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American College of Allergy, Asthma & Immunology

A PUBLICATION OF THE AMERICAN COLLEGE OF ALLERGY, ASTHMA & IMMUNOLOGY Volume 26, Number 5 • September-October 2024

Head/Neck

Chupp G, Alobid I, Lugogo NL, et al. Mepolizumab reduces systemic corticosteroid use in chronic rhinosinusitis with nasal polyps.
J Allergy Clin Immunol Pract. 2023;11(11):3504-3512

Short- and long-term use of systemic corticosteroids (SCSs) has multiple adverse effects. The phase III SYNAPSE trial showed that mepolizumab, a monoclonal antibody that targets IL-5, can reduce nasal polyp size and sinonasal symptoms, sinus surgery, and SCS use in adults with severe chronic rhinosinusitis with nasal polyps (CRSwNP). Mepolizumab is approved for this indication. In this publication, the study authors report a post hoc analysis of mepolizumab efficacy according to whether patients had previously used SCSs.

Mepolizumab was dosed as 100 mg subcutaneously every 4 weeks for 52 weeks. Of the 407 patients in the intent-to-treat population, 52% had not received SCSs for nasal polyps in the year preceding the study, 27% had received 1 course, and 21% had received more than 1 course. Improvements in study outcomes (endoscopic nasal polyp score, nasal obstruction visual analog scale score, and total SNOT-22 [22-item Sino-Nasal Outcome Test] score) were greatest in patients who had received 1 course of SCSs previously. Mepolizumab-treated patients were less likely to require an initial SCS course for nasal polyps by week 52. Among patients who received at least 1 course of SCSs during the study, mepolizumab lowered the mean total prednisolone-equivalent oral corticosteroid dose for nasal polyps. Also, fewer mepolizumab-treated patients received more than 200 mg/year. The reductions in SCS use were consistent in subpopulations of patients with different baseline blood eosinophil counts or different numbers of previous surgeries.

Mepolizumab has clinical benefits in patients with severe CRSwNP regardless of prior SCS use and has a SCS-sparing effect.

COMMENT: Patients with CRSwNP may experience difficulty in treatment. The use of mepolizumab, as compared with placebo, shows promise for our patients with this condition. Patients required fewer oral steroids, less sinus surgery, and had improvement in symptoms, regardless of prior use of SCSs. Mepolizumab may be considered as a treatment option for our patients with severe CRSwNP.
V.H.T.

Ponda P, Carr T, Rank MA, Bousquet J. Nonallergic rhinitis, allergic rhinitis, and immunotherapy: advances in the last decade.
J Allergy Clin Immunol Pract. 2023;11(1):35-42.

The article reviews advances over the past 10 years in the diagnosis, management, and treatment of allergic and nonallergic rhinitis. Nonallergic rhinitis phenotypes are categorized as inflammatory or neurogenic. NARES (nonallergic rhinitis with eosinophilia syndrome) is an inflammatory phenotype that affects older adults (>65 years of age) • • •

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'MOC' ARTICLES

2024 Editor-in-Chief Disclosure:
Stanley M. Fineman, MD Editor-in-Chief.
Research: DBV, Alladapt, Novartis. (Full editorial board disclosures can be found at college.acaai.org/aw-editors)

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- Annals of Allergy, Asthma and Immunology
- Journal of Allergy and Clinical Immunology
- American Journal of Respiratory and Critical Care Medicine
- Chest
- Clinical Experimental Allergy
- Allergy
- International Archives of Allergy and Immunology
- Annals of Internal Medicine
- Pediatrics
- Journal of Pediatrics
- Journal of Asthma
- Thorax
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- New England Journal of Medicine
- JAMA
- Lancet
- British Medical Journal
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- European Respiratory Journal
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that is responsive to intranasal steroids. Other inflammatory phenotypes are occupational rhinitis and atrophic rhinitis. Vasomotor rhinitis is a neurogenic phenotype that accounts for about half of all nonallergic rhinitis cases. These patients have upregulated expression of TRPV1, which is also called capsaicin receptor. Topical capsaicin may improve these patients' symptoms.

Genetics and environment contribute to allergic rhinitis. Patients with allergic rhinitis report that their most bothersome symptom is nasal congestion. Study of epithelial barrier function may lead to new treatments for these patients. Biologics such as omalizumab and dupilumab are also being studied. Understanding sensitization patterns can help clinicians provide advice on allergen avoidance. For example, children monosensitized to Can f 5, which is found in the prostate gland of male dogs, may tolerate female dogs.

Allergen immunotherapy is a disease-modifying treatment for allergic rhinitis. The use of subcutaneous immunotherapy and sublingual immunotherapy are well established, and evidence is growing for the efficacy of intralymphatic immunotherapy. Patient selection for allergen immunotherapy is based on an appropriate history of allergen exposure and evidence of IgE sensitization via skin testing or serum specific IgE. The search for predictive biomarkers has included study of the specific IgE to total IgE ratio and IL-35–producing regulatory T cells. Component-resolved diagnostics can improve the accuracy of diagnostic evaluation, especially for furry pet allergen, and has relevance for AIT prescribing decisions.

Digital care systems include apps such as MASK (Mobile Airways Sentinel NetworK), which can be used by adolescent and adult patients to support treatment of symptoms, and AllergyMonitor, which integrates data on pollen.

COMMENT: Our patients with rhinitis, whether allergic or nonallergic, suffer from a burden of disease. Immunotherapy, along with more recent digital tools, can be used in the treatment of our patients with rhinitis. The increasing digital health tools and apps available for use by patients with a variety of medical conditions can aid our patients with rhinitis by identifying symptoms and providing information on pollen counts.

V.H.T.

Prenner BM, Amar NJ, Hampel FC Jr, et al. Efficacy and safety of GSP301 nasal spray in children aged 6 to 11 years with seasonal allergic rhinitis.
Ann Allergy Asthma Immunol. 2022;129(5):618-626.

This phase 3 study assessed GSP301 nasal spray, a fixed-dose combination of an antihistamine (olopatadine hydrochloride) and a corticosteroid (mometasone furoate), in young children with seasonal allergic rhinitis. GSP301 had previously been evaluated in patients aged 12 and older.

Children aged between 6 and less than 12 years were studied. The study dose was half of the adult/adolescent dose and consisted of 1 spray per nostril twice daily for 14 days. Patient-reported outcomes were used to assess drug efficacy. Physician-assessed measures were completed at the final study visit. Most patients were White, and their mean age was 8.7 years.

GSP301 significantly improved average am and pm rTNSS

(reflective Total Nasal Symptom Score) compared with placebo. Individual symptom scores for nasal congestion, rhinorrhea, and nasal itching also improved. The only eye symptom that improved significantly was tearing or watering eyes. Physician-assessed measures were also significantly improved with GSP301 vs placebo. Overall scores on the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire improved with GSP301 treatment, as did scores on several domains. The percentage of patients reporting at least 1 treatment-emergent adverse effect did not differ between the GSP301 and placebo groups.

Twice-daily treatment with the GSP301 nasal spray for 14 days resulted in clinically meaningful improvement in seasonal allergic rhinitis symptoms in young children.

COMMENT: This study describes a new treatment option for our pediatric patients with seasonal allergic rhinitis. This study shows that a combination topical nasal antihistamine and steroid was well tolerated and efficacious in these young patients. The patients showed improvement in total symptom scores and pediatric rhinoconjunctivitis quality of life scores. This will offer another option in our armamentarium of treatment as pediatric allergists.

V.H.T.

Wang X, Sima Y, Zhao Y, et al. Endotypes of chronic rhinosinusitis based on inflammatory and remodeling factors. J Allergy Clin Immunol. 2023;151(2):458-468.

Chronic rhinosinusitis (CRS) can be described by endotypes. For example, primary CRS is described by type 2 and non–type 2 endotypes. These authors used cluster analysis to study specific clinical manifestations of CRS according to endotype.

A total of 152 patients were enrolled, 95 with CRS with nasal polyps, 33 with CRS without nasal polyps, and 24 control patients. A total of 48 tissue markers were measured. Sixteen biomarkers with greater expression in CRS patients than in control patients were used in the cluster analysis: IL-5, IL-8, IL-9, total IgE, granulocyte-macrophage colony-stimulating factor (GM-CSF), eosinophil cationic protein (ECP), myeloperoxidase (MPO), eotaxin, albumin, matrix metalloproteinase (MMP)-7, MMP-8, MMP-9, tissue inhibitor of metalloproteinases 2 (TIMP-2), and chemokine ligand (CCL)-2, CCL-3, and CCL-4.

Five clusters were identified. Most patients with CRS without nasal polyps were in clusters 1 and 2, which had a non–type 2 signature with low expressions of most biomarkers. Cluster 3 had a low type 2 endotype with the highest expression of proinflammatory, neutrophil, and remodeling factors. Cluster 4 had moderate type 2 inflammation. Moving from cluster 1 to cluster 5 (high type 2 endotype), the number of patients with CRS with nasal polyps increased, as did the proportion of allergies, anosmia, aspirin sensitivity, and CRS recurrence. The prevalence of asthma was highest in cluster 5.

The authors also performed hierarchical clustering for the 48 biomarkers in each of the 5 clusters. Some biomarkers were positively correlated with nasal polyp score and some with the computed tomography score. Some biomarkers of interest include IL-19, which was significantly downregulated in clusters 2 to 5 compared with cluster 1; IL-27, which was highly expressed in cluster 2 and was greater in patients with CRS without nasal polyps than in those with CRS with nasal polyps; and fibronectin and MMP-8, for which levels were high in cluster 3 along with significant neutrophil inflammation.

Further study of the inflammatory biomarkers and remodeling factors identified in the different CRS endotypes could lead to new treatment strategies.

COMMENT: Our understanding of differences in rhinitis has improved over time. This article describes varying endotypes and remodeling profiles resulting from diverse inflammatory mechanisms. This is important for individualizing the treatment of patients with different forms of rhinitis and varying degrees of inflammation.

V.H.T.

Dermatologic

Asero R, Ferrer M, Kocaturk E, Maurer M. Chronic spontaneous urticaria: the role and relevance of autoreactivity, autoimmunity, and autoallergy. J Allergy Clin Immunol Pract. 2023;11:2302-2308.

Chronic spontaneous urticaria (CSU) can be defined in terms of autoreactivity, autoimmunity, and autoallergy. Autoimmune CSU, or aiCSU, is due to autoantibodies that directly activate mast cells. aiCSU is also called type IIb CSU. Patients with aiCSU are likely to have a long duration of disease and higher disease activity and to respond slowly or not at all to omalizumab.

In some patients, CSU is an autoallergic disease, and more than 200 human proteins, such as thyroid peroxidase (TPO) and IL-23, can act as autoallergens. Autoallergic CSU (aaCSU), is more common than aiCSU. Patients with aaCSU often have normal or high IgE levels and respond well to omalizumab. In some patients, CSU cannot be categorized as autoimmune or autoallergic.

The autologous serum skin test (ASST), the first clinical test for CSU, has moderate specificity for autoantibodies against IgE or the α subunit of the high-affinity receptor for the Fc region of IgE (FcεRI). It is a test for autoreactivity and is not a specific test for aiCSU. Heparin (eg, in heparinized plasma) can turn a positive ASST result into a negative one. Figure 1 presents the recommended ASST protocol.

Two in vitro diagnostic tests for type IIb aiCSU are the basophil activation test (BAT), which detects the expression of basophil membrane activation markers, and the basophil histamine release assay (BHRA), which measures hist-

amine release. About 12% to 60% of patients with CSU have positive basophil test results.

In routine clinical practice, patients can be screened for aiCSU by assessment for elevated IgG autoantibodies to TPO and low total IgE levels. The best widely available marker for aaCSU is elevated total IgE. No currently available diagnostic test has 100% specificity for aaCSU or aiCSU. Patients should be treated according to the international urticaria guideline. New treatments are in development.

COMMENT: This review discusses the major identified endotypes of CSU, including aaCSU (type 1 CSU) and aiCSU (type IIb CSU) with the recognition of likely other unelucidated endotypes. The pathophysiologic mechanisms, proposed diagnostic testing, and possible impact on disease natural history are surveyed. Diagnostic testing is based on 3 components: ASST, anti-FcεRI IgG or anti-IgE IgG, and basophil activation testing, each discussed in depth. Unsurprisingly, diagnostic testing is extremely limited by clinical availability. Current CSU treatment guidelines can be used regardless of endotype; it is hoped that further understanding of endotypes will guide future targeted therapies.
T.G.C.

Butala S, Castelo-Soccio L, Seshadri R, et al. Biologic versus small molecule therapy for treating moderate to severe atopic dermatitis: clinical considerations.
J Allergy Clin Immunol Pract. 2023;11:1361-1373.

The article reviews biologics and systemic Janus kinase (JAK) inhibitors for moderate-to-severe atopic dermatitis (AD) that are approved by the Food and Drug Administration (FDA) or that have completed phase 3 studies.

Benefits of biologics include no requirement for laboratory monitoring. Limitations include the need for frequent injections and difficulty individualizing dose. Biologics reviewed include:

- Dupilumab is a human IgG4 monoclonal antibody that binds the IL-4 receptor α. The recommended dose for adults is 300 mg subcutaneously every 2 weeks after a 600-mg loading dose. Pediatric doses are based on age and body weight. Adverse effects (AEs) include conjunctivitis.
- Tralokinumab, a human IgG4 monoclonal antibody that targets IL-13, is approved for the treatment of adults in doses of 300 mg subcutaneously every 2 weeks after a 600-mg loading dose. Conjunctivitis may occur less often than with dupilumab.
- Lebrikizumab has a similar safety profile to tralokinumab but is not yet FDA-approved.
- Nemolizumab is an investigational monoclonal antibody that targets the IL-31 receptor. Risks include elevated creatine phosphokinase (CPK) levels.

JAK inhibitors have rapid clearance and are easy to stop and start. All require laboratory monitoring and carry a boxed warning (based on tofacitinib data) for malignancy, thrombosis, cardiovascular issues, serious infection, and death. Those reviewed are:

- Baricitinib. With 4 mg daily, more than 50% of treated patients achieved the primary study endpoints in the BREEZE-AD trials, with relief from itch as early as at 1 week. AEs include nasopharyngitis, upper respiratory tract infections, CPK elevations, and headache.
- Abrocitinib is FDA-approved for adults unresponsive to other therapy. The starting dose is 100 mg and can increase to 200 mg daily. Abrocitinib is effective for improving sleep and quality of life (QoL). Nausea is the most common AE. Plasma concentration is increased by co-administration of CYP450 inhibitors (eg, antifungals) and decreased by CYP inducers (eg, rifampin).
- Upadacitinib improves itch, QoL, anxiety and depression, and sleep. Acne is the most common treatment-emergent AE. In a head-to-head comparison with dupilumab, upadacitinib had better effects on skin clearance and itch relief. Rates of serious infection were higher with upadacitinib, whereas the rate of conjunctivitis was higher with dupilumab. A dose of 15 mg is FDA-approved for adults and adolescents who weigh at least 40 kg, with 30-mg dose escalation. Plasma levels can be increased by antifungals and decreased by rifampin.
- Ruxolitinib is a topical JAK inhibitor. The 1.5% cream is approved for treatment of up to 20% body surface area.

The safety and cost-effectiveness of combination therapy (eg, biologic/JAK inhibitor) need further study.

COMMENT: The allergists' treatment armamentarium is rapidly expanding with targeted therapies for moderate-to-severe eczema, including monoclonal antibodies and small molecule inhibitors, in the form of JAK inhibitors. The reader is referred to Tables 1 and 2, which survey study characteristics, primary and secondary outcomes, and adverse events. For clinicians considering these treatment options, Table 3 provides an excellent summary of the risks, benefits, and additional considerations for each.
T.G.C.

Liu AW, Gillis JE, Sumpter TL, Kaplan DH. Neuroimmune interactions in atopic and allergic contact dermatitis.
J Allergy Clin Immunol. 2023;151:1169-1177.

Interactions between neuropeptides and immune cell mediators are increasingly recognized to play a role in inflammatory diseases like atopic dermatitis (AD) and allergic contact dermatitis (ACD). This article reviews the findings of mouse studies investigating these neuroimmune interactions and their role in AD and ACD.

Neuron subsets in the skin include peptidergic and nonpeptidergic neurons. Peptidergic neurons express TRPV1 (transient receptor potential vanilloid 1) and other neuropeptides. Although historically nonpeptidergic neurons were defined by a lack of neuropeptide expression, some subsets do express TRPV1 and other neuropeptides. The 3 main groups of nonpeptidergic neurons are NP1, • • •

NP2, and NP3.

The neuroimmune basis of itch in AD has been defined in various mouse models. These models suggest that TRPV1-expressing neurons are required to initiate inflammation. Other neuropeptides involved in AD pathogenesis are substance P and calcitonin-gene-related peptide. Nonpeptidergic neurons are required for itch sensation and scratching behavior in mice. Mouse models show that IL-4 receptor (IL-4R) expression is required for scratching behavior. The nonpeptidergic NP3 neurons express high levels of IL-31 receptor (IL-31R). IL-31 is a strong pruritogen.

Clinical applications of research on the neuroimmune pathways in AD include treatment with botulinum toxin, which reduces pruritus and inflammation by disrupting neuropeptide release, and inhibition of IL-31R. Peptidergic neurons and nonpeptidergic neurons have also been studied for their role in mediating inflammation and itch in CHS.

The findings from mouse models of AD suggest that type 2 inflammation can generate scratching behavior. Whether scratching is required for inflammation is less clear. The "itch-scratch" cycle is likely more complex than conventionally understood.

COMMENT: Our appreciation of the role that complex neuroimmune interactions play in driving and propagating allergic diseases is growing; the authors review the evidence supporting the role of different cutaneous neuron subsets and their defining expressed neuropeptides in AD and ACD. There are 2 main subsets of cutaneous neurons pertinent to this discussion, peptidergic and nonpeptidergic neurons, and each contribute to AD and ACD in distinct fashion. Figures 1 and 2 highlight the mechanisms of these cutaneous neurons and associated neuropeptides in AD and ACD, respectively. Potential therapeutic neuroimmune targets are discussed.

T.G.C.

Ren Z, Zhao S, Li T, et al. Insights into the pathogenesis of hereditary angioedema using genetic sequencing and recombinant protein expression analyses.
J Allergy Clin Immunol. 2023;151(4):1040-1049.

Type I and type II hereditary angioedema (HAE) are caused by mutations in the gene *SERPING1*, which encodes C1-esterase inhibitor (C1-INH), resulting in C1-INH deficiency. A reduction in functional C1-INH leads to the overproduction of bradykinin, which causes the increased vascular permeability and tissue swelling in HAE. However, how different *SERPING1* variants affect the expression, structure, and function of C1-INH is not well understood, and more than 700 different variants have been identified. These authors performed whole-exome and/or whole-genome sequencing in 20 patients with HAE, created and expressed recombinant proteins for the variants identified, and then analyzed C1-INH protein folding, glycosylation, and function.

Eleven heterozygous variants were identified: 5 were pathogenic and 6 were of uncertain significance. The authors explored relations between the variants and the patients' clinical experiences.

- The I224S variant was secreted in normal quantities but was misfolded, leading to protein aggregation.
- The variant N272del, in which the N-glycosylation site N272 was deleted, disrupted C1-INH protein folding and function. Deletion of the nearby K273 in the K273del variant resulted in decreased C1-INH function but did not affect the protein level. The authors suggest that the N272 glycosylation site may be crucial for protein stability and function.
- A compound variant (P399A/L349F) led to a more severe clinical phenotype. The 14-year-old patient had experienced hand, arm, and/or abdominal swelling since 7 years of age with about 3 episodes per month.

The study was able to generate key data on several *SERPING1* variants by analyzing the expression of recombinant C1-INH protein. A limitation of the method used is the higher cost of whole-genome sequencing compared with whole-exon sequencing.

COMMENT: Genetic variants in *SERPING1* have long been recognized as the driver of most HAE clinical phenotypes. However, the impact of specific *SERPING1* variants on C1-INH expression and function has not been thoroughly investigated. In this study, the authors performed whole exome/genome sequencing, and C1-INH variants were recombinantly produced and analyzed. Table 2 summarizes the genetic variants discovered, with corresponding clinical characteristics outlined in Table 1. The authors demonstrated that specific variants led to specific C1-INH protein effects such as impaired synthesis, improper folding, or impaired glycosylation, resulting in decreased activity.

T.G.C.

Zeidler C, Raap U, Witte F, Ständer S. Clinical aspects and management of chronic itch.
J Allergy Clin Immunol. 2023;152(1):1-10.

Chronic pruritus (CP), defined as itch lasting longer than 6 weeks, is a common reason for visits to health care practitioners and impairs patients' quality of life. CP is more common in older patients and in women. Patients with CP have higher rates of comorbid hypertension, ischemic heart disease, and hyperlipidemia than those without CP.

The International Forum for the Study of Itch (IFSI) identifies 3 phenotypic groups:

- Group I: CP on lesional skin with dermatoses. The most common causes are atopic dermatitis, psoriasis, and chronic urticaria.
- Group II: CP on nonlesional skin with no dermatoses. Systemic causes include chronic kidney disease–associated pruritus, cholestatic pruritus, and pruritus caused by diabetes or iron deficiency.
- Group III: CP with chronic scratch lesions, which arises from groups I and II.

Itch intensity is the main patient-reported outcome

used for assessment. Management encompasses several domains: coping support, diagnostics, sleep restoration, itch-relieving therapy, etiology-based therapy, therapies to break the itch-scratch cycle, and skin care. Mirtazapine is a guideline-recommended tetracyclic antidepressant for reducing itch; an associated adverse effect is sleepiness. Treatment with topical steroids should be limited to the initial therapy phase, with a switch to nonsteroidal therapies like calcineurin inhibitors or capsaicin. Emollients can be applied to relieve dry skin.

CP affects patients' quality of life and sleep quality. Patient-reported outcome instruments for assessing quality of life include the Dermatology Life Quality Index and the ItchyQoL. Patients with CP report an average loss of 3 hours of sleep per night. Long durations of sleep disturbance can negatively affect patient mortality. Patients with CP frequently present with psychiatric comorbidities, such as anxiety disorders and depression. CP is also linked to stress. Nonpharmacologic treatment of stress can include cognitive-behavioral therapy or yoga.

Pruritus is a symptom of many diseases, but CP is a clinically significant entity that ranks in the top 50 most burdensome diseases worldwide.

COMMENT: CP is a commonly encountered clinical entity, with a range of contributing endotypes. This review highlights 3 core phenotypes of CP, and 6 subcategories of etiologies. The mechanisms of these different etiologies are summarized. Table 2 highlights patient-reported outcomes evaluating numerous dimensions of itch, and Figure 3 highlights a proposed treatment approach for patients with CP, which includes both management of itch as well as the numerous morbidities associated with chronic itching, such as impaired sleep and increased psychiatric symptoms.

T.G.C.

Lung

Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion f vaccine in pregnancy to prevent RSV illness in infants. N Engl J Med. 2023;388(16):1451-1464.

Respiratory syncytial virus (RSV) is a leading cause of death in infants aged less than 6 months, particularly in resource-poor countries. This phase 3 study assessed whether RSV vaccination during pregnancy reduces RSV-associated lower respiratory tract illness in newborns and infants.

Healthy pregnant women were randomly assigned to a single injection of the investigational bivalent RSV prefusion F protein–based (RSVpreF) vaccine or placebo. Women with high-risk pregnancies were excluded. The study was conducted over 4 RSV seasons. Outcomes in infants were assessed 90, 120, 150, and 180 days after birth.

A total of 7358 women received the RSV vaccine (n = 3682) or placebo (n = 3676). The vaccine showed 82% efficacy in reducing medically attended severe lower respiratory tract illness, which occurred in 6 infants in the vaccine group vs 33 infants in the placebo group within 90 days after birth. Within 180 days, vaccine efficacy was reduced to 69%, with 19 cases in the vaccine group and 62 in the placebo group. Medically attended RSV-associated illness occurred in 24 infants from the vaccine group vs 56 in the placebo group within 90 days (vaccine efficacy: 57%; NS). Beyond 180 days, the incidence of medically attended RSV-associated lower respiratory tract illness was lower in the vaccine group at all time points up to 360 days. The incidences of adverse effects were similar between groups.

Vaccination of pregnant women with the RSVpreF vaccine was effective against severe RSV-associated lower respiratory tract illness in infants.

COMMENT: RSV remains a major early childhood infection, peaking at 2 to 3 months of life, that often leads to urgent medical care or even hospitalization. Furthermore, previous studies have shown that infants hospitalized with RSV bronchiolitis are at greater than 10-fold increased risk of asthma after the age of 3. This 18-country study showed a clear decline in RSV-related medically attended cases in infants in the first 180 days of life. The key next step is to show that this decline in higher severity RSV cases leads to a decline in atopic disease later in life. Both the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine endorse RSV vaccination during pregnancy.

S.R.J.

Polosa R, Casale TB, Tashkin DP. A close look at vaping in adolescents and young adults in the United States. J Allergy Clin Immunol Pract. 2022;10(11):2831-2842.

This commentary synthesizes current findings about electronic cigarette (EC) use and its impact on behavioral and respiratory health in youth. ECs are battery-powered devices that vaporize a liquid solution containing vegetable glycerol, propylene glycol, distilled water, and flavorings; they may or may not contain nicotine. ECs do not contain tobacco and do not rely on combustion.

A meta-analysis of studies of respiratory health effects of EC use showed that adolescents who currently use or have ever used ECs have higher odds for asthma. The cross-sectional findings do not indicate causality, however. Although some studies have shown an association of EC use with developing respiratory symptoms, the authors highlight the shortcomings of those studies, such as insufficient control for cigarette smoking in the analyses.

Table 2 in the article summarizes several misperceptions about EC use. One is that ECs do not help people quit smoking. Evidence suggests that those who vape daily are 2 to 8 times more likely to quit smoking than smokers who do not vape. Other misperceptions are that ECs and tobacco

cigarettes are similarly harmful (risk with nicotine vaping is lower) and that nicotine itself is harmful (health authorities agree that nicotine does not cause cancer in humans).
Regarding EC or vaping product–associated lung injury (EVALI), the causative agent is believed to be vitamin E acetate, an additive in black-market vaping oils.

Rates of teen vaping have subsided since 2020, as have rates of smoking among high school students. These trends suggest that youth vaping is not a gateway to smoking.

COMMENT: EC use dramatically increased over the past decade, with 13.5% of middle school students having used them at least once and 0.6% using them over 20 times in the past 30 days. These percentages rise to 37.7% and 2.5%, respectively, for high school students. Studies have shown that ECs expose users to significantly less chemical (~150 chemicals) than their combustible alternatives (>7000 chemicals), and the use of combustible cigarettes has overall declined from 2012 to 2021, which has correlated with the rise in EC use. Well-conceived studies on the health risks of vaping in adolescence are lacking; however, it appears the risk is low (mainly coughing) and is improving with better regulation of vaping products in terms of quality and safety checks.
S.R.J.

Walsh EE, Pérez Marc G, Zareba AM, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. N Engl J Med. 2023;388(16):1465-1477.

About 3% to 7% of healthy older adults develop illness after respiratory syncytial virus (RSV) infection, which can lead to hospitalization and death. The investigational bivalent vaccine RSVpreF, based on the RSV prefusion F protein, has shown efficacy in phase 1–2 studies in adults aged 18 to 50. This article presents the results of a phase 3 trial in adults aged at least 60.

The study assessed the efficacy and safety of RSVpreF in preventing RSV-associated lower respiratory tract illness. The study participants had a median age of 67 years; 51% were male and 78% were White. Eleven participants in the vaccine group experienced RSV-associated respiratory illness with at least 2 symptoms, compared with 33 in the placebo group (vaccine efficacy, 67%). RSV-associated lower respiratory tract illness with at least 3 symptoms was experienced by 2 participants in the vaccine group and 14 in the placebo group (vaccine efficacy, 86%). RSV-associated acute respiratory illness occurred in 22 and 58 participants, respectively (vaccine efficacy, 62%). Vaccine efficacy was similar in groups aged 60–69, 70–79, and 80 and older.

In both groups, 0.7% or fewer participants experienced severe systemic adverse events. The percentage of participants experiencing adverse events up to 1 month after receiving the vaccine was similar between groups; the most common adverse event was cough (0.6% in both groups). One participant in the vaccine group experienced a delayed allergic reaction.

The study concludes that the RSVpreF vaccine can prevent RSV-associated respiratory illness in older adults.

COMMENT: Severity of an RSV infection can be substantial in older adults with up to a 26% mortality rate within 1 year after admission with this virus. This interim analysis of a phase 3 trial involved 34,284 patients and showed a decrease in infections involving 2 symptoms or more from 3.58 cases per 1000 person-years to 1.19 cases per 1000 person-years with vaccination. Most importantly, there was no significant difference in systemic side effects (mild increase in local injection site reactions in vaccination group). RSVpreF vaccination appears to be a safe and effective option for adults 60 years of age and older.
S.R.J.

Food and Drug Allergy/Hypersensitivity Reactions

**Hayano S, Natsume O, Yasuoka R, et al. Predictors of initial oral food challenge outcome in food protein–induced enterocolitis syndrome.
J Allergy Clin Immunol Glob. 2022;1(3):122-127.**

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-dependent food allergy for which no diagnostic markers exist. These authors sought to answer whether FPIES should be diagnosed solely by clinical history and to find predictors of FPIES oral food challenge (OFC) outcomes.

This was a retrospective case-control study of pediatric patients aged less than 15 years who met guideline criteria for acute FPIES and who underwent an OFC for diagnosis. Data for 50 children were analyzed: 30 in the FPIES group with a positive OFC result and 20 in the no allergy group with a negative OFC result.

The main culprit foods in the FPIES group were hen's egg yolk, cow's milk, soybean, and wheat. The authors found no significant differences between groups in the risk factors they studied, except for a history of asymptomatic ingestion, which was more common in the FPIES group. Nonsignificant factors included age at first episode, median number of symptomatic episodes, number of vomiting episodes, atopic dermatitis, and family history of atopic dermatitis or asthma. In children with 1, 2, 3, or 4 or more symptomatic episodes, the diagnostic rates were 40%, 54%, 75%, and 75%, respectively.

This retrospective study identified no predictive factors for a positive OFC result in children other than a history of asymptomatic ingestion. The definite diagnosis of FPIES should be based on OFC.

COMMENT: A retrospective review of 50 OFCs to diagnose FPIES highlighted the challenges of predicting FPIES by clinical history alone. No clinical factors were associated

with positive OFC results confirming FPIES diagnosis other than, interestingly, a history of asymptomatic ingestion. Although history-taking is always important, this study highlights the pitfalls of diagnosing FPIES on the basis of clinical history alone and confirms that OFC is essential to preventing both over- and under-diagnosis of FPIES.
I.M.O.

Kim EH, Keet CA, Virkud YV, et al. Open-label study of the efficacy, safety, and durability of peanut sublingual immunotherapy in peanut-allergic children.
J Allergy Clin Immunol. 2023;151(6):1558-1565.

Peanut allergy remains a common cause of emergency department visits for anaphylaxis. This study group previously reported desensitization in children after 2-mg peanut sublingual immunotherapy (SLIT), but the degree of desensitization varied. Here the authors increased the maintenance dose from 2 to 4 mg and incorporated oral food challenges (OFCs) at baseline into the study protocol.

Children aged 1 to 11 years with proven peanut allergy were treated with 4 mg peanut SLIT for 48 months. The authors used 5000-mg double-blind placebo-controlled food challenge to assess desensitization. Each participant underwent 3 challenges: at baseline, after 48 months of SLIT, and after the avoidance period.

A total of 47 children completed SLIT dosing and the 48-month food challenge; 37 completed the avoidance phase food challenge. In the per-protocol population, the successfully consumed dose increased during the 48-month period. Thirty-six percent of children achieved a successfully consumed dose of 5000 mg without symptoms; 70% achieved a dose of 800 mg or more, which was considered clinically significant desensitization. The mean successfully consumed dose was 2723 mg. Mean wheal size decreased at 48 months. Peanut-specific IgE and IgG4 levels changed as early as at 6 months. The authors also present findings for peanut-specific basophil activation and T cell cytokines. During the avoidance phase, the median time to loss of desensitization was 22 weeks.

Nearly 98% of the peanut SLIT doses were taken. Seven participants accounted for more than 80% of the reported dosing symptoms; the most common symptoms were local (eg, oropharyngeal itching, lip swelling).

The authors report that the study demonstrated "the strongest desensitization after SLIT to date." Peanut SLIT was safe and induced desensitization lasting 17 weeks or more.

COMMENT: This study investigated the efficacy and durability of peanut SLIT by conducting OFCs at baseline and at 48 months and incorporating a randomly assigned treatment avoidance period to assess time to loss of desensitization. In addition to a significant increase in tolerance of peanut protein after 48 months of SLIT, tolerance to 300 mg was maintained despite some loss of clinically significant desensitization during the 17 weeks of avoidance post-desensitization. Reassuringly, there were no reports of eosinophilic esophagitis in this SLIT study, even among 3 participants who withdrew from the study because of abdominal symptoms.
I.M.O.

Kalb B, Marenholz I, Jeanrenaud ACSN, et al. Filaggrin loss-of-function mutations are associated with persistence of egg and milk allergy.
J Allergy Clin Immunol. 2022;150(5):1125-1134.

Filaggrin (FLG) is an epidermal barrier protein. Loss-of-function (LOF) mutations in the *FLG* gene are known to be associated with eczema, but whether they are associated with food allergy has not been established. To study this question, the authors performed genotyping of *FLG* LOF mutations in 890 children in the German Genetics of Food Allergy Study.

The most common food allergies in the study population were to hen's egg, peanut, and cow's milk. About 90% of the children had other allergy-based diseases; 83% had eczema, 23% had asthma, and 24% had hay fever. Four common LOF mutations were studied: R501X, 2282del4, R2447X, and S3247X. The combined allele frequency was 13%.

As shown by logistic regression analysis, *FLG* mutations were associated with food allergy (odds ratio, 2.80). Furthermore, *FLG* mutations increased the risk for persistence of hen's egg and cow's milk allergy, even after model adjustment for eczema status. Although mutations were not associated with age at diagnosis of food allergy, they were associated with the last positive result on an oral food challenge to hen's egg or cow's milk. In a survival analysis of carriers vs noncarriers, carriers of the *FLG* mutations were more likely to experience persistence of milk and egg food allergy. The study found no difference in IgE levels between mutation carriers and noncarriers.

LOF mutations in the gene encoding the FLG epidermal protein are the first identified genetic marker for persistence of food allergy. In this ethnically homogeneous study group, these mutations were associated with persistence of egg and milk allergy independent of eczema.

COMMENT: This study analyzed associations between the 4 most common *FLG* LOF mutations and food allergy in children with challenge-proven food allergy. LOF mutations were associated with food allergies in general, and with persistence of cow's milk and hen's egg allergy. Interestingly, these associations existed independent of eczema status. Additionally, *FLG* LOF mutations were not associated with organ-specific manifestations or with reaction severity. Taken together, these findings suggest that *FLG* LOF mutations affect food allergy risk independent of eczema status and could be used to help determine the safety of oral food rechallenges.
I.M.O.

Yamamoto-Hanada K, Kobayashi T, Mikami M, et al. Enhanced early skin treatment for atopic dermatitis in infants reduces food allergy.
J Allergy Clin Immunol. 2023;152(1):126-135.

Hen's egg allergy is the leading food allergy in Australia and Asia. Atopic dermatitis in infants is a risk factor for food allergy. In studies of early interventions to prevent or treat atopic dermatitis, reactive treatment with emollients or pimecrolimus only has not been shown to prevent food allergy. This study aimed to assess the effect of early enhanced proactive treatment applied to both clinically affected and unaffected skin.

In the PACI (Prevention of Allergy via Cutaneous Intervention) study, infants aged 7 to 13 weeks with atopic dermatitis were randomly assigned to enhanced early skin treatment (n = 318) or conventional reactive treatment (n = 322) with topical corticosteroids (TCSs). The study was carried out at 16 hospitals in Japan. Infants in the enhanced group were treated for 14 days with 0.1% alclometasone dipropionate on the whole face and 0.12% betamethasone valerate on the whole body except scalp and face, followed by twice-weekly maintenance therapy until 28 weeks of age. The primary outcome was hen's egg allergy.

Hen's egg allergy was lower in the enhanced treatment group than in the conventional group (31% vs 42%), as was the proportion of infants with IgE sensitization to egg white. Wheezing episodes were similar between groups, but the enhanced group used rescue medication more often. The enhanced group had lower Eczema Area and Severity Index scores.

The enhanced group experienced more serious adverse effects, none of which were fatal, life-threatening, or permanent. At 28 weeks of age, body weight (mean difference, –422 g) and height (mean difference, –0.8 cm) were lower in the enhanced group.

Enhanced early skin treatment of atopic dermatitis can reduce hen's egg allergy in infants but lowered body weight and height at 28 weeks of age. The trial protocol is not recommended as an allergy prevention strategy.

COMMENT: This randomized controlled trial found that enhanced treatment of atopic dermatitis with proactive application of TCSs significantly reduced egg allergy at 28 weeks of age compared with as-needed application of TCSs. Of note, both treatment groups applied emollients twice daily, suggesting that moisturization is not enough to prevent food allergy onset. While this information may be helpful to address hesitancy around appropriate TCS use, it is important to note that temporary growth reduction was observed in the enhanced treatment group, and the authors therefore do not recommend widespread use of enhanced treatment.

I.M.O.

Anaphylaxis

Au EYL, Mak HWF, Yeung MHY, et al. Ten-year outcomes of Perioperative Anaphylaxis Workup Study in Hong Kong (PAWS-HK): performance of diagnostic modalities.
Ann Allergy Asthma Immunol. 2023;130(6):752-759.

The Perioperative Anaphylaxis Workup Study in Hong Kong was established to study the clinical characteristics and outcomes of patients in Asia with a confirmed diagnosis of perioperative anaphylaxis. This study reviews 10 years of data from a tertiary referral center.

The diagnostic workup included review of the anesthesia medical record, specific IgE test (sIgE), basophil activation testing (BAT), and skin-prick testing with or without drug provocation tests. Serum tryptase was measured by fluoroimmunoassay. A total of 151 patients were studied; their mean age was 59 years, and their mean American Society of Anesthesiologists grade was 2. About 62% of patients experienced anaphylaxis when undergoing general anesthesia for the first time, and about 53% experienced reactions during induction. Severe anaphylaxis was associated with female sex, older age, and elevated tryptase levels.

The culprit for perioperative anaphylaxis was identified in three-fourths of cases, mostly by skin testing. The most common culprits were neuromuscular blocking agents (NMBAs; 26%), β-lactam antibiotics (17%), chlorhexidine (14%), and gelofusine (9%). Of patients with suspected NMBA anaphylaxis, suxamethonium was the most common culprit. Ninety-five percent of the patients with suxamethonium anaphylaxis were female.

In this Asian cohort, NMBAs were the most common culprit in perioperative anaphylaxis, and skin tests were the most sensitive testing modality.

COMMENT: Perioperative anaphylaxis remains difficult to diagnose, and this study from Hong Kong compared various diagnostic modalities to determine sensitivities. NMBAs were found to be the most common culprit, followed by β-lactams and chlorhexidine. Skin testing overall remains the most sensitive, but other forms of testing proved to have higher sensitivity for specific drugs: BAT for gelofusine and in vitro sIgE for chlorhexidine. In the United States, the lack of readily available BAT and in vitro testing for chlorhexidine remains a major barrier to optimal patient care.

S.R.J.

Bonadonna P, Korosec P, Nalin F, Golden DBK. Venom anaphylaxis: decision points for a more aggressive workup.
J Allergy Clin Immunol Pract. 2023;11(7):2024-2031.

The authors outline steps in evaluating patients with an allergic reaction to an insect sting. Because the best predictor of a severe reaction is a history of previous reac-

tions, a detailed clinical history is a key component of patient evaluation. All patients with severe Hymenoptera venom allergy (HVA) should be referred to an allergist/immunologist. Diagnosis is made by stepwise skin tests. A 1-step accelerated method has been shown to be safe.

Venom allergen components for component-resolved diagnosis (CRD) are available for honeybee, yellow jacket, and common paper wasp. For honeybee, all 5 components should be tested; for yellow jacket, rVes V 5 is sufficient in most cases. Although not widely available, the basophil activation test (BAT) is a promising biomarker for identifying patients at high risk for an allergic reaction.

Mast cell disorders are a significant risk factor for severe sting anaphylaxis. The most easily tested marker is the baseline serum tryptase level (bST). Baseline levels should be measured at least 24 hours after a reaction; acute levels are measured within 30 to 120 minutes. Clinicians can consider measuring bST in all patients who are candidates for venom immunotherapy (VIT). Elevated levels are associated with more severe sting reactions and high risk for relapse after discontinuing VIT. The REMA (Red Espanola de Mastocytosis) score, which includes gender, clinical symptoms, and bST, can be used in screening patients with suspected mastocytosis with HVA without typical skin lesions.

No preventive pharmacologic treatments are available for HVA. VIT can reduce morbidity and mortality; for long-term effectiveness, patients need to be treated for at least 5 years.
COMMENT: This review article highlights key features of venom allergy evaluation and management. Neither skin testing nor in vitro specific IgE can predict the severity of reaction and can at times be negative despite a convincing history. In these cases, repeat testing should be considered 1 to 2 months later. While component testing does not predict severity as in food allergy, it is important in diagnosing honeybee allergy to Api m 10 (often low or absent in commercially available whole extract) and cross-reactive sensitivities, specifically for dual honeybee and vespid sensitization. The BAT, on the other hand, can be helpful in determining severity of reaction as well as risk and efficacy of VIT.
S.R.J.

Pouessel G, Deschildre A, Dribin TE, et al. Refractory anaphylaxis: a new entity for severe anaphylaxis. J Allergy Clin Immunol Pract. 2023;11(7):2043-2048.

Consensus is lacking over how to define the different severities of anaphylaxis and how to best define *refractory anaphylaxis*. These authors review the epidemiology, management, and risk prediction of refractory anaphylaxis.

Various definitions of refractory anaphylaxis exist. Some use a criterion of a suboptimal response to at least 2 doses of intramuscular epinephrine. A US expert panel proposed a definition including the need for 3 or more doses of epinephrine (or initiation of intravenous epinephrine) in addition to symptom-directed management. A literature review conducted by the authors using the definition of "3 or more doses" concluded that refractory anaphylaxis by this definition occurs in 2% of anaphylaxis reactions.

The Resuscitation Council UK management algorithm recommends low-dose intravenous infusion of epinephrine with fluid resuscitation. Evidence is lacking to recommend a specific vasopressor. Metaraminol is unlikely to be effective in reactions refractory to intravenous epinephrine.

Studies of risk factors for severe reactions have been limited by low numbers of patients. Global consensus on the definition of refractory anaphylaxis could improve recognition and management and help to identify predictors.
COMMENT: Refractory anaphylaxis is defined as a suboptimal response to multiple doses of epinephrine and occurs in 2% to 3% of reactions. Medications are the most common trigger in adults and children, particularly in the hospital or perioperative setting. The UK guidelines recommend a low-dose intravenous epinephrine infusion and sufficient fluid resuscitation with consideration for additional vasopressors or consideration of glucagon if the patient is taking a β-blocker. Although asthma and malignant disease have been suspected as risk factors, multivariate analyses do not show significant associations owing to a low number of cases.
G.B.L.

Shaker M, Abrams EM, Sublett JW. Contextual community epinephrine prescribing: is more always better? Ann Allergy Asthma Immunol. 2023;131(2):176-184.

Epinephrine is the mainstay of anaphylaxis treatment, and patients with severe or refractory anaphylaxis may require more than 1 dose. Patients are thus usually encouraged to carry multiple epinephrine autoinjector (EAI) devices. In this narrative review, the authors examine this advice and consider whether multiple EAIs should be universally prescribed.

In the "1-2-3" management guideline, the first step in treating anaphylaxis is an initial intramuscular dose of epinephrine into the anterolateral thigh. The patient should be properly positioned supine, and emergency medical services should be contacted if the patient's symptoms do not resolve immediately. Second and third doses along with intravenous fluids are considered in a stepwise fashion in patients with poor response.

The authors suggest that the management of community anaphylaxis should focus on availability of the first epinephrine dose rather than the second. One review concluded that 90% or more of reactions do not require a second dose, but shared decision-making is recommended to consider how patients feel about a 5% to 10% risk for needing a second dose.

Controversy remains regarding whether all patients need multiple EAI devices. On the one hand, a patient may require multiple doses, and device malfunction and misuse do occur. On the other hand, universal prescribing of 2 devices is not cost-effective with current device costs, and the diffi-

culty of carrying multiple devices may reduce patient adherence.

According to the authors, the following patients may benefit from a multiple-EAI prescribing strategy:

- patients with a history of anaphylaxis,
- patients with risk factors for severe anaphylaxis, and
- patients who prefer to be better prepared.

Patients for whom a single EAI device may be appropriate include:

- patients with no history of asthma or underlying cardiovascular disease,
- patients who do not have a high-risk allergen,
- patients with an oral allergy syndrome,
- patients who demonstrate ability to use the EAI device, and
- patients near to emergency medical services.

COMMENT: This review explores the risks and benefits of prescribing a single EAI rather than a dual pack. Concerns about dual-pack EAIs include cost, waste, shortages, and decreased adherence. Fatal anaphylaxis is thankfully rare, with an annual incidence less than that for death due to fire or murder. Additionally, 5% to 10% of reactions appear to require more than 1 epinephrine dose. However, patients with risk factors for complicated anaphylaxis, who lack access to medical services or additional epinephrine, or with patient preference based on shared decision-making should continue to receive dual-pack EAIs.

G.B.L.

Tanimoto S, Kaliner M, Lockey RF, et al.
Pharmacokinetic and pharmacodynamic comparison of epinephrine, administered intranasally and intramuscularly: an integrated analysis.
Ann Allergy Asthma Immunol. 2023;130(4):508-514.

Few data are available comparing the pharmacokinetics and pharmacodynamics of epinephrine administered either by manual intramuscular (IM) injection or with an epinephrine autoinjector (EAI). Using data from 4 randomized phase 1 trials, these authors compared the pharmacokinetics and pharmacodynamics of different means of epinephrine administration.

The analysis compared a 1-mg intranasal epinephrine spray (neffy; ARS Pharmaceuticals), manual IM injection of 0.3 mg epinephrine, and 2 EAIs delivering 0.3 mg epinephrine (EpiPen [Mylan] and Symjepi [Adamis]). Data were from 175 study participants.

Mean epinephrine concentration was highest for the EpiPen EAI, followed by the Symjepi EAI, the intranasal spray, and IM injection. Maximum concentrations were 254 pg/mL for IM injection, 258 pg/mL for the intranasal spray, 438 pg/mL for the Symjepi EAI, and 503 pg/mL for the EpiPen EAI. The median time to maximum concentration was longest for IM injection (45 minutes vs 20 minutes for the EpiPen EAI). Increases in mean systolic blood pressure were similar for the 2 EAIs and the intranasal spray; the change with IM injection was lower. The intranasal spray was the only product that increased mean diastolic blood pressure. Peak mean heart rate was highest for the EpiPen EAI, followed by the intranasal spray, IM injection, and the Symjepi EAI.

The authors conclude that intranasal administration of epinephrine results in pharmacodynamic responses comparable to or higher than those for EAIs and IM injection, although the maximum plasma epinephrine concentration was lower with intranasal administration.

COMMENT: This study showed that intranasal epinephrine demonstrated comparable or increased pharmacokinetics compared with IM forms of epinephrine administration. The commercial EAI showed the highest concentration after administration, whereas intranasal epinephrine and manual IM epinephrine had the lowest. Despite a lower maximum concentration, intranasal epinephrine had a comparable increase in mean systolic blood pressure and only intranasal epinephrine showed an increase in mean diastolic blood pressure. Having needle-free and equally effective epinephrine routes will be beneficial, particularly for those patients who are hesitant to use their injectors.

S.M.K.

Immune Hypersensitivity Disorders

Copaescu AM, Rosa Duque JS, Phillips EJ. What have we learned about the allergenicity and adverse reactions associated with the severe acute respiratory syndrome coronavirus 2 vaccines: one year later.
Ann Allergy Asthma Immunol. 2022;129(1):40-51.

This narrative review describes the mechanisms of allergic reactions to COVID-19 vaccines relevant to allergists and immunologists. In the United States, information on vaccine adverse events can be found in the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink. In the first VAERS report for the Pfizer-BioNTech vaccine in December 2020, the vaccine rate of anaphylaxis was 11.1 per million doses administered, which decreased as more people were vaccinated. The initial reactions reported during vaccine rollout were primarily in women and occurred within 15 minutes.

Adverse reactions to the COVID-19 vaccines can be classified as immediate or nonimmediate, local or systemic, and immune-mediated or non-immune-mediated. Vasovagal reactions are common, which clinicians need to distinguish from anaphylaxis. Also of consideration in a differential diagnosis is an immunization-related stress response, which can include symptoms such as fainting and hyperventilation. Local nonimmediate reactions include injection-site swelling, soreness, and erythema. Delayed indurated-erythematous reactions have been reported with the Moderna vaccine.

Immune-mediated systemic reactions can include new-onset acute urticaria or flare of chronic spontaneous

urticaria. Other systemic delayed reactions include lymphadenopathy, which is more common after the third booster dose, and myocarditis, primarily after a second mRNA vaccine dose and more prevalent in men under 30. Ischemic and hemorrhagic strokes and seizures are rare.

Recommendations for managing patients with a history of anaphylaxis to a vaccine component or anaphylaxis after an mRNA vaccine are summarized in Table 3. Most patients with a reaction to an initial vaccine dose will tolerate a second dose.

COMMENT: This study highlights that the COVID-19 mRNA vaccines are deemed safe and the benefit of protection with vaccination largely outweighs the risk for a reaction. Although initial data revealed that those with anaphylactic reactions to the COVID-19 vaccine were likely to be women with preexisting atopic disease and culprit allergens included polyethylene glycol and polysorbate, further evidence suggests that the mechanism is not an IgE-mediated one given that most of those patients will tolerate the second vaccination. Common non-IgE-mediated reactions include vasovagal reactions, large local reactions, and benign skin rashes (morbilliform and urticarial). Expert guidance has shifted to recommend against routine percutaneous skin testing to the vaccine and excipients after a COVID-19 vaccination reaction and for physician-observed challenges.
S.M.K.

Diaz VL, Gribbons KB, Yazdi-Nejad K, et al. Cold urticaria syndromes: diagnosis and management.
J Allergy Clin Immunol Pract. 2023;11(8):2275-2285.

The article reviews different forms of cold-induced urticaria and presents a diagnostic algorithm. Although it is most common in young adults, acquired cold urticaria (ACU) can occur at all ages. The clinical presentation can include pruritic wheals, angioedema, or both. ACU is diagnosed by the cold contact test (also called the ice cube test). In contrast with primary and secondary ACU, for which ice cube test results are positive, results are negative for systemic atypical ACU.

Clinical pearls summarized in Table 2 include the following:

- Rash in ACU usually develops within 5 to 30 minutes of cold exposure or during rewarming.
- In familial cold autoinflammatory syndrome (FCAS1) and FCAS2, rash symptoms appear 1 to 2 hours after cold exposure.
- In FCAS1, symptoms usually present by 6 months of age.
- In FCAS3, the rash is mediated by mast cells and occurs within 5 minutes of cold exposure.

Other diagnostic tests include the cold stimulation timed test (CSTT), which gives the minimum time for induction of a wheal or angioedema. The test result is inversely related to the patient's sensitivity to cold. Cold hand immersion is an alternative to the CSTT, but clinicians should note that patients have experienced post-test systemic reactions.

More than 80% of patients with ACU respond to H1-receptor antagonist therapy. Topical capsaicin can reduce symptoms. High-dose corticosteroids are not recommended. Patients with chronic urticaria syndromes may experience delays in diagnosis and complications from medical interventions like cryoablation or even the use of ice packs or cold compresses postoperatively. The authors suggest adding a history of cold urticaria to surgical intake forms.

COMMENT: ACU is one of the most common forms of physical urticaria, estimated at 0.05% of the population, diagnosed via ice cube test, classified as primary or secondary, and typically lasting a mean of 4 to 5 years. The most common cause of secondary ACU is cryoglobulinemia, followed by infection (such as mononucleosis). Cold-induced systemic reactions have occurred in 28% to 60% of children and adults, most commonly related to immersion such as swimming. Monogenic disorders, such as FCAS, are summarized well in Table 2, and a helpful diagnostic algorithm is shown in Figure 2. Treatment for ACU may include H2 antihistamines and even omalizumab, similar to chronic spontaneous urticaria. Treatment for hereditary forms may require targeted therapies such as IL-1 antagonists.
S.M.K.

Hausmann J, Dedeoglu F, Broderick L. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome and syndrome of unexplained recurrent fevers in children and adults.
J Allergy Clin Immunol Pract. 2023;11(6):1676-1687.

Practical information about treating periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome and syndrome of undifferentiated recurrent fevers (SURF) is reviewed. The incidence of PFAPA is estimated to be 2.3 in 10,000 children. PFAPA does not have a single genetic etiology, although subsets of patients have variants in autoinflammatory genes like *MEFV*. Many patients have a family history of similar fevers. The modified Marshall criteria of diagnosis include regularly recurring fevers occurring at less than 5 years of age, constitutional symptoms in the absence of upper respiratory infection, at least one "-APA" symptom (ie, aphthous stomatitis, pharyngitis, cervical lymphadenitis), and exclusion of cyclic neutropenia. Children are asymptomatic with normal growth between fever episodes. Regarding treatment, the authors note that although glucocorticoids can resolve fever in children, they do not cure the syndrome and may increase the frequency of fever episodes. Glucocorticoids are less effective in adults. Vitamin D has attracted attention in patient groups, and families should be counseled about vitamin D overdose.

Proposed diagnostic criteria for SURF include mandatory fevers (3 or more episodes in 6 months) and other supporting features such as attacks lasting 3 to 5 days and occurring monthly, fatigue, abdominal pain, and response to colchicine.

The authors offer practical questions for use in the workup of these patients, such as:

- Are febrile flares truly episodic and associated with features of inflammation?
- Are there triggers for the episode?
- Have the patient's growth and development been appropriate for age?
- Is there a relevant family history?
- Which medications have shown a clinical effect?

The authors advise a broad differential diagnosis in the evaluation of these patients that considers infections, immunodeficiencies, anatomic or metabolic abnormalities, inflammatory bowel disease, malignancy, and other rheumatologic conditions.

COMMENT: PFAPA and SURF criteria (Tables 2 and 5, respectively) and treatment are outlined. PFAPA has been largely considered a pediatric diagnosis; however, these authors note that adult-onset PFAPA is an evolving entity. While children typically have recurring symptoms on regular intervals, adults have a more sporadic occurrence. Adults tend to have additional symptoms such as malaise, headaches, arthralgias, and myalgias. Children have responded well to tonsillectomy; this is less true for adults. Treatment may also include immunosuppressant agents and anti-inflammatories, of which adults have responded well to nonsteroidal anti-inflammatory drugs and colchicine. Likewise, the most common treatment in SURF is colchicine.

S.M.K.

Immunodeficiencies

Cannon L, Pan A, Kovalick L, Sarkissian A, Wu EY. Secondary immunodeficiencies and infectious considerations of biologic immunomodulatory therapies. Ann Allergy Asthma Immunol. 2023;130(6):718-726.

Biologics are approved for the treatment of many conditions but can impair host defense mechanisms and increase a patient's risk for infection. To aid providers in mitigating this risk, this review makes recommendations for monitoring and screening for infectious complications in patients undergoing biologic therapy. These considerations include the following:

- Tumor necrosis factor-α (TNF-α) inhibitors: Risk for infection is highest with infliximab and then adalimumab and lowest with etanercept. Reactivation of herpes simplex virus, hepatitis B virus, and varicella zoster virus can occur. Patient history should include vaccination status.
- Interleukin (IL)-1 inhibitors: These include anakinra, canakinumab, and rilonacept. Overall infectious risk is low, and respiratory infections are most common.
- IL-6 inhibitors: Upper respiratory tract infections and skin infections are most common.
- IL-12/IL-23 inhibitors: Nasopharyngitis and upper respiratory tract infections are the most common. Some studies report an increased incidence of *Candida* infections with ustekinumab.
- IL-17 inhibitors: Increased risk of *Candida* infections compared with other biologics.
- IL-4/IL-13 and IL-5 inhibitors, anti-IgE therapy: Dupilumab inhibits IL-4 and IL-13 signaling; mepolizumab, reslizumab, and benralizumab target the IL-5 pathway; and omalizumab is an anti-IgE monoclonal antibody. These therapies have a potential increased risk for parasitic infections.
- Anti–T cell therapies: Patients receiving abatacept should be counseled on general infection prevention strategies; no alteration of infection prevention strategies is necessary for addition of basiliximab to another immunomodulatory therapy.
- Anti–B cell therapies: Infectious risk is lower for belimumab. Rituximab has a black box warning for hepatitis B virus reactivation. A subset of patients develop persistent hypogammaglobulinemia, including low levels of IgG, IgM, and IgA.

COMMENT: This review summarizes in Table 1 the infectious considerations and recommended screening before initiation of the major classes of biologics. Updating vaccines before biologic initiation and avoiding live vaccines while patients are receiving therapy is a universal recommendation. TNF-α inhibitors are most associated with reactivation of latent tuberculosis (TB) and viral hepatitis; therefore, screening for TB, viral infections, and potentially *Clostridioides difficile* and *Strongyloides* species is recommended. IL-17 inhibitors may increase *Candida* infections. Immunoglobulins should be monitored before and during anti–B cell therapies. Parasite screening can be considered for patients starting anti-IgE or anti-T2 biologic medications. Bacterial infections can also occur (ie, *Escherichia coli*, coagulase-negative staphylococci).

G.B.L.

Convers KD, Slack M, Kanarek HJ. Take a leap of faith: implement routine genetic testing in your office. J Allergy Clin Immunol Pract. 2022;10(7):1676-1687.

Genetic testing has been used in the diagnosis of primary immunodeficiency disorders (PIDs) since 1993 and has recently become more available and affordable. Testing to identify underlying genetic mutations can shorten delays in diagnosis. The article offers guidance on the use of genetic testing by allergists and immunologists practicing outside an academic setting.

Genetic testing can be used prenatally for screening in families with a well-defined genetic PID. As a diagnostic tool, genetic testing can be considered for patients with immune abnormalities and a history of recurrent infections, refractory hives, severe atopic dermatitis, or recurrent fever. A patient's prognosis can be informed by genetic information. For example, phenotypes of Wiskott-Aldrich syndrome differ according to whether the causative mutation results in expression of some or no protein.

The authors recommend considering genetic testing in specific patient populations, such as patients with a family history of infant death in males caused by recurrent respiratory infections and Pneumocystis pneumonia; patients with a family history of unusual infections such as encephalitis due to herpes simplex virus; and patients with frequent, recurrent bacterial, viral, and/or fungal infections.

In testing results, mutations are reported as negative or as 1 of 5 positive variant classifications: benign, likely benign, pathogenic, likely pathogenic, or variant of uncertain significance (VUS). Providing a detailed clinical and family history when ordering genetic testing can help to reduce the likelihood of a VUS being reported. Ordering genetic testing has been made easier with the availability of online dashboards in which testing panels are organized by type of PIDs. Many health insurance plans will cover all or part of the testing cost. The authors encourage all practicing allergists and immunologists to add genetic testing to their toolkit to improve the care of patients with PIDs.

COMMENT: Indications for genetic testing for a suspected inborn error of immunity include a strong family history, unusually severe infections, unusual pathogens, syndromic features, granulomatous disease, lymphoproliferative disease, and severe inflammatory disease. Although screening genetic panels are often used, single-gene Sanger sequencing is useful for targeted familial testing or if the responsible variant may be a deep intronic or untranslated region of DNA, such as certain forms of chronic granulomatous disease, X-linked severe combined immunodeficiency, or IKBKG (NEMO) deficiency. A genetic diagnosis allows for precision therapies (such as anti-CTLA-4 [cytotoxic T lymphocyte–associated protein 4] or phosphoinositide 3-kinase inhibition) and monitoring for known complications.

G.B.L.

Mustafa SS. Steroid-induced secondary immune deficiency.
Ann Allergy Asthma Immunol. 2023;130(6):713-717.

Oral corticosteroids (OCSs) are widely prescribed worldwide but have well-known adverse effects, including immunosuppression. This review article covers the mechanisms of action of OCSs and presents strategies to minimize their negative effects.

Even short courses (5-10 days) of OCSs can affect IgG levels; IgA and IgM are less affected. A patient's IgA levels can help to distinguish primary from secondary immunodeficiency. Patients with immunodeficiency from OCS use will have preserved IgA levels; IgA is likely to be reduced or absent in patients with immune defects. Patients with IgG levels less than 400 mg/dL should be screened for other causes of immunodeficiency.

Studies in children and adults suggest that people with OCS-induced hypogammaglobinemia have adequate responses to vaccination with tetanus, diphtheria, and pneumococcal polysaccharide vaccines. Some studies suggest that OCS use may decrease the magnitude of the antibody response to influenza vaccine. OCS use increases risk for clinically meaningful infectious complications. The risk for invasive fungal and viral infections is greatest in bone marrow transplant recipients.

Strategies to minimize risk include limiting the duration of therapy, minimizing the cumulative OCS dose (eg, goal prednisone dose of 5-10 mg/d), administering vaccines before the start of long courses of OCS therapy, and passive immunization. Patients treated with 20 mg prednisone daily for more than 1 month should receive prophylaxis against *Pneumocystis jirovecii* infection.

COMMENT: OCSs are an effective immune suppressant because of their inhibition of proinflammatory transcription factors (nuclear factor kappa B, activator protein-1) and inhibition of expression of proinflammatory genes and mediators. Although leukocytosis is seen in OCS use, bandemia suggests a potential infection. $CD4^+$ T cell lymphopenia is the most common immune defect with chronic OCS use, although hypogammaglobulinemia is seen primarily in IgG with preservation of IgA. *Pneumocystis jirovecii*, atypical mycobacterial, viral, and fungal infections and decreased COVID-19 vaccine responses can be seen with high-dose OCS use (eg, prednisone 20 mg daily for more than 1 month). Use of lower doses or alternate-day dosing can minimize OCS immune effects.

G.B.L.

Eosinophilic or Gastrointestinal Disorders

Guarnieri KM, Saba NK, Schwartz JT, et al. Food allergy characteristics associated with coexisting eosinophilic esophagitis in FARE Registry participants.
J Allergy Clin Immunol Pract. 2023;11(5):1509-1521.

Many patients with IgE-mediated food allergy also have eosinophilic esophagitis (EoE). Using data from 2 surveys in the Food Allergy Research and Education (FARE) Patient Registry, the authors evaluated the likelihood of having both food allergy and EoE according to specific patient characteristics.

The data analyzed were from 6074 registry participants ranging in age from less than 1 year to older than 80 years (57% female; 83% White). Only 5% of the patients with food allergy reported having EoE. In a multivariable regression model including sex, age, race, ethnicity, and geographic location, male participants were more likely to have EoE than females (adjusted odds ratio [aOR], 1.3) and Asian participants were less likely than White participants (aOR, 0.24). In the analysis of participant characteristics, having a close relative with food allergy and having asthma, allergic rhinitis, oral allergy syndrome, food protein–induced entero-

colitis (FPIES), or hyper-IgE syndrome were associated with higher odds for coexisting EoE. In an analysis adjusted for all comorbidities, arrhythmia, gluten sensitivity, and heartburn were also associated with higher odds of reporting EoE. Health care–related variables that affected the likelihood of reporting EoE included having a greater number of food-related allergic reactions per year, having ever experienced anaphylaxis, and having ever used urgent care or emergency department services. Participants with EoE were more likely to report use of H1-antagonists, H2-antagonists, oral corticosteroids, bronchodilators, and oxygen therapy.

The study findings suggest that coexisting EoE should be considered in patients with an increased number of food allergies, food-related allergic symptoms, or greater reaction severity.

COMMENT: Patients with EoE are more likely to have IgE-mediated food allergy than the general population. Self-reported data from more than 6000 FARE survey respondents revealed a 5% prevalence of concomitant EoE. Based on logistic regression, the odds of concomitant EoE were higher for males, those with a parent or sibling with food allergy, those with multiple food allergies, and those with atopic comorbidities other than atopic dermatitis. Peanut allergy showed no significant association with EoE. Despite study limitations, these findings highlight the need for monitoring for EoE among our food-allergic patients.

S.W.S.

Nhu QM, Aceves SS. Current state of biologics in treating eosinophilic esophagitis.
Ann Allergy Asthma Immunol. 2023;130(1):15-20.

The article reviews biologic therapies for eosinophilic esophagitis (EoE), a chronic type 2 inflammatory disease of the esophagus. In addition to eosinophils, mast cells, GPR15+ pathogenic CD4 T cells, basophils, and innate lymphoid cells contribute to the pathology in EoE. Off-label treatments include topical corticosteroids and proton pump inhibitors. Dietary exclusion therapy can be effective but is challenging for patients to maintain long term. In patients with EoE, TH2 cytokines express interleukin (IL)-4, IL-5, and IL-13, and these are targeted in biologic therapy.

IL-5 or IL-5 receptor blockade: Mepolizumab and reslizumab are anti–IL-5 monoclonal antibodies (mAbs) used in the treatment of severe asthma but no longer being studied for EoE. Benralizumab is an anti–IL-5 receptor-α (anti–IL-5Rα) mAb for which histologic remission has been reported in case reports; clinical response is heterogeneous.

IL-13 blockade: Cendakimab (anti–IL-13 mAb) has been shown to reduce eosinophilia and improve endoscopic features and dysphagia. A phase 3 trial is ongoing. Dupilumab, which targets the α-chain of the IL-4/13 receptor (IL-4Rα) achieved significant and sustained decreases in eosinophilia and symptoms. The clinical trial used a 600-mg subcutaneous loading dose followed by weekly 300-mg subcutaneous injections. The Food and Drug Administration (FDA)-approved regimen does not include the loading dose.

Other studied biologics have included infliximab and omalizumab, which were shown to not be effective for treating EoE.

COMMENT: Without adequate treatment, the eosinophil-predominant T2 inflammation in EoE can progress to tissue remodeling and strictures. Dupilumab, an anti–IL-4Rα mAb, is the only FDA-approved therapy to date. Tezepelumab, a mAb against thymic stromal lymphopoietin (TSLP) has received orphan drug designation. Cendakimab, an anti–IL-13 mAb in phase 3 trial, has improved symptoms and endoscopic features. QAX576, another anti–IL-13 mAb, reduced tissue eosinophilia and expression of eotaxin-3 and periostin, but did not improve symptoms. Anti–IL-5, anti–IL-5Rα, and anti–Siglec-8 agents have not demonstrated complete clinical remission.

S.W.S.

Sindher SB, Barshow S, Tirumalasetty J, et al. The role of biologics in pediatric food allergy and eosinophilic gastrointestinal disorders.
J Allergy Clin Immunol. 2023;151(3):595-606.

Pediatric food allergy and eosinophilic gastrointestinal disorders (EGIDs) have similar disease mechanisms. Skin barrier defects, as in atopic dermatitis, food allergy, and eosinophilic esophagitis (EoE), induce secretion of signaling molecules like interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP), which in turn activate type 2 allergic inflammation. The biologic therapies being studied for the treatment of these T_H2 cell–driven disorders are reviewed.

In adults with food allergy, omalizumab treatment before oral immunotherapy (OIT) improves the safety of OIT to a single or multiple foods and reduces the time to reach a target maintenance dose. The optimal dose of omalizumab is still being studied. Ligelizumab, which has higher binding affinity for free IgE than omalizumab, is also being studied for treatment of food allergy. Dupilumab, an anti–IL-4 receptor-α (anti–IL-4Rα) antibody, is being studied as an adjunct treatment with OIT.

In EGID, eosinophil counts rise above normal, ie, above 5 eosinophils/high-power field (HPF) in the esophagus, 30 eosinophils/HPF in the stomach, and 26 eosinophils/HPF in the duodenum. Dupilumab is the first biologic approved for the treatment of EoE. Reslizumab and mepolizumab, both of which target IL-5, reduced peak eosinophil counts but did not significantly reduce EoE symptoms or EoE physician global assessment compared with placebo. Benralizumab, an anti–IL-5Rα antibody, was shown to improve histologic disease remission but not symptoms of dysphagia.

The authors note that "biologics targeting eosinophils only may not alleviate the disease process." Remaining gaps in knowledge include how best to track the effectiveness of a biologic, whether use of biologics in combination

would increase efficacy, and how durable the effects of biologics are.

COMMENT: The number of potential target therapies for food allergy is growing. Omalizumab significantly increases the reaction threshold dose and reduces the severity of IgE-mediated reactions. Dupilumab's mechanism and its indication for treatment of EoE are enticing factors in the setting of food allergy. Clinical trials examining its use as a monotherapy, as an adjunct with OIT, or in combination with omalizumab are underway. For EoE/EGID, biologics that target eosinophilic inflammation have failed to reduce symptoms. However, vedolizumab, an anti-α4β7 integrin, may reduce dysphagia and tissue eosinophilia in these patients.

S.W.S.

Underwood B, Troutman TD, Schwartz JT. Breaking down the complex pathophysiology of eosinophilic esophagitis.
Ann Allergy Asthma Immunol. 2023;130(1):28-39.

Eosinophilic esophagitis (EoE) is a chronic, progressive allergen-driven disease characterized by a buildup of eosinophils in the esophagus. It is a common cause of feeding problems in children, who may present with vomiting, heartburn, abdominal pain, and failure to thrive. Endoscopically, EoE appears as linear furrows, esophageal rings, white plaques, and esophageal narrowing; however, the esophagus will appear normal in up to 30% of children. Active disease is defined histopathologically as a tissue eosinophil density greater than or equal to 15 eosinophils/high-power field (HPF).

The pathophysiology of EoE, as modeled in Figure 2, has genetic, environmental, and immunologic components. Genome-wide association studies have identified risk loci for EoE on human chromosomes. These include 5q22, 2p23, 11q13, and 16p13. Milk, egg, wheat, and soy allergens can trigger disease, as can aeroallergens. People with an IgE-mediated food allergy are at greater risk of developing EoE than people without food allergy; one study estimated the risk to be nearly 100-fold higher.

Allergens trigger the production of the alarmin cytokines thymic stromal lymphopoietin (TSLP) and interleukin (IL)-33. IL-33 is released via an intracellular allergen sensor called the RIPK1–caspase-8 ripoptosome complex. The impaired mucosal barrier allows food antigens to pass to dendritic cells, which present them to $CD4^+$ T cells. IL-4, IL-13, and IL-5 are produced, which recruit and activate mast cells, eosinophils, and basophils. IL-13 directs changes to the epithelium associated with barrier dysfunction. IL-4 promotes differentiation of T_H2 cells and regulates eosinophil trafficking. Dupilumab, which is approved for the treatment of EoE, targets both IL-4 and IL-13 signaling. Other immune mediators that affect eosinophil function include CCL26 and IL-5.

Mast cells and eosinophils lead to epithelial changes that further impair barrier function. Clinically, mast cell numbers correlate with patient-reported pain. The dysregulated epithelial and immune cell responses generate a feed-forward cycle leading to chronic inflammation. EoE progresses from an inflammatory disease to a fibrostenotic disease, and recent research is examining the molecular components involved in fibrostenosis, such as tetraspanin 12 (TSPAN12) and thrombospondin-1 (TSP-1).

COMMENT: This eloquent review offers clinicians greater insight regarding EoE susceptibility factors, potential triggers, and immunopathogenesis. New pathways, including the RipIL-33 allergen-sensing pathway, and potential targets are highlighted. Additionally, efforts to characterize EoE endotypes are beginning to emerge. With time and further refinement, this will hopefully translate to more targeted and individualized therapy options for patients suffering from this chronic, heterogeneous condition.

S.W.S.

Wechsler ME, Hellmich B, Cid MC, et al. Unmet needs and evidence gaps in hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis.
J Allergy Clin Immunol. 2023;151(6):1415-1428.

Hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA) are rare diseases characterized by elevated blood eosinophils and eosinophil infiltration into tissues leading to end-organ damage or dysfunction. A history of asthma or atopic disease is more common in patients with EGPA. Both diseases have a usual onset during adulthood. EGPA is typically characterized by necrotizing vasculitis of small vessels.

HES is classified as being idiopathic (I), myeloid (M), lymphocytic (L), or familial. Most cases are idiopathic. In M-HES, eosinophils expand in a primary myeloid neoplasm. More than 80% of patients with M-HES have a deletion in chromosome 4. Only one family with familial HES has been described in the literature. Diagnostic criteria for HES are blood eosinophil count greater than 1500 cells/μL and tissue eosinophilia causing target organ damage. The differential diagnosis should include underlying causes of hypereosinophilia such as adverse drug reactions and helminthiasis.

In EGPA, eosinophils and interleukin (IL)-5 play pathogenic roles. Anti–IL-5 therapy can reduce disease activity in both HES and EGPA. About 30% of patients have antibodies against myeloperoxidase (MPO) and antineutrophil cytoplasmic antibody (ANCA). An unanswered question is whether there are distinct drivers of symptoms in patients with ANCA-positive vs ANCA-negative disease. Vasculitis must be present for a diagnosis of EGPA. The differential diagnosis should include other causes of hypereosinophilia, especially diseases of the airways like chronic eosinophilic pneumonia. The Five Factor Score and the Birmingham Vasculitis Activity Score can be used to assess disease activity.

Systemic corticosteroids are the main treatment. Several biologic therapies are approved or are undergoing tri-

als for the treatment of HES and EGPA.

COMMENT: HES and EGPA are difficult to diagnose, distinguish, and manage. In addition to outlining challenges and knowledge gaps, this article also highlights promising developments, including the identification of urine eosinophil-derived neurotoxin concentration as a potential marker of disease activity and relapse. Mepolizumab is approved for treatment of HES and EGPA and has demonstrated clinical benefits, including reduction in flares and systemic steroid use. Phase 3 studies with benralizumab in HES and EGPA are underway. Rituximab may offer a steroid-sparing option for ANCA-positive EGPA patients. Biomarkers to measure treatment response and stratify treatment are greatly needed.

S.W.S.

Emerging National Health Priorities

Davis CM, Flohr C, Gupta MR, et al. Managing atopic dermatitis in patients with skin of color.
J Allergy Clin Immunol Pract. 2023;11(5):1376-1383.

People of color with atopic dermatitis (AD) may experience more severe disease. The authors define this population to include people identifying as Black/African, Hispanic/Latinx, Asian/Pacific Islander, American Indian/Native American, Indigenous Australian, Middle Eastern, biracial/multiracial, and non-White. In one case report described by the authors, the family of a toddler had difficulty adhering to a management plan with twice-daily 0.1% mometasone ointment on the body, 0.03% tacrolimus ointment on the face, and 0.01% fluocinolone oil on the scalp because their public health insurance did not cover enough medication. When dupilumab was prescribed, not all family members administered it consistently. As summarized in Table 1, considerations when treating people of color with AD include the following:

- In US and UK urban areas, AD is more prevalent among Black children.
- Loss-of-function mutations in *FLG*, which encodes the skin barrier protein filaggrin, are a risk factor in all ethnic groups but may be less prevalent in Asian populations.
- Colonizing strains of *Staphylococcus aureus*, which trigger AD flares, may differ between ethnic populations.
- On the Fitzpatrick skin type scale, skin of color is currently defined as skin types IV, V, and VI. Alternatives to this scale are being developed.
- Erythema is more difficult to assess in skin of color and may appear with more violet tones. Black children may present with pruritus without skin lesions. Asian patients may present with features more common in psoriasis, such as prominent epidermal hyperplasia and hypogranulosis. Xerosis may be more stigmatizing in persons of color because scale and dryness are more visible on the skin.
- Common scoring systems may underestimate disease severity in persons of color.
- Black children may require higher cyclosporine doses to achieve therapeutic levels. In Asian children, cyclosporine levels may depend on CYP3A4*1 G genotype.

The authors suggest that increasing referrals and access to specialists, referrals for patch testing to identify allergic contact dermatitis, and modification of scoring systems to reduce the importance of erythema in the score could improve outcomes in patients of color with AD.

COMMENT: This manuscript reminds the practicing allergist that every patient with AD has different needs. Appreciating these differences will improve the care of our patients of color with AD. A need exists to recognize challenges in the diagnosis of AD in our patients of color, who are more likely to have persistent and severe AD for a variety of reasons, including environmental factors. We must recognize the differences to address the disparities that exist.

V.H.T.

Josey KP, Delaney SW, Wu X, et al. Air pollution and mortality at the intersection of race and social class.
N Engl J Med. 2023;388(15):1396-1404.

People exposed to air pollution containing fine particulate matter, which is defined as particles sized less than or equal to 2.5 μm ($PM_{2.5}$), experience adverse health effects including greater mortality. These effects are disproportionately experienced by low-income and Black Americans. These authors estimated exposure–response curves for $PM_{2.5}$ exposure and mortality in subpopulations defined simultaneously by race (Black vs White) and income (Medicaid eligible vs ineligible).

In this nationally representative study sample, Black persons had higher $PM_{2.5}$ exposure than White persons. Among Black persons but not White persons, average annual exposure was also higher in low-income persons. Exposure–response curves differed in some subpopulations. As $PM_{2.5}$ exposure decreased, the hazard ratio for death dropped faster among Black persons than in White persons. In the higher-income subpopulation, the decrease in mortality associated with a decrease in $PM_{2.5}$ exposure from 12 to 8 $\mu g/m^3$ in Black persons was almost double that in White persons. In the low-income subpopulation, exposure–response curves were similar between Black and White persons.

The authors conclude that racial identity and socioeconomic status may together affect exposure–response curves such that Black higher-income, Black low-income, and White low-income persons may benefit more from a lower National Ambient Air Quality Standard (NAAQS) for particulate matter than White higher-income persons. A lower $PM_{2.5}$ NAAQS could help to reduce environmental inequities in exposure to air pollution.

COMMENT: The Environmental Protection Agency

(EPA) requires air quality standards that set prescribed levels of exposure to particulate matter less than or equal to 2.5 μm based on strong evidence that fine particulate matter of this size or smaller is associated with increased risk for premature death. This study of adults 65 years and older showed that the average annual $PM_{2.5}$ exposure over the 16-year study period was 9.8 (SD, 3.2) $\mu g/m^3$. In general, White persons were exposed to lower $PM_{2.5}$ than Black persons and racial identity was the distinguishing factor associated with $PM_{2.5}$ levels. The authors also found that decreasing $PM_{2.5}$ exposure from 12 to 6 $\mu g/m^3$ was associated with a lower hazard ratio for death. Importantly, the racial disparity in exposure to harmful air pollution is apparent and a lower annual $PM_{2.5}$ NAAQS would be largely beneficial.
S.M.K.

Seastedt H, Nadeau K. Factors by which global warming worsens allergic disease.
Ann Allergy Asthma Immunol. 2023;131(6):694-702.

Allergic diseases have become more prevalent in the past 50 years, and increased air pollution caused by climate change has played a role in this increase. Particulate matter (PM) is a major air pollutant affecting allergic disease. PM less than 2.5 μm is most harmful because it can cross into the bronchioles and alveoli of the lungs and enter the bloodstream. Pollen is a natural source of air pollution, and the length of the pollen season and pollen concentrations are affected by increasing heat and carbon dioxide levels and by climate events like thunderstorms. Pollen concentrations are expected to increase by 200% by the end of the century. One study showed that ozone affects the severity of pollen allergy symptoms. The epithelial barrier hypothesis suggests that detergents, allergens, and other pollutants disrupt the epithelial barrier and promote inflammation.

The major climate change events that increase atopic conditions are wildfires, sand and dust storms, thunderstorms, heatwaves, and flooding. Wildfires and sand and dust storms increase levels of PM, ozone, and carbon monoxide. After one wildfire in California, levels of $PM_{2.5}$, ozone, and carbon monoxide increased by 220%, 20%, and 151%, respectively. Wildfire smoke increases rates of asthma. Sand and dust storms include bacteria, fungi, and spores, which can travel long distances. Thunderstorm asthma refers to increases in asthma after thunderstorms when pollen counts are high. The high humidity causes pollen grains to rupture into subpollen allergic particles. Heatwaves have increased in frequency, duration, and intensity. Temperatures above 105°F are dangerous to human health, and some studies suggest that extreme heat exposure may be a risk factor for asthma. Mold spores proliferate after major flooding.

The authors conclude that "Physicians as trusted members of the community should educate their patients on climate change and be role models for decreasing their and the health care sector's carbon footprint."

COMMENT: Climate change and pollution are impacting the health of many through a myriad of different avenues, including both indoor and outdoor air pollution, PM (particularly that smaller than 2.5 μm), increasing pollen counts, ozone, and the introduction of harmful metals into water. Additionally, natural events including wildfires, sandstorms, thunderstorms and flooding, and extremes of temperature have been found to negatively affect health, particularly asthma. Importantly, while it is generally acknowledged that climate change affects health, many physicians report feeling inadequately prepared to counsel patients on this topic, highlighting a need for additional education during medical training.
I.M.O.