.

Glucocorticoids (GC) are the first-line treatment for patients with platelet-derived growth factor α *(PDGFRA)*-negative hypereosinophilic syndrome (HES). Clinical factors affecting the response to GC – and thus the need for second-line agents – are not well-defined. This retrospective study examined predictors of GC response in a series of 164 patients with *PDGFRA*-negative HES.

Ninety percent of patients had a response to GC, defined as symptom control with a reduction in absolute eosinophil count (AEC) to less than 1,000/mm^3. Response was achieved at a prednisone dose of 10 mg or less in 39% of patients, 11 to 20 mg in 35%, and 21 mg or higher in 17%. The remaining 9% were GC nonresponders. The main clinical predictor of GC response was HES subtype, with odds ratios of 0.34 for patients with lymphocytic variants and 0.013 for those with myeloid forms (with idiopathic HES as the reference group).

The diagnostic subtype of HES predicts the likelihood of response to systemic GC in *PDGFRA*-negative HES. The findings may have implications for the decision to proceed to second-line therapies in patients with lymphocytic or myeloid forms of HES.

COMMENT: The goal for our patients with HES is to prevent life-threatening manifestations, but no standardized management guidelines exist for this condition. This study reminds us that the HES subtype needs to be defined to optimize patient management, as GC responsiveness varies by subtype. In patients with *PDGFRA*-negative HES, the authors found that those with lymphocytic and myeloid forms would likely benefit from second-line agents as opposed to GC, due to the need for moderate to high doses of GC to achieve disease control in the former subtype and lack of GC responsiveness in the latter subtype. Further studies are needed regarding the reasons for variability in GC responsiveness. This information is essential in aiding allergists to provide optimal treatment to our HES patients.

V.H.-T.

Barbosa AC, Castro FM, Meireles P, et al: Eosinophilic esophagitis: latent disease in patients with anaphylactic reaction to cow's milk.
J Allergy Clin Immunol Pract. 2018;6:451-456.

The relationship between food allergy and eosinophilic esophagitis (EoE) remains unclear, but may have important clinical implications. Studies have reported children who developed EoE after food allergy, or during or after oral immunotherapy for allergy to cow's milk. This study evaluated the presence of esophageal eosinophilia and EoE in children with a history of anaphylactic reactions to cow's milk.

The study included 89 children with persistent cow's milk allergy and manifestations of anaphylaxis, seen at a Brazilian university hospital over 5 years. The patients were 63 boys and 26 girls, median age 8 years. All underwent endoscopy , whether or not they had gastrointestinal symptoms.

Esophageal eosinophilia, defined as at least 15 eosinophils/hpf in at least 1 hpf, was found in biopsy specimens from 34 patients (38.2%). Five patients (7.1%) had esophageal eosinophilia that responded to proton-pump inhibitor therapy, while 10 patients (14.2%) had EoE. Clinical manifestations of esophageal eosinophilia were highly variable; in many cases, parents did not recognize a link between their child's symptoms and food allergy. Overall, 29.4% of children with esophageal eosinophilia had no symptoms, 23.5% had nonspecific symptoms, 23.5% had persistent typical symptoms, and 23.5% had intermittent typical symptoms. Inflammatory changes of the esophagus were present in 61.7% of patients.

This study finds a 38% frequency of esophageal eosinophilia in children with a history of anaphylactic reaction to cow's milk. The findings suggest that EoE may commonly accompany IgE-mediated food allergy, often with no or nonspecific symptoms.

COMMENT: The pathogenesis of EoE appears distinct from that of IgE-mediated food allergy. In this study, a staggering 38% of patients with a history of anaphylaxis to milk are found to have concomitant esophageal eosinophilia. This is the highest prevalence of esophageal eosinophilia in food allergy yet reported, and raises the question that EoE may be a "silent" coexistent disease. Many (but not all) patients with esophageal eosinophilia are indeed found to be symptomatic, but only on specific direct questioning.

D.A.K.

Wechsler J, Hirano I: Biological therapies for eosinophilic gastrointestinal diseases.
J Allergy Clin Immunol. 2018;142:24-31.

Biologic agents targeting specific immune pathways could offer important advantages in the treatment of eosinophilic gastrointestinal diseases (EGID) and eosinophilic esophagitis (EoE). The authors present an update on the evidence regarding biologic therapies for EGID and EoE.

Therapeutic endpoints are a key issue in trials of biologics for EGID and EoE: symptom assessments have important limitations, while methods and thresholds for assessment of mucosal eosinophilia have been variable. A growing body of evidence supports the use of objective endoscopic assessments in EoE clinical trials. The authors discuss several potentially interesting targets for biologic therapy of EGID for which there are not yet published clinical trials: sialic acid-binding IgG-like lectin 8, thymic stromal lymphopoietin, integrins, eotaxins, and transforming growth factor β-1.

Published trials are available for several other targets, with mixed results. Based on limited data, anti-IgE therapies may be more effective for patients with EGID rather than EoE. A trial of a chemoattractant receptor-homologous molecule on Th2 (CRTH2) antagonist showed a reduction in eosinophil density, but no improvement in EoE symptoms or endoscopic findings. Anti-interleukin (IL)-5 therapies have shown modest but significant effects on esophageal eosinophilic inflammation, but no improvement in symptoms. A recent trial of anti-IL-13 therapy suggested reduced esophageal eosinophil count and endoscopic improvements, with a trend toward symptom improvement. Trials of the anti-IL-4, anti-IL-13 monoclonal antibody dupilumab have shown histologic and clinical improvements, with promising initial results in steroid-refractory patients. The authors highlight the need for continued trials to develop "novel effective, and safe biologic treatment strategies" for patients with EGID.

COMMENT: This review discusses previous clinical trials evaluating the use of biologics in EoE. Demonstrating efficacy in improving EoE has been challenging because of the lack of well-validated or consistent outcome assessments in symptoms and histology. Patient-reported outcomes (eg, EoE symptoms) did not have validated questionnaires in previous studies and also can be affected by changes in feeding habits or diet. Of the biologics studied, anti-IgE therapy did not show significant improvement in symptoms or histology. Anti-IL-5, Anti-CRTH2, and anti-IL-13 therapies reduced tissue eosinophil counts, but not symptoms. The anti-IL-4/IL-13 biologic dupilumab, however, improved both symptoms and esophageal eosinophilia.

G.B.L.

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